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V.U./E.R. S. C. Chantrain (CHC-Liège), M. Raes (KUL)
UZ Leuven, Herestraat 49, 3000 Leuven
E-mail: BJ-Ped@hotmail.com

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BEXSERO

Vaccin méningococcique groupe B (ADNr, composant, adsorbé)

Le **premier** vaccin contre le méningocoque de **sérogroupe B**.[1]

Le **seul** indiqué dès l'âge de **2 mois**.[1,2]

2+1

pour les nourrissons à partir de **2 mois**.[1]

RÉSUMÉ ABRÉGÉ DES CARACTÉRISTIQUES DU PRODUIT Veuillez vous référer au Résumé des Caractéristiques du Produit pour une information complète concernant l'usage de ce médicament. **DÉNOMINATION DU MÉDICAMENT** Bexsero suspension injectable en seringue préremplie Vaccin méningococcique groupe B (ADNr, composant, adsorbé) EU/1/12/812/001 EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004 Classe pharmacothérapeutique : vaccins méningococciques, Code ATC : J07AH09 **COMPOSITION QUALITATIVE ET QUANTITATIVE** Une dose (0,5 ml) contient : Protéine de fusion recombinante NHBA de *Neisseria meningitidis* groupe B [1,2,3] 50 microgrammes Protéine recombinante NadA de *Neisseria meningitidis* groupe B [1,2,3] 50 microgrammes Protéine de fusion recombinante fHbp de *Neisseria meningitidis* groupe B [1, 2, 3] 50 microgrammes Vésicules de membrane externe (OMV) de *Neisseria meningitidis groupe* B, souche NZ98/254 mesurée en tant que proportion de l'ensemble des protéines contenant l'antigène PorA P1.4 [2] 25 microgrammes [1] produite dans des cellules d'*E. coli* par la technique de l'ADN recombinant [2] adsorbée sur hydroxyde d'aluminium (0,5 mg Al^{3+}) [3] NHBA (antigène de liaison à l'héparine de Neisseria), NadA (adhésine A de Neisseria), fHbp (protéine de liaison du facteur H) **Indications thérapeutiques** Bexsero est indiqué pour l'immunisation active des sujets à partir de l'âge de 2 mois contre l'infection invasive méningococcique causée par *Neisseria meningitidis* de groupe B. L'impact de l'infection invasive à différentes tranches d'âge ainsi que la variabilité épidémiologique des antigènes des souches du groupe B dans différentes zones géographiques doivent être pris en compte lors de la vaccination. Voir rubrique 5.1 du RCP complet pour plus d'informations sur la protection contre les souches spécifiques au groupe B. Ce vaccin doit être utilisé conformément aux recommandations officielles. **Posologie et mode d'administration** Posologie **Tableau 1. Résumé de la posologie**

Age lors de la première dose	Primovaccination	Intervalles entre les doses de primovaccination	Rappel
Nourrissons de 2 à 5 mois[a]	Trois doses de 0,5 ml chacune	1 mois minimum	Oui, une dose entre l'âge de 12 et 15 mois avec un intervalle d'au moins 6 mois entre la primovaccination et la dose de rappel [b, c]
	Deux doses de 0,5 ml chacune	2 mois minimum	
Nourrissons de 6 à 11 mois	Deux doses de 0,5 ml chacune	2 mois minimum	Oui, une dose au cours de la deuxième année avec un intervalle d'au moins 2 mois entre la primovaccination et la dose de rappel [c]
Enfants de 12 à 23 mois	Deux doses de 0,5 ml chacune	2 mois minimum	Oui, une dose avec un intervalle de 12 à 23 mois entre la primovaccination et la dose de rappel [c]
Enfants de 2 à 10 ans	Deux doses de 0,5 ml chacune	1 mois minimum	Selon les recommandations officielles, une dose de rappel peut être envisagée chez les sujets présentant un risque continu d'exposition à infection méningococcique[d]
Adolescents (à partir de 11 ans) et adultes*			

[a] La première dose ne doit pas être administrée avant l'âge de 2 mois. La sécurité et l'efficacité de Bexsero chez les nourrissons de moins de 8 semaines n'ont pas encore été établies. Aucune donnée n'est disponible. [b] En cas de retard, la dose de rappel ne doit pas être administrée audelà de l'âge de *24 mois.* [c] Voir rubrique 5.1 du RCP complet La nécessité et le moment d'administration d'une dose de rappel n'ont pas encore été déterminés. [d] Voir rubrique 5.1 du RCP complet * Il n'existe aucune donnée chez les adultes de plus de 50 ans. Mode d'administration Le vaccin est administré par une injection intramusculaire profonde, de préférence dans la face antérolatérale de la cuisse chez le nourrisson ou dans la région du muscle deltoïde du haut du bras chez les sujets plus âgés. Des sites d'injection distincts doivent être utilisés si plusieurs vaccins sont administrés simultanément. Le vaccin ne doit pas être injecté par voie intraveineuse, souscutanée ni intradermique et ne doit pas être mélangé avec d'autres vaccins dans la même seringue. Pour les instructions concernant la manipulation du vaccin avant administration, voir la rubrique 6.6 du RCP complet. **Contreindications** Hypersensibilité aux substances actives ou à l'un des excipients mentionnés à la rubrique 6.1 du RCP complet. **Mises en garde spéciales et précautions d'emploi** Comme pour les autres vaccins l'administration de Bexsero doit être reportée chez des sujets souffrant de maladie fébrile sévère aiguë. Toutefois, la présence d'une infection mineure, telle qu'un rhume, ne doit pas entraîner le report de la vaccination. Ne pas injecter par voie intravasculaire. Comme pour tout vaccin injectable, un traitement médical approprié et une surveillance adéquate doivent toujours être disponibles en cas de réaction anaphylactique consécutive à l'administration du vaccin. Des réactions en rapport avec l'anxiété, y compris des réactions vasovagales (syncope), de l'hyperventilation ou des réactions en rapport avec le stress peuvent survenir lors de la vaccination comme réaction psychogène à l'injection avec une aiguille (voir rubrique « Effets indésirables »). Il est important que des mesures soient mises en place afin d'éviter toute blessure en cas d'évanouissement. Ce vaccin ne doit pas être administré aux patients ayant une thrombocytopénie ou tout autre trouble de la coagulation qui serait une contreindication à une injection par voie intramusculaire, à moins que le bénéfice potentiel ne soit clairement supérieur aux risques inhérents à l'administration. Comme tout vaccin, la vaccination par Bexsero peut ne pas protéger tous les sujets vaccinés. Il n'est pas attendu que Bexsero assure une protection contre la totalité des souches de méningocoque B en circulation. Comme pour de nombreux vaccins, les professionnels de santé doivent savoir qu'une élévation de la température corporelle peut survenir suite à la vaccination des nourrissons et des enfants (de moins de 2 ans). L'administration d'antipyrétiques à titre prophylactique pendant et juste après la vaccination peut réduire l'incidence et la sévérité des réactions fébriles postvaccinales. Un traitement antipyrétique doit être mis en place conformément aux recommandations locales chez les nourrissons et les enfants (de moins de 2 ans). Les personnes dont la réponse immunitaire est altérée soit par la prise d'un traitement immunosuppresseur, une anomalie génétique ou par d'autres causes, peuvent avoir une réponse en anticorps réduite après vaccination. Des données d'immunogénicité sont disponibles chez les patients présentant un déficit en complément, une asplénie ou une dysfonction splénique. Les personnes ayant des déficits héréditaires du complément (par exemple les déficits en C3 ou C5) et les personnes recevant un traitement inhibiteur de l'activation de la fraction terminale du complément (par exemple, l'éculizumab) ont un risque accru de maladie invasive due à *Neisseria meningitidis* du groupe B, même après avoir développé des anticorps après vaccination par Bexsero. Il n'existe aucune donnée sur l'utilisation de Bexsero chez les sujets de plus de 50 ans et il existe des données limitées chez les patients atteints de maladies chroniques. Le risque potentiel d'apnée et la nécessité d'une surveillance respiratoire pendant 48 à 72 heures doivent soigneusement être pris en compte lors de l'administration des doses de primovaccination chez des grands prématurés (nés à 28 semaines de grossesse ou moins), en particulier chez ceux ayant des antécédents d'immaturité respiratoire. En raison du bénéfice élevé de la vaccination chez ces nourrissons, l'administration ne doit pas être suspendue ou reportée. Le capuchon de la seringue peut contenir du latex de caoutchouc naturel. Bien que le risque de développer des réactions allergiques soit très faible, les professionnels de santé doivent évaluer le rapport bénéfices/risques avant d'administrer ce vaccin à des sujets présentant des antécédents connus d'hypersensibilité au latex. La kanamycine est utilisée au début du procédé de fabrication et est éliminée au cours des étapes ultérieures de la fabrication. Les taux de kanamycine éventuellement détectables dans le vaccin final sont inférieurs à 0,01 microgramme par dose. L'innocuité de Bexsero chez les sujets sensibles à la kanamycine n'a pas été établie. Traçabilité Afin d'améliorer la traçabilité des médicaments biologiques, le nom et le numéro de lot du produit administré doivent être clairement enregistrés. **EFFETS INDÉSIRABLES** Résumé du profil de sécurité La sécurité de Bexsero a été évaluée lors de 17 études, dont 10 essais cliniques randomisés contrôlés portant sur 10565 sujets (âgés de 2 mois minimum) ayant reçu au moins une dose de Bexsero. Parmi les sujets vaccinés par Bexsero, 6837 étaient des nourrissons et des enfants (de moins de 2 ans), 1051 étaient des enfants (entre 2 et 10 ans) et 2677 étaient des adolescents et des adultes. Parmi les nourrissons ayant reçu les doses de primovaccination de Bexsero, 3285 ont reçu une dose de rappel au cours de leur deuxième année de vie.. Chez les nourrissons et les enfants (de moins de 2 ans), les réactions indésirables locales et systémiques les plus fréquemment observées lors des essais cliniques étaient : sensibilité et érythème au site d'injection, fièvre et irritabilité. Dans les études cliniques menées chez les nourrissons vaccinés à 2, 4 et 6 mois, la fièvre (≥ 38 °C) était rapportée chez 69% à 79 % des sujets lorsque Bexsero était coadministré avec des vaccins de routine (contenant les antigènes suivants : pneumococcique heptavalent conjugué, diphtérie, tétanos, coqueluche acellulaire, hépatite B, poliomyélite inactivée et *Haemophilus influenzae* de type b), contre 44% à 59 % des sujets recevant les vaccins de routine seuls. Une utilisation plus fréquente d'antipyrétiques était également rapportée chez les nourrissons vaccinés par Bexsero et des vaccins de routine. Lorsque Bexsero était administré seul, la fréquence de la fièvre était similaire à celle associée aux vaccins de routine administrés aux nourrissons pendant les essais cliniques. Les cas de fièvre suivaient généralement un schéma prévisible, se résolvant généralement le lendemain de la vaccination. Chez les adolescents et les adultes, les réactions indésirables locales et systémiques les plus fréquemment observées étaient : douleur au point d'injection, malaise et céphalée. Aucune augmentation de l'incidence ou de la sévérité des réactions indésirables n'a été constatée avec les doses successives du schéma de vaccination. Liste tabulée des effets indésirables Les effets indésirables (consécutifs à la primovaccination ou à la dose de rappel) considérés comme étant au moins probablement liés à la vaccination ont été classés par fréquence. Les fréquences sont définies comme suit : Très fréquent : (≥ 1/10) Fréquent : (≥ 1/100 à < 1/10) Peu fréquent : (≥ 1/1 000 à < 1/100) Rare : (≥ 1/10 000 à < 1/1 000) Très rare : (< 1/10 000) Fréquence indéterminée : (ne peut être estimée sur la base des données disponibles) Dans chaque groupe de fréquence, les effets indésirables sont présentés par ordre de sévérité décroissante. Outre les événements rapportés lors des essais cliniques, les réactions spontanées rapportées dans le monde pour Bexsero depuis sa commercialisation sont décrites dans la liste ci dessous. Comme ces réactions ont été rapportées volontairement à partir d'une population de taille inconnue, il n'est pas toujours possible d'estimer de façon fiable leur fréquence. Ces réactions sont, en conséquence, listées avec une fréquence indéterminée. **Nourrissons et enfants (jusqu'à l'âge de 10 ans)** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Troubles du métabolisme et de la nutrition Très fréquent : troubles alimentaires Affections du système nerveux Très fréquent : somnolence, pleurs inhabituels, céphalée Peu fréquent : convulsions (y compris convulsions fébriles) Fréquence indéterminée : épisode d'hypotonie-hyporéactivité, irritation des **méninges** (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections vasculaires Peu fréquent : pâleur (rare après le rappel) Rare : syndrome de Kawasaki Affections gastrointestinales Très fréquent : diarrhée, vomissements (peu fréquents après le rappel) Affections de la peau et du tissu souscutané Très fréquent : rash (enfants âgés de 12 à 23 mois) (peu fréquent après le rappel) Fréquent : rash (nourrissons et enfants âgés de 2 à 10 ans) Peu fréquent : eczéma Rare : urticaire Affections musculosquelettiques et systémiques Très fréquent : arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : fièvre (≥ 38 °C), sensibilité au niveau du site d'injection (y compris sensibilité sévère au site d'injection définie par des pleurs lors d'un mouvement du membre ayant reçu l'injection), érythème au site d'injection, gonflement du site d'injection, induration au site d'injection, irritabilité Peu fréquent : fièvre (≥ 40 °C) Fréquence indéterminée : réactions au site d'injection (incluant un gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister pendant plus d'un mois) **Adolescents (à partir de 11 ans) et adultes** Affections du système immunitaire Fréquence indéterminée : réactions allergiques (y compris réactions anaphylactiques) Affections du système nerveux Très fréquent : céphalée Fréquence indéterminée : syncope ou réaction vasovagale à l'injection, irritation des méninges (des signes d'irritation des méninges, tels qu'une raideur de la nuque ou une photophobie, ont été rapportés sporadiquement peu de temps après la vaccination. Ces symptômes ont été de nature légère et transitoire) Affections gastrointestinales Très fréquent : nausées Affections de la peau et du tissu sous-cutané Fréquence indéterminée : rash Affections musculosquelettiques et systémiques Très fréquent : myalgies, arthralgies Troubles généraux et anomalies au site d'administration Très fréquent : douleur au point d'injection (y compris douleur sévère au point d'injection définie par une incapacité à mener à bien des activités quotidiennes normales), gonflement du site d'injection, induration au point d'injection, érythème au site d'injection, malaise Fréquence indéterminée : fièvre, réactions au site d'injection (incluant gonflement étendu du membre vacciné, vésicules au point d'injection ou autour du site d'injection et nodule au site d'injection pouvant persister plus d'un mois) Déclaration des effets indésirables suspectés La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via le système national de déclaration : **Belgique** Agence fédérale des médicaments et des produits de santé Division Vigilance Boîte Postale 97 B-1000 Bruxelles Madou Site internet: www.afmps.be e-mail: adversedrugreactions@fagg-afmps.be **Luxembourg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy – Hôpitaux de Brabois Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX Tél : (+33) 3 83 65 60 85 / 87 Fax : (+33) 3 83 65 61 33 E-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments Allée Marconi - Villa Louvigny L-2120 Luxembourg Tél. : (+352) 2478 5592 Fax : (+352) 2479 5615 E-mail : pharmacovigilance@ms.etat.lu Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **TITULAIRE DE L'AUTORISATION DE MISE SUR LE MARCHÉ** GSK Vaccines S.r.l., Via Fiorentina 1, 53100 Sienne, Italie **DATE D'APPROBATION DU TEXTE** 02/07/2020 (v11) **MODE DE DELIVRANCE** Sur prescription médicale.

1. Medini D, Stella M, Wassil J, Vaccine 2015; 33; 2629-2636. 2. Bexsero SMPC.

PM-BE-BEX-ADVT-210002 - Mars 2021 - E.R.: GlaxoSmithKline Pharmaceuticals s.a., av Pascal 2-4-6, 1300 Wavre

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Editorial

Dear colleagues,

Dear friends,

Over the past months and year, we learned more than ever that life is an adventure with many unforeseeable events. We learned how to deal with fears about our world and our future. We learned to realize that uncertainty can not be excluded and is part of our existence and hopefully we learned to prepare or to be prepared for the unexpected.

We learned how complex human beings are, driven by rational, emotional, economic, cultural, personal, societal forces. We learned how important and essential it is to tackle a worldwide crisis in solidarity, balancing "me" and "we", balancing regional and global interests, balancing science and politics, balancing physical and psycho-social wellbeing, exceeding borders, understanding each other avoiding disregard or indifference.

Gradually, restrictions are turned down so "normal" life is coming back for most of us in the different sectors in society. Elderly can meet their grandchildren, children and youngsters can have more social contacts, cultural and ceremonial events can be organized on a larger scale, work and recreation can be reorganized… all that realized by one of the most important and most valuable aspects of health care and of the whole society: **prevention**. There is no discussion that these pandemic stresses how important it is to focus on and to invest in prevention, needed to be implemented not only within health services but on a broader societal scale, in a systematic way, cross-sectional, cross-governmental and globally, and in **solidarity.**

This being said, we are pleased to present this issue of the *Belgian Journal of Paediatrics*. In the last months, we have received more and more submissions that increase the relevance of our journal and illustrate the dynamism of the Belgian paediatric community around this media. We are aware of the sometimes long delays between submission and final response to the review process. This process requires the involvement of experts who are also willing to support the learning of young authors and to guarantee the quality of our publications. We would like to thank them warmly for this important work behind the scenes. Two new members have also joined the board : Dr Els Duval and Karolien Van De Maele. We welcome and thank them for their commitment to the journal.

Once again, SARS-Cov-2 is present in this summer's issue with a reflection by F. De Meulder and J. Witters on its impact on the digitalization of care. L. and E. Bijker provide an outstanding overview on the specificities of clinical disease and transmission in children. M. Demey and colleagues also report the clinical histories of 2 adolescents with Sickle Cell anemia who developed pulmonary embolism associated with possible SARS-COV2 infection. Other infectious diseases are also discussed with an article about neuroborreliosis by J. Vanbekbergen and colleagues and an overview about diagnosis and management of osteoarticular infections in children by T. Alliet and colleagues. A case of mycoplasma pneumonia meningo-encephalitis is also reported by Z. Casier and colleagues. L. Blomme and her team present an original study about the screening for autism in young children with trisomy 21.

For young paediatricians in training, our "case report" section gives the opportunity to describe and to update their and our knowledge about unusual situations or problems that are so common that we, sometimes, forget the physiopathology. S. Pohlen reports on hemoptysis caused by the unilateral absence of pulmonary artery. W. Van Hoe illustrates extensively two cases of PIK3CA-related overgrowth spectrum. M. Verjans discusses the difference between benign coccygeal dimple and dermal sinus tract. E. Lambert reminds that febrile cholestasis may be an unusual presentation of Kawasaki disease and S. Van de Velde explores the association between PICA syndrome and iron deficiency. H. Hubinont explains how neonatal hypoxic ischemic encephalopathy may hide a spinal cord lesion. L. Neven and colleagues reported on intracranial pressure and bilateral papilledema in a boy with homocystinuria.

As usual we publish summaries of doctoral theses under the section "Made In Belgium": "Desmopressin resistant monosymptomatic nocturnal enuresis: new pathophysiological and pharmacological insights" is developed by Lien Dossche and "Micturition reeducation on children with cerebral palsy" is presented by Bieke Samijn. The thesis of Els Van de Vijver, "Chronic abdominal pain, fatigue and inflammatory bowel disease in children" is also reported.

Our paediatric Cochrane Corner section gets back to a controversial subject that was already discussed in previous issues: "Is the use of probiotics in the treatment of acute infectious diarrhoea no longer supported by the evidence ? "

We finish with the beginning… As Belgian journal, we are also proud to have a cover illustrated by comics and we hope that you will appreciate the cartoon of this summer, drawn in exclusivity for us by Serge Ernst.

With this entertaining image and on behalf of the editorial board, we wish you a fruitful reading and pleasant summer holidays.

Marc Raes and Christophe Chantrain

Uw vragen of commentaar
Vos questions ou commentaires

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Comité de rédaction - Redactieraad
M. Raes - Chr Chantrain

Gasthuisberg - Kindergeneeskunde

Herestraat 49 - 3000 Leuven
E-mail BJ-Ped@hotmail.com

PIET VANHAESEBROUCK
(1950-2021)

On June 1st 2021 we lost emeritus professor dr. Piet Vanhaesebrouck. He was one of the pioneers of modern neonatal intensive care in Flanders. To many of us Piet was known as a gifted and passionate clinician.

Piet got his training in neonatal intensive care at the NICU of the University Hospitals Gasthuisberg (prof. dr. Hugo Devlieger) and at the neonatal intensive care units of the Southmead Hospital and the Bristol Maternity Hospital in Bristol, England (prof. dr. Peter M. Dunn).

On August 1st 1983 he commenced modern neonatal intensive care in the Children's Hospital 'C. Hooft' of the Ghent University Hospital, and he was head of the NICU Ghent untill 2014, when he retired.

In 1985 he obtained the title 'doctor in biomedical sciences' with his thesis entitled 'Influence of a modified clinical methodology on mortality and morbidity of low- and very-low-birthweight babies'. In 1994 he succesfully defended his PhD thesis entitled 'Biochemical evaluation of fetal growth velocity'. In 1995 Piet was appointed associate professor at the Ghent University and became professor by special appointment in 2005.

In addition to his carreer in the clinical neonatology field, Piet chaired in many organisations. He was member of several advisory boards (Vlaamse adviescommissie voor Perinatale Zorg – 1988-2000; Interdisciplinaire adviescommissie Kind & Gezin – 1989-1993; COS Gent – 1995-1998; Nationale Raad voor Ziekenhuisvoorzieningen (NRZV, CNEH; 2007-2014). Piet was chairman of the neonatology section of the "Vlaamse Vereniging voor Kindergeneeskunde" (1996-1998), co-founder, secretary (1998-2000) and president (2000-2003) of the "Belgische Vereniging voor Neonatologie-Groupement Belge de Néonatologie", and president of the "College van geneesheren – intensieve neonatologie" (1999-2004). He developed the NICaudit, the well-known national database that is still in use in many NICU's.

Piet will be deeply missed. We want to express our sincerest condolences to mrs Vanhaesebrouck, his children Karel, An and Bruno, and to Piet's family and friends.

Koenraad Smets, MD PhD
Medical head Neonatal Intensive Care Unit
Ghent University Hospital

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IREGISTRATIONS:

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The future of the hospitals
How did covid-19 catalyse technology and digitalization?

Frederic De Meulder [a], Jan Witters [b]

[a] Gasthuiszusters Antwerpen (GZA), department of Paediatrics
[b] Gasthuiszusters Antwerpen (GZA), director of processes and innovation

Frederic.DeMeulder@gza.be

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Digital is the new normal in healthcare and hospitalization. Simultaneously there is an evolution; patients are becoming partners in care. This implies a transformation, a reorganization of our care and more specifically our hospitals. Covid-19 boosts the technological evolution.

What will the future bring?

The fact that patient data is stored digitally is established for some time now. The value of this data is vital. The Integrated Electronic Health Record (EHR) system which evolved from just a data collector system into a tool in the sense of a colleague or even a mentor, is key to this data and will help us to provide real time health care. The EHR system will share the essential (clouded) data with and from all care providers (general practitioner, specialist, physiotherapist, pharmacist, dentist and health insurance fund). Indeed, the collected data must be perfectly interchangeable.

Artificial Intelligence (AI) has more and more applications in the medical world and will be integrated in the EHR system. Radiology is at the forefront of this. Diagnosis and medical imaging are areas in which AI already excels today. An AI system can analyse photos and scans by using self-learning algorithms.

AI is also suitable for exposing patterns in large amounts of data (analytics). It will contribute to an objective synthesis and adequate interpretation of data (business intelligence). As a clinical decision support tool AI will propose and so predict diseases. Also integrated biological data provided by gene sequencing and editing (phenotyping) will contribute to the lead of an anticipative (predictive) health care.

The volume of digital data in the healthcare sector is exponentially growing. It will further increase due to medical and/or lifestyle sensors registering parameters such as heart rate and physical activity. All this data needs to be integrated in the EHR system.

During the first Covid wave an extra 15 billion dollars (12.8 billion euros) a week was spent on technology worldwide. Covid boosted the development of health care applications: apps for communication improvement, or for risk screening and online sorting, or for tele monitoring. Covid speeded up the development of basic ventilator systems, drug development, rapid screening tests and vaccines.

Covid helped to develop and to realize large-scale tele- and video consultations. Telemedicine is a communication facilitator; it gives a better access on nearness of the physician and the patient due to the large number of registered demands and is more cost effective. However, we have to safeguard a good patient-physician relationship. In this matter further work is required to ensure that therapy proposed during direct-to-consumer telemedicine encounters (e.g., antibiotics) is guideline concordant.

The acquisition, processing and exchange of data must take place with due attention for the privacy of the patient and the security of his data according the General Data Protection Regulation (GDPR).

From patient to partner in care

Over the past decade, consumers are able to arrange quite a lot on their smartphone: from ordering a pizza to booking a hotel room or managing banking affairs. This general consumer trend will also appear in healthcare in the coming decades.

Patient (and family) expects a personalised, real-time access to health care (via mobile apps). Using the new digital healthcare technologies, the patient himself will be involved in the decision-making process and in educational programs (= patient empowerment). A context of transparent communication and correct information about quality of care (e.g., by publishing public reports) is essential for good self-care.

The aging population leads to more chronic illness and multi-disease with long-term functional limitations. In senior care, the first digital care applications are already in use, whereby aged people can live independently at home for longer. In the future, healthcare providers will increasingly rely on digital healthcare technologies to monitor these patients at home, providing additional comfort in a well-known environment. The state-of-the-art EHR's will provide great opportunities to visualize and engage the social network of informal caregivers, close to the patient to cooperate in monitoring their mother, father, brother, sister or friend.

Covid-19 boosted this principle of self-care. The corona alert app on smartphones for example, will continuously scan Covid risk contacts. Once there is a risk contact, the smartphone user will be asked to follow the recommendations for Covid screening and/or for quarantine. People are invited for self-care. This principle of digital registration can be extrapolated to many other features (e.g., cardiorespiratory monitoring, continuous glucose measurement or blood pressure monitoring, …).

(Organization of) the Hospital of the future (figure 1)

The new technologies will help to realize the shift from inpatient (hospital admission or hospital concentrated care) to an outpatient care (ambulatory care). Since decades hospitals are experiencing a shift from classical hospitalizations to more day care activities, especially for surgery disciplines. The classic (shortened) hospital admission of the patient will become a part of a care continuum. A patient focused care or proxy-care implies an optimization of coordination and continuity of care (trans mural care) with lesser fragmentation. Together with the first line general practitioner, as key person, and efficient data exchange, the patient will be empowered in his own care. The patient focused care requires new care professions (disease managers or geriatric co-managers) and the elaboration of home care facilities.

Hospitals have to collaborate and create clinical networks. This will create opportunities, stimulate better services and save costs. Proxy care needs smaller nearby general hospitals. More specialized care will be provided in centres of reference (technological centres) whilst the highly specialized care will be devoted to university hospitals. Hospitals of the future need to be more user-friendly in order to provide personalized care (= precision medicine). They will be customized with the appropriate facilities for family and visits. They will be able to provide easy interactivity with the care providers, and this from the hospital bed.

The hospital of the future will be a place for providing ambulatory services (polyclinics, day care, focused units, …) and a bed house. It will connect homes (transitional care) and chronic care facilities. Additionally, as required, some technological platforms (radiology, emergency, ICU, surgery, …) would be part of it. Administration and logistics could be outsourced.

Last but not least, Generation Z is connected with everyone, every time and everywhere… Not only patients expect self-service and interactivity, but also for our nurses and physicians of the future, digitization will be as "bread and butter" with high expectations towards the organization they want to be part of (or identify with). This will become a crucial element in winning the "war for talent".

To manage covid-19 pandemic, the directive board of hospitals and the government need real time reliable and accurate information about bed occupancy on ICU and number of hospitalizations. IT departments try to produce daily overviews or dashboards with all this required information. The hospital of the future with a high end EHR system will be able to monitor in real time all patient flows including their necessary care processes, from admission in emergency to discharge home and, … even further after discharge. Business intelligence processing power is evolving and shifting fast from managing short term operational activities to mid-term tactical decision making and even beyond… strategic planning on long term.

Digitization and new healthcare technologies will redesign the future of our healthcare.

Big data is the new oil.

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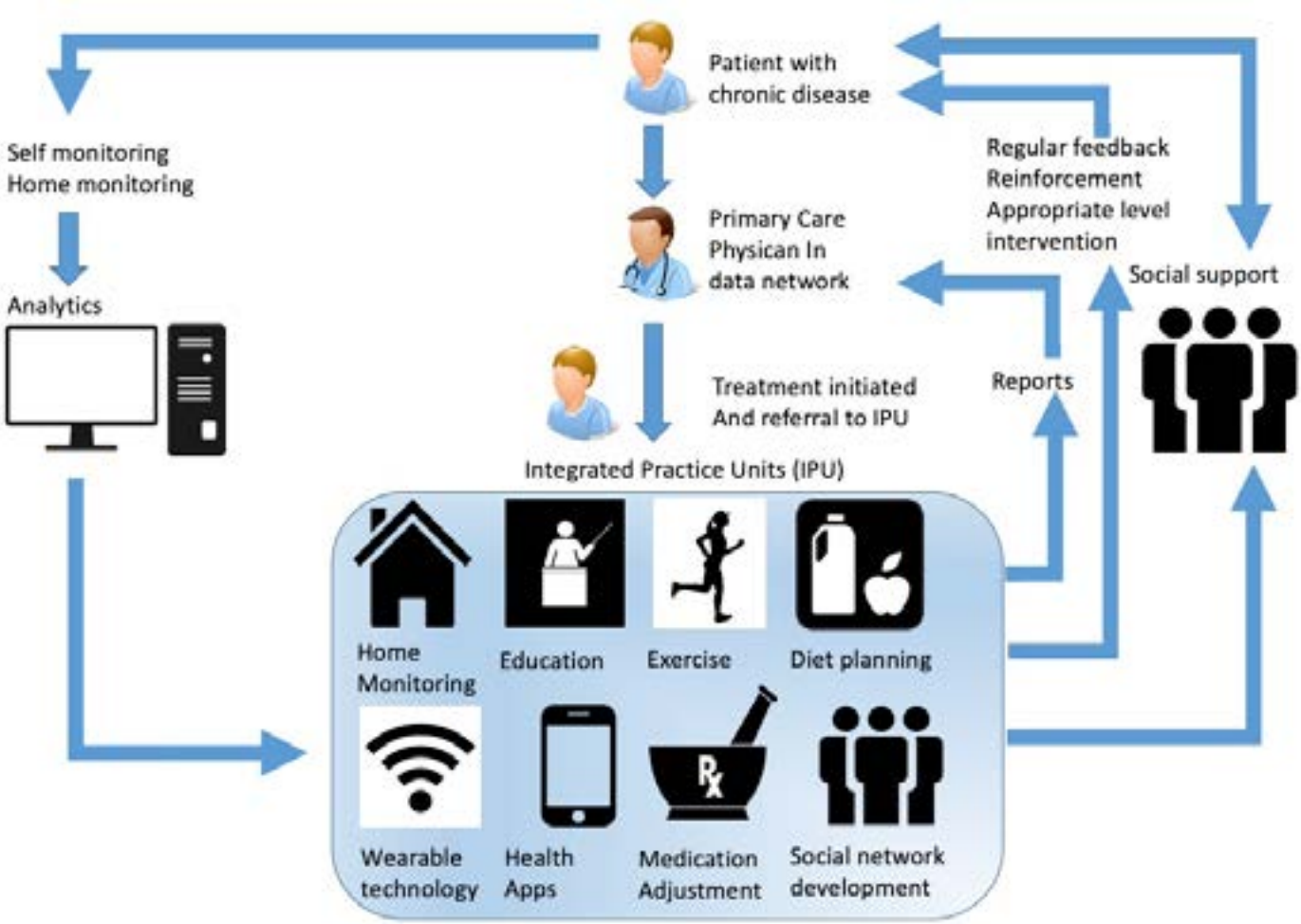
Figure 1: *Healthcare 2021*



Approach of pediatric neuroborreliosis.

Julie Vanbekbergen[a], Liesbeth De Waele[a,b], Katrien Jansen[a,b]

[a] UZ Leuven, department of Pediatrics, Faculty of Medicine
[b] UZ Leuven, department of Pediatrics, department of Development and Regeneration

julie.vanbekbergen@uzleuven.be

Keywords

Neuroborreliosis, Lyme disease, Facial nerve palsy, Borrelia Burgdorferi

Abstract

Diagnosing Lyme neuroborreliosis in the pediatric population can be challenging, especially in absence of erythema chronicum migrans or explicit neurological symptoms. Consensus on the diagnostic process in children is lacking. This retrospective study gives an overview of most frequent presenting symptoms, work up and management at the University Hospitals Leuven, Belgium.

A retrospective analysis was performed of 20 pediatric patients with Lyme neuroborreliosis treated at the University Hospitals of Leuven from 2014 until 2019. Medical records were reviewed and data, including peripheral blood and cerebrospinal fluid results, imaging reports and treatment methods were collected.

All patients presented during spring or summer time. In only a minority of patients (25%) a history of a tick bite was reported, and erythema chronicum migrans lesions were never even noted. Clinical presentation varied but facial nerve palsy was the main presenting symptom (75%). Only fifty percent of these children had a positive immunoblot in peripheral blood, while eighty percent had intrathecal synthesis of *Borrelia* antibodies. All patients were treated with intravenous antibiotics, of which seventy percent had complete clinical resolution. Fifteen percent of the patients had only minimal sequelae, other data were lacking.

Pediatric Lyme neuroborreliosis can be difficult to diagnose. Serological testing alone is not sufficient for the diagnosis. A lumbar puncture, although invasive, is necessary for confirmation of the diagnosis by detection of intrathecal synthesis of *Borrelia* antibodies. Overall, prognosis is good after adequate antibiotic treatment.

Introduction

Lyme disease is the most common tick-borne disease in Europe and the United States, and is caused by the spirochete *Borrelia burgdorferi* sensu lato. In Europe *B. burgdorferi* sensu stricto, *B. afzelii* and *B. garinii* are the most frequent species, whereas the latter two are not to be found in America. Lyme borreliosis usually occurs in summer time and can be divided in 3 stages, depending on the clinical manifestations. Early localized disease occurs within 2-3 weeks after the tick bite and classically presents with an erythema chronicum migrans (ECM) lesion, often without other symptoms. Without adequate therapy, early or late disseminated Lyme disease may emerge after several weeks or even months. By that time the spirochete has entered the blood stream or invaded other tissues. Lyme neuroborreliosis (LNB) occurs when there is invasion of het central nervous system, which is in up to 15% of the affected children. The most typical presentation of LNB in children is facial nerve palsy or meningitis, but also more nonspecific symptoms may occur. Children can, for example, present with headache, loss of appetite, behavioral change , vertigo, … The diagnosis of LNB is based on the combination of a history of tick bite, neurological signs, anti-*Borrelia* antibodies in serum and cerebrospinal fluid (CSF), often associated with CSF pleiocytosis. Therapy consists of antibiotic treatment and is successful in the majority of cases (1-4).

Diagnosis and work up of pediatric LNB can be challenging, since clinical presentation can be variable. This retrospective study aims to highlight the different neurological manifestations of LNB in children, and tries to give a clear overview of work up and management.

Methods

A retrospective analysis of all pediatric (<18 years old) patients treated for LNB at the University Hospitals of Leuven from 2014 to 2019, was performed. Diagnosis of definite LNB was made after fulfilling following criteria: presence of neurological symptoms suggestive for LNB, CSF pleiocytosis and intrathecal synthesis of *Borrelia* antibodies. If only 2 of these criteria were met, it was considered a case of possible LNB. Both definite and possible LNB patients were included in this study. Children with pre-existing neurological conditions were excluded. Medical records of all patients were reviewed. Information about the presenting symptoms and clinical signs (general and neurological, presence of prior tick bite or ECM,…) were gathered. The timing (month of the year) and duration of symptoms were also taken into account. Data, including peripheral blood and CSF results, imaging reports and treatment methods were collected. If both available, an immunoblot was performed on serum as well as CSF, after which their intensity was compared. Intrathecal synthesis was suspected in case of higher intensity of the CSF blot.

Approval of the ethics committee was granted (reference number: MP016134).

Results

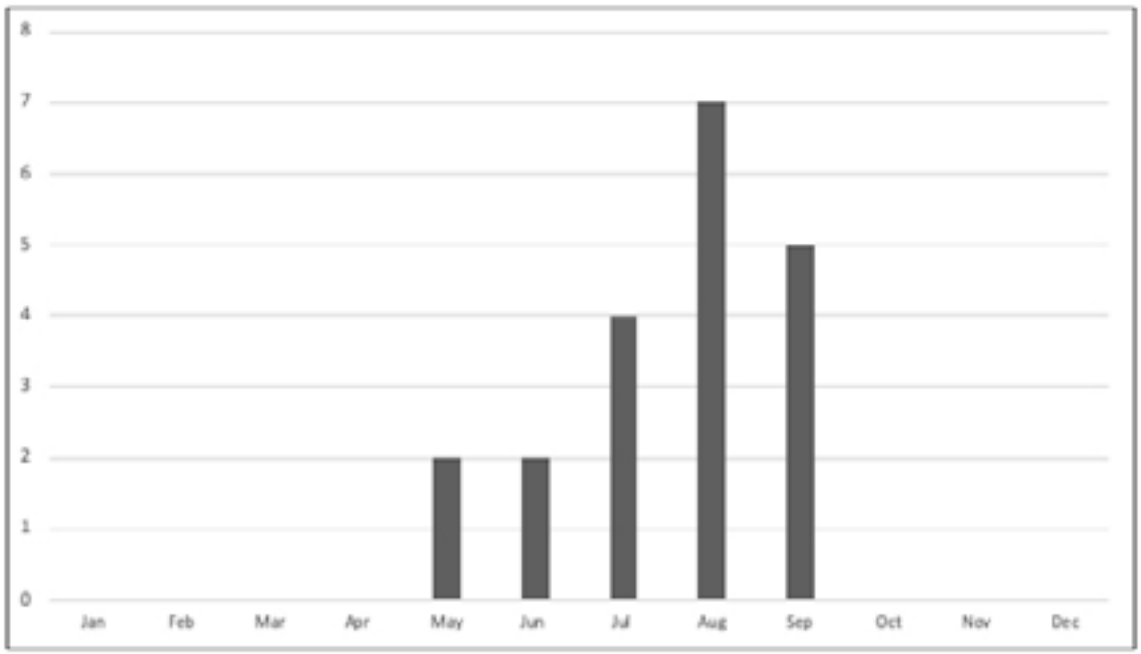
Patient characteristics

During the study period, 20 patients were treated at our hospital for LNB and included in the analysis. The majority of the children were female (75%). The median age was 8 years, with an average age of 7.9 years. The youngest child was 3 years old, the oldest 12 years. None of the patients had a history of neurological comorbidities. Only 5 patients mentioned the occurrence of a tick bite, none of these children's parents noticed an ECM prior to presentation. All patients presented during spring or summer (May to September, Figure 1).

Clinical manifestations

The main presenting symptom was cranial nerve palsy (Table 1). Seventy-five percent of these children developed a facial nerve palsy, only one an oculomotor nerve palsy with ptosis and anisocoria. One girl presented with diplopia, without clear ophthalmological or cranial nerve abnormalities. Only one boy developed bilateral facial nerve palsy, after first presenting with typical symptoms of meningitis. Of all patients only one child presented with fever. Pain was another common symptom, with 9 patients (45%) complaining of acute neck/back pain or headache. One girl suffered from generalized pain and developed a Guillain-Barre syndrome. Three patients (15%) presented with typical signs of meningitis. The majority of children was diagnosed with LNB within the first week of symptoms. Three patients had symptoms for more than 1 month.

Figure 1: *CTiming of presentation. Y axis = number of patients, x-axis = months*



Laboratory results

A blood test and lumbar puncture was performed in all patients (table 2). None of the children had an elevated C-reactive protein (CRP) in peripheral blood, two patients had a slightly elevated white blood cell (WBC) count. Mean WBC count in CSF was 258/µL (normal value WBC <5/µL), with a minimum of 0.4/µL and maximum of 2391/µL (table 2). In all patients WBC differentiation showed a preponderance of lymphocytes. In 3 cases WBC count was below 5/µL. Mean CSF glucose and protein levels were respectively 53 mg/dL and 591 mg/L.

Borrelia enzyme linked immunosorbent assay (ELISA) and immunoblot were performed on serum samples. ELISA tested positive in 16 of the cases, negative in 4. Of those 16 patients 5 eventually had a negative immunoblot. In total 50 percent of the children tested positive after immunoblotting. Eighty percent of the patients had obvious intrathecal synthesis of *Borrelia* antibodies. In 2 cases the immunoblot on CSF was not performed. In 2 other cases results were indecisive: both immunoblots detected only small amounts of *Borrelia* antibodies in CSF, insufficient for evident intrathecal synthesis. CSF samples tested positive in 3 patients with negative ELISA and 7 patients with negative immunoblot on serum samples. In 7 patients *Borrelia* PCR (polymerase chain reaction) was tested on CSF. All but one came back negative, despite positive immunoblot. Of all children treated at our hospital, 14 patients were diagnosed with definite LNB, in 6 patients diagnosis was suspected but only 2 diagnostic criteria were met (possible LNB).

Table 1: *Overview of presenting symptoms of patients with LNB*

Presenting symptom	Number of patients
Cranial nerve palsy	16 (80%)
Facial nerve palsy	15 (75%)
- Unilateral	14 (70%)
- Bilateral	1 (5%)
Oculomotor nerve palsy	1 (5%)
Diplopia	1 (5%)
Meningitis	3 (15%)
Guillain Barré syndrome	1 (5%)
Fever	1 (5%)
Vomiting	1 (5%)
Weight Loss	1 (5%)
Limb pain	3 (15%)
Headache	7 (35%)
Neck/back pain	7 (35%)

Imaging

Thirteen patients (65%) underwent central imaging. A brain computed tomography (CT) scan was performed in 9 cases, magnetic resonance imaging (MRI) of the brain was also executed 9 times. Five patients underwent both MRI and CT of the brain. The majority of the patients had imaging while being hospitalized (n=7), five already had imaging before admission. In one case brain MRI was performed 2 months after therapy, because of persisting facial nerve palsy. MRI confirmed facial neuritis. Central imaging of all other children did not show any abnormalities. Two patients underwent electromyography (EMG) for a persistent facial nerve palsy, both showed signs of regeneration.

Treatment

All patients were treated with intravenous (IV) ceftriaxone, most of them (n=16) for 3 weeks. In three cases IV treatment had to be ceased because of sudden skin rash, two of them (10 and 12 years of age) switched to doxycyclin, a younger child (5 years old) to amoxicillin. Two patients were treated for only 2 weeks. Six patients received alternative treatment before changing to ceftriaxone, because of uncertain diagnosis at that time (table 3).

Outcome

Complete clinical resolution was noted in the majority of the patients (n=13). In two patients a discrete facial asymmetry persisted, while one patient continued having mild anisocoria. There was full motoric remission of the child with Guillain-Barré syndrome. One girl had to be readmitted because of post viral asthenia, but eventually fully recovered. Three children were lost to follow up.

Table 2: *Serology results of peripheral blood and CSF samples*

Patient	Peripheral blood			Cerebrospinal fluid			Conclusion LNB
No	ELISA	IgM	IgG	IgM	IgG	WBC	
1	+	+	+	+	+	192	Definite
2	+	+	UC	+	+	186,8	Definite
3	+	-	UC	+	+	145,6	Definite
4	+	+	UC	NA	NA	22,8	Possible
5	+	+	UC	+	+	41	Definite
6	+	-	UC	+	+	127,7	Definite
7	-	UC	-	UC	UC	1,4	Possible
8	+	-	UC	+	+	48,4	Definite
9	+	+	UC	+	UC	24	Definite
10	-	-	-	+	+	135	Definite
11	+	+	-	+	UC	137	Definite
12	+	+	UC	+	+	0,4	Possible
13	+	+	-	NA	NA	625	Possible
14	+	-	+	+	+	110	Definite
15	-	-	-	+	+	900	Definite
16	+	-	UC	+	+	2391	Definite
17	+	UC	UC	UC	UC	26,8	Possible
18	-	UC	-	+	-	10	Definite
19	+	-	+	+	+	40	Definite
20	+	-	-	+	+	3	Possible

Abbreviations: *UC unclear ; NA not available; WBC white blood cell (normal amount in CSF <5WBC/µL)*

Table 3: *Serology results of peripheral blood and CSF samples*

Treatment	No of patients
IV ceftriaxone	16
Before ceftriaxone treatment	
IV cefotaxime	1
IV cefotaxime + Acyclovir	2
PO cefuroxime	1
IV pulse steroids (3 days)	2
IV steroids (7 days)	1
PO methylprednisolon	1
Switch after skin reaction	
PO doxycyclin	2
PO amoxicillin	2

Abbreviations: *PO perorally ; IV intravenous*

Discussion

Cranial nerve palsy, more specifically facial nerve palsy, is the most common clinical manifestation of LNB in the pediatric population (1-4). Of our group of patients 75% presented with facial nerve palsy. In the last decades, the occurrence of Lyme disease in children presenting with facial nerve palsy has increased. Still, numbers can strongly differ between endemic areas, with mainly a European preponderance. A recent Northern American study confirmed LNB in up to 34% of the children with facial nerve palsy, which made it the most frequently diagnosed etiology. In the majority of patients (66%) no clear cause was found (Bell's palsy or idiopathic facial nerve) (5). In a different Norwegian study LNB was mentioned to be the cause of facial nerve palsy in up to 75% of the children (6).

Besides cranial nerve palsy 15% of our patients showed clinical signs of meningitis. However, less specific symptoms, as for example headache, fatigue or fever, did also occur (Table 1). Therefore, in combination with the absence of erythema chronicum migrans or noticed tick bites, correct diagnosis of LNB can be difficult. Studies showed a delay of LNB diagnosis in children with more nonspecific symptoms or absence of cranial nerve palsy. Compared to adults, painful meningoradiculitis, radiculoneuritis and encephalopathy are less common presenting symptoms in children (3-4).

Serological testing of Lyme disease is most often performed by the 'two step procedure' (7,8). This method combines a sensitive enzyme immunoassay with an additional immunoblot. While ELISA is a very sensitive and cost-effective method for detecting *Borrelia* antibodies, immunoblotting is a more qualitative, time consuming and high-cost procedure with higher specificity. Therefore, immunoblotting is generally preserved for positive ELISA samples.

By itself, the two-tier procedure is insufficient for diagnosis of LNB. For example, in patients with acute neuroborreliosis, antibody testing can be negative in serum, while already being positive in CSF (7-9). Thus, because of this seronegative window negative serology cannot exclude diagnosis of LNB. Of all our study patients only 50% (n=10) tested positive after the two-tier procedure, while 80% (n=16) showed intrathecal *Borrelia* antibodies. Serological follow-up can be useful to detect seroconversion in case of early negative serological testing but in case of long lasting symptoms (>6 weeks) a negative two step procedure helps to rule out Lyme infection (4,11).

Besides difficulties with diagnosing early manifestations of Lyme disease, also the possibility of false-positivity has to be taken into account (5,7). In 2016 an American study found that only 71% of the children with a positive IgM but negative IgG immunoblot had Lyme disease (10). A positive IgM immunoblot is thus not always a sign of active infection and can lead to important over-diagnosis. This IgM false-positivity is mostly caused by cross-reactivity or previous infection. IgM immunoblot is known to remain positive for a long time after infection. We therefore advise to only perform testing when there is real clinical suspicion of Lyme disease. This increase in pre-test probability will lead to a better positive predictive value of the two-tier procedure.

In literature international consensus about diagnostic evaluation of LNB in children is still lacking. In 2012 the European Federation of Neurological Societies (EFNS) published renewed guidelines concerning diagnosis and management of European LNB. Mygland and colleagues applied following diagnostic criteria: presence of neurological symptoms suggestive for LNB without other clear causes, CSF pleiocytosis and presence of intrathecal synthesis of *Borrelia* antibodies. They spoke of 'definite' LNB when all 3 criteria were met, and of 'possible' LNB when only 2 criteria were fulfilled. This implies performing lumbar punctures with every suspicion of LNB. The EFNS also mentioned that when intrathecal antibody production is lacking, *Borrelia* antibodies have to be found in serum after a duration of 6 weeks to confirm diagnosis (12,13). The Infectious Disease Society of America (IDSA) on the other hand suggested that a lumbar puncture solely is indicated when clinical signs of meningitis are present (ie nuchal rigidity, headache). They stated that, for children with isolated facial nerve palsy, lumbar puncture was not needed (14). Current Belgian guidelines (BAPCOC) are similar to those of the IDSA and EFNS. In their opinion a lumbar puncture is not always needed in case of a child presenting with facial nerve palsy and positive *Borrelia* serology. In all other cases (ie. adults or children without facial nerve palsy), they advise to do CSF testing (15).

Since clinical presentation of LNB in children is not always clear cut and diagnostic testing takes time, other neurological conditions have to be taken into account. This is why all our patients underwent a lumbar puncture and in 65 percent of the cases central imaging was performed (brain MRI and/or CT). The majority of our patients had a lymphocyte-predominant pleiocytosis in CSF. In 80% there was evident intrathecal synthesis of *Borrelia* antibodies, confirming the diagnosis of LNB. Viral PCRs (including for example *Herpes simplex virus, Cytomegalovirus, Enterovirus*,…) and cultures were performed on CSF in almost all patients, in order to rule out other possible viral and bacterial causes. Central imaging came back negative in all of our patients.

During the last decade, studies have suggested CXCL13 (CXC motif ligand 13) to be an early diagnostic marker for LNB (11, 16-19). This chemokine is produced in non-lymphoid tissues during inflammation and attracts B cells to the central nervous system, resulting in intrathecal synthesis of *Borrelia* antibodies. Henningsson et al demonstrated a statistically significant difference in CXCL13

concentrations between LNB and non-LNB patients, along with a rapid decrease after adequate therapy. A meta-analysis in 2018 evaluated the accuracy of CXCL13 as a diagnostic tool for LNB (20). They found an acceptable pooled sensitivity and specificity of 89% and 96% respectively, using a cut-off value of 162 pg/mL. Rupprecht and colleagues also stated that intrathecal *Borrelia* antibody index tested negative in 10-30% of the patients with symptom duration less than 6 weeks. CSF CXCL13 measurement could thus be a supplemental early marker in diagnosing acute LNB. However, consensus about the right cut-off value has still to be reached. CXCL13 was not tested in our study patients but should be considered as a possible valuable addition to our diagnostic approach. CXCL13 testing can be done in our hospital's laboratory, since it functions as national reference center for *Borrelia spp.* No additional costs are charged.

Borrelia PCR is another diagnostic method for LNB. Specificity is acceptable but sensitivity is low (10-30%). Therefore PCR is less useful in diagnosing LNB (8,11,16). In our patients PCR of CSF was performed 7 times, of which only one tested positive. A positive PCR of CSF appears to be more frequent in patients with a shorter duration of symptoms (<2 weeks) (8). Isolating *Borrelia* by culture is no standard procedure either, since it is expensive and results are only available after more than 2 weeks. The sensitivity of a culture is only 3 – 17% in CSF samples. Therefore a negative culture cannot exclude LNB (21).

Consensus is not only lacking in diagnosing LNB, also regarding to LNB treatment opinions differ. The EFNS advised parenteral antibiotic treatment (IV ceftriaxone) of LNB with CNS manifestations (myelitis, encephalitis, vasculitis) (12). In absence of CNS manifestations (meningitis, cranial nerve palsy, radiculopathy, peripheral neuropathy) European studies showed that oral doxycycline and intravenous ceftriaxone, penicillin or cefotaxime were equally effective and safe (22). Although it has excellent central nervous system penetration, doxycycline is not used in children under the age of 8 years because of the risk of irreversible tooth discoloration. These children were generally treated with amoxicillin or cefuroxime axetil. The American guidelines, for example of IDSA and the American Academy of Neurology (AAN), also approved oral treatment of cranial nerve palsy, but didn't agree on other subjects (14,21,23). The IDSA guidelines for example recommended IV treatment in case of meningitis, radiculopathy or late LNB. The AAN on the other hand accepted oral therapy in patients with meningitis or neurological syndromes with CSF pleiocytosis, but suggested IV treatment in those patients with more severe symptoms. All aforementioned studies advised a total duration of treatment of 14 days (10-28 days).

The majority of our patients was treated with parenteral antibiotics (ceftriaxone monotherapy) once correctly diagnosed with LNB. Thirty percent of the children received other therapy prior to diagnosis, because LNB was not yet confirmed. Only four patients switched to oral treatment, all of them because of an allergic skin reaction after IV administration of ceftriaxone. Based on current guidelines, oral treatment could also have been considered in our patients.

Prognosis after treatment for LNB is generally good. The majority of our children with LNB had complete resolution of their symptoms. A recent review mentioned complete recovery in 70-85% of the LNB patients within 6-12 months (21). Even over 90% of their children with cranial nerve palsy fully recovered. Previous studies showed the importance of early treatment. Treatment delay seemed to increase the chance of residual symptoms (1). Besides fast and adequate treatment, preventive measurements (such as tick repellents, protective clothing) are of course equally important, since the majority of children who developed LNB were not aware of a previous tick bite (24-27).

Conclusion

Facial nerve palsy is the most common presenting symptom of LNB in the pediatric population, though more nonspecific presentation is possible. LNB needs to be considered if a child presents with neurological symptoms, especially in spring or summertime. The majority of patients will have no clear notion of a previous tick bite or erythema migrans lesion. The diagnostic process of LNB in children is often challenging, and consensus concerning diagnostic work up is lacking. Although invasive for children, we suggest performing lumbar punctures in order to look for pleiocytosis, suggestive for LNB, and to confirm intrathecal synthesis of *Borrelia* antibodies. If necessary other investigations are indicated to rule out other possible causes. Treatment consists of adequate antibiotic therapy, after which there is a good resolution of symptoms. In absence of CNS manifestations or without an ill appearing child, antibiotics could be administered orally, although in reality, based on the presence of pleiocytosis, IV treatment is often more frequently preferred.

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Screening for autism spectrum disorder in young children with trisomy 21

Lies Blomme [a], Miek Claes [b], Inge Schramme [c], Marek Wojciechowski [b], Tine Boiy [b], Jo Lebeer [d]

[a] AZ Nikolaas, department of Neurology
[b] University of Antwerp, Antwerp University Hospital, department of Paediatrics
[c] University of Antwerp, Antwerp University Hospital, Centre for Developmental Disorders
[d] University of Antwerp, Disability Studies, Primary and Interdisciplinary Health Care

marek.wojciechowski@uza.be

Keywords

Trisomy 21, Down syndrome, child, autism spectrum disorder, screening

Abstract

Children with trisomy 21 are at increased risk for autism spectrum disorder. A prevalence between 9 and 42% is reported in the literature. Early diagnosis of autism spectrum disorder has multiple potential benefits for the child and its environment.

Several screening tools have been developed for children with intellectual disabilities. The PDD-MRS scale (Pervasive Developmental Disorder in Mentally Retarded Persons Scale) was originally designed and validated in Dutch. We aimed to evaluate the accuracy of this scale as screening test in our trisomy 21 clinic.

Method:

22 children (11 girls, 11 boys) with trisomy 21, aged 24-84 months (mean 56,2 months) were included and screened with the PDD-MRS. After screening all children completed a comprehensive multidisciplinary diagnostic evaluation at the Centre for Developmental Disorders. The results of the PDD-MRS screening test and the full multidisciplinary evaluation were compared.

Results:

Autism spectrum disorder was diagnosed with multidisciplinary diagnostic evaluation in 59% of our population. The PDD-MRS results in two outcome scores: a clean points score based on the parents' answers to the questionnaire and a clinical score based on both the answers and the observation of the child's behaviour by the examiner. The sensitivity and specificity of PDD-MRS were as follows: clean points score: sensitivity 0.69, specificity 0.56; clinical score: sensitivity 0.92, specificity 0.67. The feasibility of the PDD-MRS was good.

Conclusion:

In our population, the accuracy of the PDD-MRS scale as screening test is moderate. The sensitivity of the clinical score, combining parents' answers and functional observation, is clearly better than the clean score, but that might be determined by the examiner's experience.

Introduction

Trisomy 21 (Down syndrome) is the most common genetic cause of intellectual disability worldwide. As life expectancy of people with trisomy 21 has increased to an average of 60 years, they represent an important population (1). Trisomy 21 is characterized by intellectual disability and the occurrence of several additional problems such as congenital and acquired health disorders, specific difficulties with language and autism spectrum disorder (2-4). The reported prevalence of autism spectrum disorder in trisomy 21 varies as widely as 9 to 42%, the higher prevalence being reported in recent studies (4-9).

Diagnosis of autism spectrum disorder is always challenging but even more so in children with trisomy 21 because of a certain overlap of symptoms. Stubborn behaviour and difficulties in adjusting to change are often regarded as a typical behavioural feature of trisomy 21, but they can also be a sign of autism spectrum disorder. Language development is delayed in trisomy 21 and can be delayed in autism spectrum disorder but is even more hampered in children with both conditions. This overlap in symptoms is one of the reasons for under- and over-diagnosis of autism spectrum disorder in children with trisomy 21 (10-14).

Timely diagnosis of autism spectrum disorder is important as it allows for early intervention, prevention of regression and secondary behavioural problems, and additional support for children and their families. For parents it can be a relief to understand why their child is different from other children with trisomy 21 (15-18). In order to enable early diagnosis and intervention, the Council on Children with Disabilities of the American Academy of Pediatrics issued in 2020 an update of the 2007 recommendation to screen all children for symptoms of autism spectrum disorder through a combination of developmental surveillance and standardised autism-specific screening tests at 18 and 24 months of age (19, 20).

Several screening tools for autism spectrum disorder have been used in children with intellectual disability. The Scale of Pervasive Developmental Disorder in Mentally Retarded Persons (PDD-MRS) was developed in the Netherlands by Kraijer et al. for individuals with intellectual disability from 2 to 70 years. Kraijer reports a has a high sensitivity and specificity, both 92.4%, based on testing of 254 persons with trisomy 21, both children and adults. The scale has been validated from the age of 24 months (21).

Another screening test is the Modified Checklist for Autism in Toddlers (M-CHAT) validated for children 16-30 months old. The test consists of 23 yes/no questions with 6 critical questions. DiGiuseppi et al. reported a sensitivity of 81.8% (95% CI: 55-96.4%) and a specificity of 46.8% (95%CI: 33.2-60.7%) for the diagnosis of autism spectrum disorder in young children with trisomy 21(6). The M-CHAT was improved in 2014 by Robins et al. (22). The new version is named M-CHAT-R/F (M-CHAT-Revised with Follow-up), a 2 stage screening test with an improved accuracy in comparison to the M-CHAT. The first stage consists of 20 yes/no questions after which a child is classified as low, medium or high risk. For low risk children no other evaluation is planned, high risk children are immediately referred for

diagnostic evaluation; in medium risk children the follow-up questionnaire (20 questions) is administered to determine whether referral is necessary. We did not find any publication reporting the use of the M-CHAT-R/F in children with trisomy 21.

The Social Communication Questionnaire is another screening test with 40 yes/no questions. This test requires more developed language skills and can therefore be used for children with DS from the age of 4 years old. Sensitivity is 0.85 - 0.88 and specificity is 0.72 - 0.75 in both children and adults with trisomy 21 (23).

Because the PDD-MRS was designed and validated in Dutch (which is the language in which we communicate with our patients in our hospital), we wanted to evaluate whether we could use this test to screen children with trisomy 21 for autism spectrum disorder in our hospital's trisomy 21 clinic.

Methods

Children with trisomy 21 aged 24 to 84 months from the Antwerp University Hospital trisomy 21 clinic were invited by letter to participate in the study. The only exclusion criterion was previous diagnostic testing for autism spectrum disorder. The parents had the possibility, without obligation, to mention why they accepted or refused participation. The study was approved by the Ethical Committee of the University Hospital of Antwerp (Belgian registration number B300201215833).

After informed consent given by one of the parents, the PDD-MRS was administered by a senior speech therapist, trained in the administration of the PDD-MRS, who is experienced in intellectual disability and autism spectrum disorder, and is also a staff member of the trisomy 21 clinic. The PDD-MRS consists of 19 questions in 12 categories all answered by a caregiver of the child. Categories are 1) quality of contact with an adult, 2) contact with age-related peers, 3) no active language, 4) language and speech with deviant content, 5) language and speech with deviant production, 6) obsessive interests, 7) stereotypical manipulations of objects, 8) stereotypical handling of own body, 9) patterns and rituals, 10) self-injury, 11) unpredictable behaviour and 12) unusual fears. It takes approximately 1 hour to perform the test.

The PDD-MRS results in 2 scores, a clean points score based on the answers to the questionnaire and a clinical score based on both the answers to the questions and the observation of the child's behaviour by the examiner. Both scores result in 3 possible outcomes: 'pervasive development disorder' (PDD), 'possible PDD' and 'no PDD'. The results of the screening test were not communicated yet to the parents, nor to the staff of the Centre for Developmental Disorders.

After conducting the PDD-MRS in the trisomy 21 clinic, the children were referred to our Centre for Developmental Disorders for a full multidisciplinary functional evaluation, including the administration of the Autism Diagnostic Observation Schedule test (15), evaluation of intellectual development by a child psychologist, of receptive and expressive language skills, speech development and communication by a speech therapist, of gross and fine motor development and coordination by a physiotherapist and clinical evaluation by a child neurologist. The final diagnosis was made at the Centre for Developmental Disorders and communicated to the parents.

Birth date, gender, age at time of PDD-MRS, the PDD-MRS scores, diagnosis at the Centre for Developmental Disorders, severity of intellectual disability, behavioural problems as mentioned by parents, suspicion of autism spectrum disorder by parents and the presence of a first degree relative with autism spectrum disorder were entered into a SPSS 21 database. Furthermore, medical records were checked for any additional data, in particular a history or presence of epilepsy, as a higher prevalence of seizures has been described in children with trisomy 21 and autism spectrum disorder (13).

Variables were analysed by frequency and, if applicable, minimum and maximum. Prevalence of variables was calculated with 95% confidence interval (CI). Prevalence of autism spectrum disorder was calculated on the basis of the results of the full diagnosis at the Centre for Developmental Disorders. Sensitivity and specificity of the PDD-MRS questionnaire score, the PDD-MRS clinical score and the combination of both were calculated in comparison to the final diagnosis at the Centre for Developmental Disorders. A logistic regression analysis was done to evaluate the relationship between the additional variables and the result of the PDD-MRS.

Results

Parents of 99 children, aged 24 – 84 months, were invited to participate. We received a response from 36. 11 chose not to participate. Reasons for non-participation were given by 8: distance to specialty clinic [1], too many doctor visits [2], feeling sure that their child has no autism spectrum disorder [2], fear of diagnosis [1], already tested on autism spectrum disorder [1]. Two parents indicated that suspicion of autism spectrum disorder was the motivation to participate in the study. 25 gave informed consent; 3 children were excluded from analysis because they did not complete both the PDD-MRS screening test and the diagnostic test at the Centre for Developmental Disorders.

22 children were included in our analysis, 11 girls and 11 boys. The age range was 28 tot 79 months (mean 56,2 months, median 53 months, 9 children ≤ 48 months, 13 children > 48 months).

The diagnosis of autism spectrum disorder was made in 13/22 (59%) children after full diagnostic evaluation. As described above, the PDD-MRS results in 2 outcome scores: a clean points score and a clinical score given by the examiner. The outcomes of both scores can be: 'negative', 'doubtful' and 'positive' for autism spectrum disorder. The result of the PDD-MRS, the comparison with the result of the full diagnostic test, the sensitivity, specificity, positive predictive value, negative predictive value and likelihood ratios of the PDD-MRS score (considering doubtful tests as positive, as this would be an indication for referral) are shown in table 1 for the clean points score and in table 2 for the clinical score.

Epilepsy was present in 4/22 (18%). Two had a first degree relative with autism spectrum disorder. Behavioural problems were reported by parents in 8 children (36%). Categories of intellectual disability were as follows: 4 children mild (IQ 55-80), 13 moderate (IQ 30-55), 4 severe (IQ 15-30), 1 profound (IQ <15). With logistic regression analysis none of these associated features, i.e. epilepsy, behavioural problems and degree of disability, were found to be a significant predictor of a correct result of the PDD-MRS.

In the 2 children, whose parents had indicated that they suspected autism spectrum disorder, this diagnosis was not confirmed.

Table1: results of the clean points score of the PDD-MRS screening test as compared to the full diagnostic standard for autism spectrum disorder

Negative		Diagnostic standard for autism spectrum disorder	
		Positive	
PDD-MRS screening test	Negative	5	4
	Doubtful	1	2
	Positive	3	7
Total	22	9	13
Sensitivity	0.69	95% CI 0.39-0.91	
Specificity	0.56	95% CI 0.21-0.81	
PPV	0.69		
NPV	0.56		
LR +	1.56		
LR -	0.55		

PPV= positive predictive value; NPV = negative predictive value; LR+ = likelihood ratio for a positive result; LR- = likelihood ratio for a negative result

Table2: results of the clinical score of the PDD-MRS screening test as compared to the full diagnostic standard for autism spectrum disorder

Negative		Diagnostic standard for autism spectrum disorder	
		Positive	
PDD-MRS screening test	Negative	6	1
	Doubtful	3	1
	Positive	0	11
Total	22	9	13
Sensitivity	0.92	95% CI 0.64-1.0	
Specificity	0.67	95% CI 0.30-0.93	
PPV	0.80		
NPV	0.86		
LR +	2.77		
LR -	0.12		

PPV= positive predictive value; NPV = negative predictive value; LR+ = likelihood ratio for a positive result; LR- = likelihood ratio for a negative result

Discussion

A significant number of children with trisomy 21 have autism spectrum disorder. The prevalence as described in the literature varies from 9 to 42% (4, 6, 7, 24, 25). We found a prevalence of 59% which is still a lot higher than the 42% described by Oxelgren et al. A probable explanation is selection bias. As our study included a full diagnostic evaluation at the Centre for Developmental Disorders, parents who had doubt or suspicion about the diagnosis of autism spectrum disorder could have been more motivated to participate. Nonetheless, we believe that there is a significant proportion of people with trisomy 21 who have autism spectrum disorder and that early recognition should be included in routine health supervision.

As described in the introduction, several screening tests for detection of autism spectrum disorder in young children with disabilities have been developed (21, 23, 26). Moreover, children at risk for autism spectrum disorder can also be identified by an approach within a functional framework, particularly evaluating cognitive function, language development, communication, and reciprocal social interaction (27, 28). Additionally, a functional framework provides the opportunity to take action to improve specific areas of functioning. We believe that there is no conflict between screening tests and functional approach. Routine implementation of a screening test in the health supervision schedule could be a helpful tool to address certain problems in development and behaviour that would not be discussed otherwise and to evaluate if additional interventions and support would be desirable, even if there is no suspicion of autism spectrum disorder.

Whatever the approach, one should always keep in mind that behaviour in children with trisomy 21 could also be influenced by different organic problems.

What ultimately counts is that children with suspected autism spectrum disorder, whether based on a functional approach, a screening test or both, are referred for a comprehensive diagnostic evaluation. In addition, it is our experience that a formal diagnosis of autism spectrum disorder is necessary to initiate specialised counselling, support and therapy. Although the diagnosis is a relief for some parents, others may be dumbfounded by the burden of a double diagnosis. The diagnosis should be communicated to parents in a sensitive manner, with emphasis on the fact that while it does not change their child, it can change the way their child is approached for the better.

In our study we have evaluated the PDD-MRS as screening test for autism spectrum disorder in children with trisomy 21. We have not experienced any problem with regard to the feasibility of the test. Regarding the accuracy, the sensitivity (0,69) and specificity (0,56) of the clean points PDD-MRS score are significantly lower in our population than in the original study of Kraijer et al. (sensitivity and specificity both 0,92) (21). The sensitivity and specificity are also lower compared to the M-CHAT used by Wong et al. (sensitivity 0,93, specificity 0,77) (26). However, the clinical score, obtained via observational interpretation by the examiner, results in a remarkable increase in sensitivity (0,92) and small increase in specificity (0,67). This discrepancy is due to the fact that in the clean points score the researcher has to quote the answers of the parents as indicated by them, even if there is a clear difference with the observed behaviour. That also indicates that the critical reflection of a well-trained clinical observer contributes significantly to the accuracy of the test, meaning that the test should be done by an experienced practitioner. Even then, a false positive result must be taken into account in about 1/3 and a false negative result in 1/10.

Apart from the value as screening test in itself, administering the test also offers the opportunity to raise issues that are more difficult to address in a regular consultation.

Limitations of our study are the low number of responders and participants.

Conclusion

We have evaluated the accuracy of the PDD-MRS scale as screening test for autism spectrum disorder in children with trisomy 21, aged 24 - 84 months. The sensitivity and specificity of the clean points score are low (respectively 0,69 and 0,56) but increase remarkably in the clinical score, obtained by observational interpretation of the examiner (sensitivity 0,92, specificity 0,67). Thus, the accuracy may also depend on the experience of the examiner. The test is well feasible for young children in the setting of a trisomy 21 clinic to select children for comprehensive, multidisciplinary diagnostic testing, but cannot replace it.

The results of our study are consistent with reports in literature about the increased prevalence of autism spectrum disorder in children with trisomy 21. Systematic evaluation within a functional framework and/or with a screening test should be implemented in the routine health supervision of young children with trisomy 21, aged 24-84 months, to identify these children who should be referred for comprehensive diagnostic evaluation.

Different screening tools for autism spectrum disorder in young children have been described but little research has been done in children with trisomy 21. More research would be welcome.

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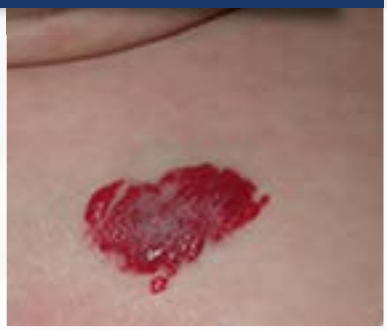

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Diagnosis and management of osteoarticular infections in children.

An overview of the literature and retrospective cohort study in a single tertiary care centre

Tine Alliet [a], Liesbeth Cappaert [a], Jasmine Rooryck [a], Marijke Proesmans [b], François Vermeulen [b], Sandra Prinsen [c], Lieven Vermuyten [c], Mieke Boon [b]

[a] Department of Paediatrics, University Hospitals Leuven, Leuven, Belgium
[b] Department of Paediatric Infectious and Respiratory Diseases, University Hospitals Leuven, Leuven, Belgium
[c] Department of Orthopaedics, University Hospitals Leuven, Leuven, Belgium

Tine.alliet@uzleuven.be

Keywords

Osteoarticular infections, osteomyelitis, septic arthritis, spondylodiscitis

Abstract

Objective: To perform a systematic review on the diagnosis and management of osteoarticular infections and to describe the cohort of patients with osteoarticular infections in a Belgian tertiary care centre over a 5-year period.

Methods: A systematic literature search was conducted in MEDLINE. Secondly, we did a retrospective cohort study in a single tertiary care centre.

Results: We included 69 patients with a median age of 1,25 years (interquartile range: 0,9-6,0). They were diagnosed with osteomyelitis in 32/69 (46,4%), septic arthritis in 25/69 (36,2%), spondylodiscitis in 8/69 (11,6%) and a combined osteomyelitis and septic arthritis in 4/69 (5,8%). Delay in presentation was longer in the spondylodiscitis group (p=0,003). C-reactive protein and white blood cell count were significantly higher in the septic arthritis group (p=0,014 and p<0,001).

Blood cultures identified the causative organism in 18/66 (27,3%). Samples from infectious site were positive in 18/34 (52,9%) of whom 10 had negative blood cultures. Polymerase chain reaction identified the organism in 3/6 (50%). In total, 30/69 (43,5%) had a microbiological diagnosis. Total antibiotic course varied from 20 to 64 days. Treatment duration was significantly longer for the Staphylococcus aureus group.

Conclusion: An increase in cultures from the infectious site and the use of polymerase chain reaction techniques could greatly improve microbiological diagnosis and enable targeted antimicrobial therapy. Magnetic resonance imaging remains the most sensitive and specific investigation and should be more easily available to avoid a delay in diagnosis. These findings should be taken into consideration when setting up local and national guidelines/protocols, currently still lacking for the management of paediatric osteoarticular infections.

Introduction

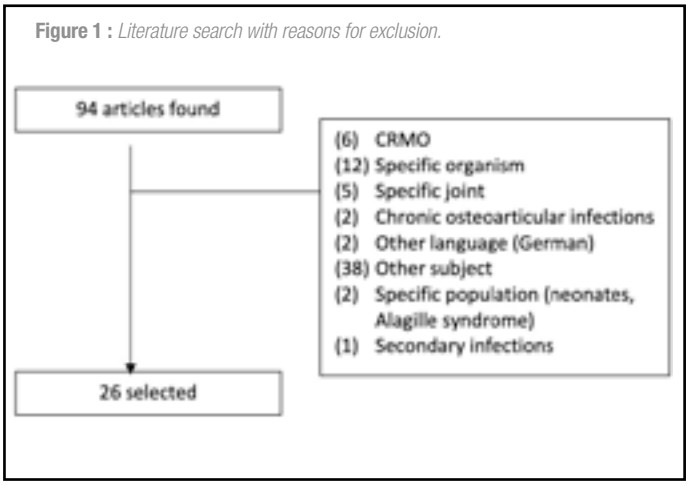
Osteoarticular infections (OAI) are not uncommon in children. Three main types are described: osteomyelitis (OM), septic arthritis (SA) and spondylodiscitis (SD). Delayed diagnosis and treatment can result in severe complications and morbidities (1,2). Until today, there is ongoing discussion regarding the optimal management of these infections and clear algorithms to guide diagnosis and treatment are lacking. The aim of this study was to perform a systematic review on the diagnosis and management of OAI and to describe the cohort of patients with OAI in a Belgian tertiary care centre over a 5-year period.

Materials and Methods

A systematic literature search was conducted in MEDLINE. The following terms were used: "osteomyelitis", "osteoarticular infections", "spondylodiscitis" and "septic arthritis" with one or more of the terms "children" and "paediatric". Results were limited to the past five years and the paediatric population (<18 years). All clinical trials, randomised controlled trials, meta-analyses and (systematic) reviews were selected. Articles in other languages than English, Dutch, French or Spanish were excluded as re publications that focused on one pathogen or neonates only. We found 26 relevant articles which were used to compare our findings with and to provide an update on current knowledge about OAI (Figure 1). Belgian (BVIKM) and European (ESPID) guidelines were also included.

Secondly, all paediatric files within a 5-year period (13.11.2012 - 13.11.2017) were searched through the hospital computer system KWS (Clinical Working Station) for one or more of the following hits: "osteoarticular infections", "septic arthritis", "osteomyelitis" and "spondylodiscitis". Ethics committee approval was obtained. Inclusion criteria were age < 18 years and a formal diagnosis of OAI, with or without a confirmed pathogen. Exclusion criteria were: age <3 months (more often multifocal and complicated infections), confirmed Lyme disease, congenital or acquired immunodeficiency, secondary infections (recent history of important skin wounds, open fracture, surgery at the site of infection or in contiguous areas), sickle cell disease, relapse of AOI, presence of prosthetic materials and insufficient data.

Figure 1 : *Literature search with reasons for exclusion.*



Information was retrieved and entered into an electronic, anonymised database: demographic and clinical details at presentation, final diagnosis and site of infection, laboratory results, imaging results, clinical management (type, route and duration of antibiotics, surgery), clinical and radiographic recovery at follow-up and sequelae. Polymerase chain reaction (PCR) technique used in the lab is 16S rRNA gene sequencing. Imaging results were defined as diagnostic if OAI was the only diagnosis mentioned, as suspicious if mentioned as part of a differential diagnosis, as other signs if there were signs related to OAI but the term itself was not used (eg. intra-articular fluid, periosteal reaction, Brodie Abscess,...) or as normal.

Patients were divided into four groups: OM, SA, SD or mixed type (combination of OM and SA). Statistics were performed through SPSS using Mann-Whitney and Fisher's Exact test. A p-value <0,05 was considered significant.

State of the art literature update

Definition and epidemiology

OM causes inflammation of the bone and marrow following infection. Its incidence varies widely between 1,94 to 13 children per 100.000 in developed countries and up to 80 per 100.000 children in developing countries (2,3). An increase in incidence over the past 2 decades has been noticed (4,5). The lower limb is most often the locus of infection with estimated prevalence of 27-36% in the femur and 22-33% in the tibia (4,6,7). Multifocal disease is more common in neonates (22%) but only occurs in 5-7% of paediatric cases (5).

SA develops after bacterial invasion of a joint and occurs in about 5 to 12 children per 100.000 per year, with similar geographical variability with a higher incidence in developing countries (8,9). Peak incidence is around the age of 3 years and up to 80% of the cases involve the hip or knee (10,11). Both OM and SA have a male predominance (4,6).

SD, infection of the vertebral disc and subsequently the adjacent vertebral bodies, is much less common with an estimated incidence of 1 per 250.000. Three peak age groups have been described: a few weeks to several months old, 6 months to end of preschool age and school-aged children (1,12). The lumbar spine is most often affected, in 75% of the cases (12). In discitis, the infection is limited to the vertebral disc. This entity is much less common in young children because of the rich vascularisation in the metaphysis of the vertebral body below the age of 8 years (1,12). We will focus on SD in this paper.

More than half of all children with OAI are younger than 5 years old and a third of the children with SA is less than 2 years old (4,5,9).

Pathogenesis

The most common origin of childhood OAI is haematogenous dissemination following transient bacteraemia from a previously existing site of infection or from the respiratory tract (1,4). Hence, the most vascularised areas are more often affected. The intervertebral disc for example is extremely vascularised in children compared to adults, particularly below the age of 8 years (12). OM typically occurs in the metaphyseal region of long bones where bacteria presumably aggregate due to the tortuous blood flow. Subsequently, infection can spread and form intraosseous, subperiostal and extraperiostal abscesses (4,7). In young children < 18 months with OM, transphyseal blood vessels predispose to the development of secondary SA, which is much less common in older children when the physis becomes relatively avascular (6,7). Especially the shoulder, elbow, hip and ankle are prone to develop this type of secondary infection (10,13). Other pathogenic mechanisms are spreading of infection from an adjacent area (e.g. cellulitis) or direct inoculation (e.g. trauma, surgery) (8,13). The greater exposure to microtraumata is possibly the explanation for male predominance in SA and OM (3,4).

Microbiologic aetiology

Staphylococcus aureus (S. aureus) is the most frequent cause of all paediatric OAI; up to 70-90% of positive cultures in OM, 25-60% in SA and 80% in SD (1,5,13). Group B streptococcus and gram-negative rods are potential pathogens in newborns whereas Streptococcus pyogenes and Streptococcus pneumoniae should also be considered in older children (7,8). Another important pathogen is Kingella kingae, increasingly detected as aetiology in children and a major pathogen between 6 months and 4 years (1,4). On the other hand, Haemophilus influenzae type B (HiB) has become exceptional since the introduction of successful vaccines (5,13).

Methicillin resistant S. aureus (MRSA), is an emerging problem, especially in southern European countries and the USA. MRSA prevalence is low in northern European countries and Canada (14). Infections with MRSA tend to cause a more severe disease course, with longer need for IV treatment and more systemic complications (7,15). S. aureus carrying the Panton-Valentine leukocidin (PVL) gene, predominantly present in the US, produce a destructive cytotoxin that is responsible for a more severe SA and OM (5,8).

Salmonella is uncommon in Western countries but is a known pathogen in developing countries and in patients with sickle cell disease (9,16). Infections with non-bacterial organisms, e.g. fungi and parasites, are very rare in immunocompetent children (5,9).

In a substantial part of patients with OAI, no aetiological organism is found (17).

Diagnosis

The diagnosis is based on clinical signs, supported by biochemical tests, positive tissue or blood cultures and radiological signs (13). Typical signs and symptoms at presentation in OM and/or SA are fever, malaise, local erythema, swelling and/or pain, limitation of function such as painful and limited range of motion, refusal to weight-bear or to sit and antalgic gait. In neonates, symptoms can be more nonspecific and fever can be absent (5-7). Clinical presentation can also vary depending on the causative organism (2). Mostly, children present within 3-4 days after onset of symptoms (4). Unfortunately, this is not the case in SD where delay in presentation is frequent and diagnosis can take up to 4 months because of mild and nonspecific symptoms such as general malaise, irritability, fever, torticollis, back pain, stiffness, etc. Significant neurological signs on admission are rather infrequent. Therefore, a high index of suspicion is warranted to allow early diagnosis (1,12).

Laboratory findings show increased inflammatory markers in most patients. C-reactive protein (CRP) peaks early (within 48h) after symptom onset and can be helpful in disease monitoring as well (normalisation within 7 days after initiation of appropriate treatment). Erythrocyte sedimentation rate (ESR) rises more slowly (3-5 days to reach its peak) and takes several weeks to normalize (4,6). The combination of CRP and ESR is probably best to estimate disease likelihood, especially when both are within normal limits in which case OAI is highly unlikely though not impossible (7). Moreover, the peak level of CRP is indicative for disease severity and risk of complicated infection (15). White blood cell count can be normal or only slightly elevated, especially in newborns and younger children (2,9). In SD, laboratory findings can be unremarkable (1). Procalcitonin may be more specific than white blood cell count (WBC), CRP and ESR in adult studies (95%). Its sensitivity on the other hand is suboptimal (54%), thus, it is not suitable to exclude the diagnosis. Compared to CRP it increases earlier, has a shorter half-life and it does not rise significantly in response to viral or non-infectious diseases. However, little data is available in children and therefore more research is required before implementing procalcitonin in daily practice (1,15,18).

Ideally, a pathogen is found, allowing directed rather than empirical antimicrobial therapy. Nevertheless, finding the causative pathogen is not easy (17). Blood cultures only require venepuncture but are negative in 16-42% of patients with acute OM, 18%-70% in SA, and almost always negative in SD (1,4,13). Repeated blood cultures don't increase the likelihood of a positive culture (7). Joint fluid and tissue cultures yield better results than blood cultures, with 60-90% positive cultures in OM and 45-77% in SA, at the expense of invasive procedures which often require general anaesthesia. For SD, bacteriological sampling through percutaneous or surgical procedures should be reserved for children with unclear diagnosis, who fail to improve with antibiotic therapy, or if atypical organisms are suspected (6,9,12). Panbacterial or species-specific polymerase chain reaction (PCR) improves detection of pathogens but does not allow susceptibility testing (19). Identification of Kingella kingae is challenging as the organism is difficult to grow. Inoculation on blood culture systems or chocolate agar plates improve recovery rates. Use of PCR in samples from the infected site or on throat swabs increases the chance of identifying this organism (12,17,20).

Several imaging modalities are available to explore OAI.

In OM, x-ray is recommended as a first step to exclude other diseases such as malignancies or trauma (3,4,7). Non-specific soft tissue swelling is the most frequent x-ray abnormality and can be detected within 48 hours (7). Lytic changes in the bone, seen in OM, only become visible when 50-75% of the bone mineral density is depleted, mostly after 1-2 weeks (4). Ultrasound is reserved to assess soft tissue changes or subperiosteal collections, and can also be used for guided needle aspiration (3,4,6). Bone scintigraphy can be useful in young children where OM is suspected but the site of infection is clinically unclear. Its diagnostic yield is limited in neonates because of lower mineralization of bone (16,21,22). Computed tomography is excellent to assess bone and articular pathology, such as pathologic fractures, bone destruction, sequestration, subluxation, etc. It is also helpful to guide biopsies (12). Its diagnostic role however is limited with sensitivities and specificities of 66-97% (4).

In SA, indirect signs of joint effusion such as soft tissue swelling and increased joint space can be present on x-ray (10). Ultrasound is most useful as it can detect effusions as small as 1-2 ml. However, distinction between sterile, purulent and haemorrhagic fluid accumulations is impossible and ultrasound can be falsely negative within 24 hours after onset of symptoms (2,10,13).

Narrowing of the intervertebral disc space and destruction of adjacent vertebral endplates only become visible after 2-3 weeks on spine x-ray in SD. However, it remains a good test for initial evaluation (1). As in OM, ultrasound is an easy and non-invasive method to assess abscesses but is not useful for diagnosis (3,4,6). Bone scintigraphy can highlight inflammatory changes within 1-2 days of disease onset with a sensitivity of >90% but lacks spatial resolution. Positron emission tomography with 18 fluorodeoxyglucose (FDG-PET) has good sensitivity (85,1%) and specificity (92,8%) but the current role in paediatric OAI is limited because of radiation exposure and better alternatives. In the adult population, it can be useful to distinguish between inflammatory and degenerative changes which is impossible with bone scintigraphy (1,12,16,22,23).

The most sensitive imaging method remains magnetic resonance imaging (MRI) with high sensitivity and specificity for all types of OAI: respectively 95,6% and 80,7% for OM and 96% and 93% for SD (1,3,23). Moreover, MRI is very sensitive even in the initial stage of the infection when there is only minimal bone oedema (7). MRI also allows the diagnosis of local complications such as abscesses and guides surgical interventions (7,12). Despite this excellent performances, quick access to MRI is often compromised by the need for anaesthesia in young children.

Differential diagnosis should include traumatic, rheumatologic/inflammatory and neoplastic causes (5). Differentiation between SA and other types of arthritis like Lyme disease, transient synovitis, juvenile idiopathic arthritis and reactive arthritis can be difficult (10). Clinical examination, lab tests, cultures and imaging allow differential diagnosis in most children.

Treatment

Prompt treatment is needed to avoid sequelae (joint destruction, growth disturbances). In SA, the combination of bacterial invasion and host inflammation causes joint damage. In joints like the hip, ischemia can play a role as well due to impaired blood and nutrient supply caused by compression of blood vessels (13).

Although antibiotic treatment is evidently the appropriate treatment for OAI, no consensus has been reached regarding the optimal regimen, the mode of administration and the duration of treatment. In general, it is advised to cover Staphylococcal and Streptococcal species for all age groups, gram-negative organisms in neonates and Kingella kingae in children < 4 years (1,8).

Suggested antibiotic management is an anti-staphylococcal penicillin (ASP) (e.g. flucloxacillin) or a third generation cephalosporin (e.g. cefotaxime) combined with gentamicin for neonates <3 months. An alternative for this age group is a combination of ASP with third generation cephalosporin. First generation cephalosporin (e.g. cefazolin) should be used in the group between 6 months and 4 years (Kingella kingae) and ASP or first generation cephalosporin in older patients (6,9,10,24). In areas where the prevalence of MRSA is >10%, clindamycin or vancomycin (if clindamycin resistance rate >10%) is a better choice for empirical treatment (9,10). Neither of these antibiotics cover Kingella kingae so at least a first generation cephalosporin should be added if K. kingae is suspected (6,10). Preferential treatment according to the Belgian guidelines are a combination of cefotaxime with ASP for neonates <3 months, cefazolin or ASP for children between 3 months and 5 years of age and ASP for older children (25).

Historically, routine treatment consisted of six weeks of IV antibiotics. Nowadays, shorter parenteral treatment of 3-4 days with subsequent oral antibiotics for another 1-4 weeks can be advised for uncomplicated OAI and has been shown to be equally effective compared to longer treatment (1,2,4,26). This not only reduces cost (shorter hospitalisation) but also the risk for complications related to IV access and prolonged IV administration (4,7,27). Also, shorter antibiotic treatment than the classic 4-6 weeks can be successful in OM with the exception of vertebral OM (26). This is also shown in a prospective study in Finland which compares 20 to 30 days of treatment for hematogenous osteomyelitis (28). However, individualised decision making is advised to guide treatment and overall, transition to oral antibiotics is only advised in previously healthy children with clinical improvement, normalising CRP, settling of temperature and ability to take oral medications. Close follow-up, within 1-2 weeks after discharge is recommended to monitor further improvement (6,24,29). An average duration of therapy of 2-3 weeks for SA and 3-4 weeks of OM should be respected (24).

In SD, relative rest can be useful to allow optimal healing, normal position of the spine and to prevent progressive deformities. In cases without resolution in the first weeks of treatment short immobilisation and bracing/casting should be considered (1).

Surgical or percutaneous drainage is recommended in all patients with SA and removing all purulent material from the joint to avoid destruction is urgent (2,9,24). In OM, surgical or percutaneous drainage of subperiosteal collections and large abscesses is warranted (4). In SD surgery is only applied for children with neurological deficit, spinal instability, progressive deformity or unmanageable pain (12). When surgery is performed, appropriate cultures and biopsies should be taken (4).

A meta-analysis with 4 RCT's compared the use of dexamethasone (0,15-0,2 mg/kg, 4 times daily for 4 consecutive days) to placebo as adjuvant therapy with antibiotics for children with SA and strongly advocated for the use of corticosteroids (30). However, a Cochrane review which included 2 of these 4 RCT's, didn't draw the same conclusion and warranted that the current evidence for corticosteroids is of low quality needing further research (31).

Outcome and prognosis

Complications occur in approximately 6% of children with OM and 10-25% of children with SA. Early complications are related to persistent bacteraemia. Deep venous thrombosis for example occurs in 0,4-6%, especially in MRSA related infections (4,13). Late complications include chronic infection (1,7% in OM), avascular necrosis, growth disturbance due to involvement of the growth plate (1,8% in OM), stiffness and/or pain and pathologic fractures (1,7% in OM) (4,32). Long-term follow-up is indicated, especially in patients with infections near the growth plate (10). In SD, severe spinal deformities like scoliosis and kyphosis are possible and radiologically, the disc space can remain reduced in size and progress to a block vertebra (fusion of the adjacent vertebra) (1,12).

Described risk factors for poor outcome in OM and SA are delay in diagnosis, contiguous infection of bone and joint, neonatal infections and infections with more aggressive organisms like MRSA (13,33).

Outcome and prognosis might benefit from a consensus on classification and an algorithmic treatment approach. However, up until today, these are not available for children and long-term studies are needed to prove whether these initiatives could positively influence outcome and prognosis of OAI (4).

Retrospective cohort study

The retrospective search yielded 196 different contact files of 168 different patients. Based on the in- and exclusion criteria, 69 patients were included.

Reasons for exclusion were: other diagnosis (68), Lyme disease (4), age <3 months (6), prosthetic materials (3), chronic recurrent multifocal OM (4), relapse (3), secondary infections (6), immunodeficiency (3), insufficient data due to (partial) treatment in a district hospital (2).

Median age was 1,25 years (interquartile range (IQR): 0,9-6,0) with 42/69 (60,9%) males. Previous trauma was reported in 6/69 (8,7%) and 19/69 (27,5%) had a recent viral illness. Final diagnosis was OM in 32/69 (46,4%), SA in 25/69 (36,2%), SD in 8/69 (11,6%) and a combined OM and SA in 4/69 (5,8%). We had no cases of discitis only. The most common site of infection was the femur (10/32; 31,3%) followed by the tibia (8/32; 25%) in OM, the knee (9/25; 36%) followed by the hip and sacroiliac joint (both 5/25; 20%) in SA and the lumbar spine in SD (7/8; 87,5%).

Median interval between onset of symptoms and presentation was 2 days (IQR: 1-6). Delay in presentation was significantly longer in the SD group (median 12,5 days; IQR 2,5-19,3; p=0,003). Patients came on their own initiative in 30/69 (43,5%) and were referred by the general practitioner or the paediatrician/district hospital in 13/69 (18,8%) and 26/69 (37,7%) of the cases respectively. Swelling, pain and local warmth were significantly less present in the SD group (p=0,006, p=0,012, p=0,019 respectively) (Table 1a). Other symptoms did not differ. Median temperature at diagnosis was 38,5°C (IQR 37,1-39,5). Twenty-three patients (33,3%) were afebrile: 12/32 in the OM group, 5/25 in the SA group, 5/8 in the SD group and 1/4 in the combined OM and SA group. Six patients received antibiotics before diagnosis for other indications: ear infection (2), upper airway infection (1), suspected cellulitis (2) and fever of unknown origin(1).

CRP and WBC count were significantly higher in the SA group compared to the other groups (p=0,014 and p<0,001) (Table 1b). Blood cultures were taken in all but 3 patients. Samples from the infectious site were obtained in 24/69 (34,8%) before and in 10/69 (14,5%) after start of antibiotics of which 7/32 (21,9%) in OM (bone biopsy in 4, drainage of collection in 3), 22/25 (88%) in SA, 1/8 (12,5%) in SD and 4/4 (100%) in the combined group. In 25/34 patients additional irrigation was required (4/32 with OM, 16/25 with SA, 1/8 with SD and 4/4 with combined OM and SA). Three patients with SA underwent needle aspiration twice.

Blood cultures identified the causative organism in 18/66 (27,3%). Samples from the infectious site were positive in 18/34 (52,9%) of whom 10 had negative blood cultures. PCR identified the causative organism in 3/6 (50%, 2/3 Kingella kingae, 1/3 Streptococcus dysgalactiae) of which 2 were not detected by other methods. In total, 30/69 (43,5%) had a microbiological diagnosis (Figure 2a). In half of the cases (3/6) receiving antibiotics before diagnosis, the organism was not found. Patients with Kingella kingae infection (5/30) were significantly younger with a median age of 0,86 years (IQR 0,60-1,44) compared to other organisms (median age 3,71 years; IQR 1,03-11,73; p=0,031) and had a lower maximum temperature (38,4°C, IQR 37,4-38,6 vs. 39,3°C; IQR: 38,3-39,7; p=0,04). S. aureus infections (13/30) on the other hand were associated with significantly older age (median 11,7 years; IQR 8,75-12,95 vs. 0,98 years; IQR 0,80-1,87; p<0,001), lower WBC count (9.490/µL, IQR 7.370-11.175 vs. 14.050/µL, IQR 12.100-17.375; p<0,001), longer oral (median 35 days, IQR 23,5-38,5 vs. 22 days, IQR 14-28; p=0,008) and total (median 44 days, IQR 41,5-54 vs. 32 days, IQR 23-40; p<0,001) antibiotic treatment . No cases of MRSA were detected.

Figure 2a : *Final microbiological identification.*

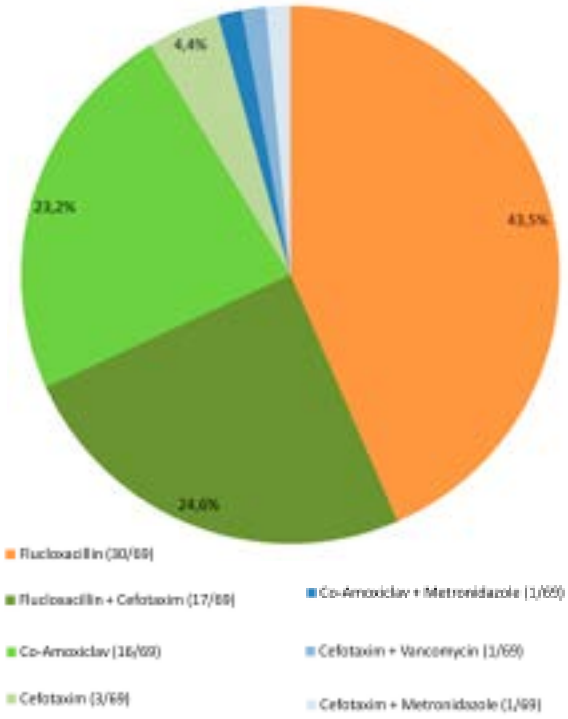


Table 1a: *Clinical signs at presentation. Groups compared using Fisher Exact.*

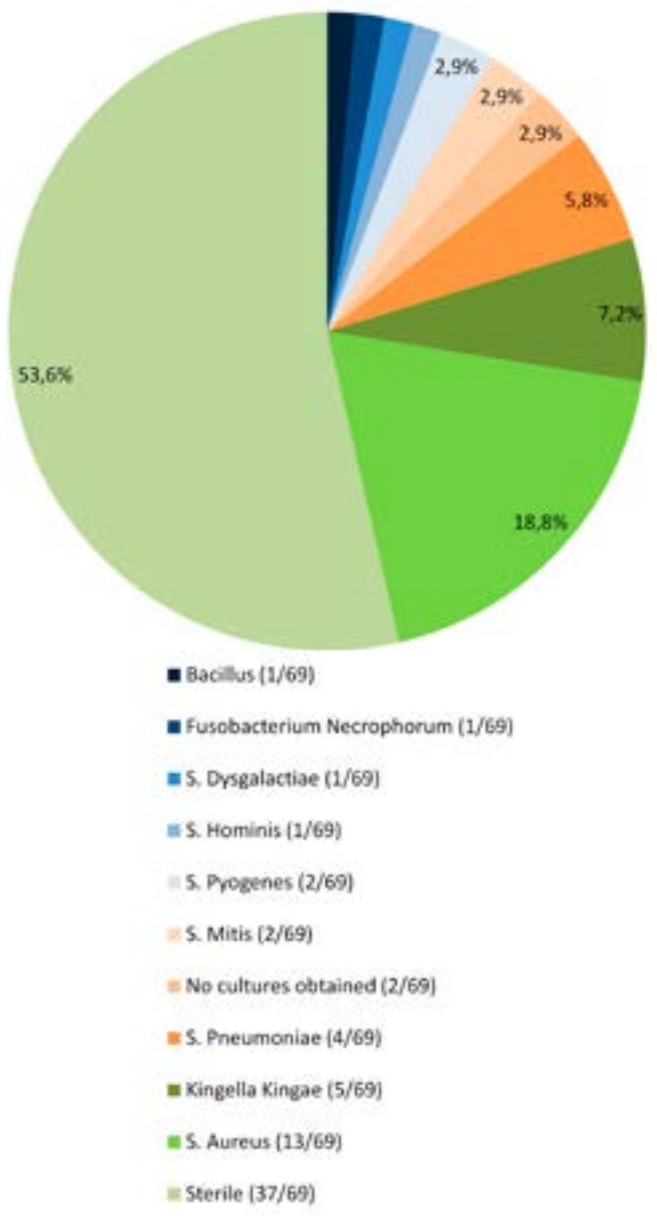
	Osteomyelitis	Septic arthritis	Spondylodiscitis	Mixed	P-value
Rubor	13/32 (40,6%)	6/25 (24%)	0/8 (0%)	0/4 (0%)	0,058
Calor	13/32 (40,6%)	11/25 (44%)	0/8 (0%)	3/4 (75%)	0,055
Dolor	32/32 (100%)	25/25 (100%)	6/8 (75%)	4/4 (100%)	0,001
Tumor	18/32 (56,3%)	11/25 (44%)	0/8 (0%)	3/4 (75%)	0,023
Functio laesa	30/32 (93,8%)	25/25 (100%)	8/8 (100%)	4/4 (100%)	0,497
Fever	20/32 (62,5%)	20/25 (80%)	3/8 (37.5%)	3/4 (75%)	0,142
Tenderness on palpation	27/32 (84,4%)	20/25 (80%)	5/8 (62,5%)	4/4 (100%)	0,393

Table 1b: *Inflammatory signs at presentation, median shown with interquartile range (IQR).*

	Osteomyelitis	Septic arthritis	Spondylodiscitis	Mixed
CRP (mg/L)	24,3 (4,4-53,8)	48,8 (24,6-82,4)	12,6 (3,1-28,7)	45,5 (22,8-166,4)
Sedimentation (mm/h)	30 (16,5-42,5)	46 (22,5-61,5)	45 (37-70)	34 (28-65)
WBC (/µL)	10.380 (8,3-12,7)	14.020 (11,8-17,1)	10.665 (9,0-13,8)	13.440 (7,0-19,9)

In our population, CT, MRI and scintigraphy were all equally diagnostically helpful (Table 2). The median waiting time for MRI was 3 days (IQR: 0-7). This was not related to a longer delay in diagnosis. If we take all diagnostic, suggestive and other signs related to OAI into account, MRI was most useful with 24/26 (92,3%) positive cases followed by CT (9/10 ; 90%) and scintigraphy (22/26 ; 84,6%). We noticed that MRI was executed more often in the second half of the study period (8/28 ; 28.6% in the first half (13.11.2012 - 13.05.2015) vs. 18/41 ; 43.9% in the second half (14.05.2015 - 13.11.2017)). We also found that MRI was executed after all other investigations in most cases (20/26 ; 76,9%), suggesting that MRI was necessary to confirm the diagnosis.

Figure 2b : *Choice of initial antibiotic treatment.*



IV antibiotic treatment was started in all patients for a median period of 8 days (IQR 6-11). Subsequently, oral therapy was given for a median of 28 days (IQR 21-36,5). Total antibiotic course varied from 20 to 64 days (median 41 days, IQR 29,5-44). Intravenous treatment duration was comparable in all groups (p=0,49). Length of oral and total treatment on the other hand was significantly shorter in the SA group compared to the other groups (21 days, IQR 17-28 vs. 35 days, IQR 26,3-39 and 28 days, IQR 23,5-40 vs. 42 days, IQR 35-46,8 respectively; both p<0,001). As stated above, treatment duration was significantly longer for the S. aureus group. Choice of antibiotics differed greatly (Figure 2b). In the group of 5 years and older, most children received flucloxacillin (15/20; 75%). In the group of 3 months to 4 years (49), none received first generation cephalosporin. Instead they received ASP (15/49), amoxicillin-clavulanate (16/49), ASP combined with a third generation cephalosporin (17/49) or a third generation cephalosporin only (1/49).

Complications during admission were abscess formation in 11/69 (15,9%) and venous thrombosis in 1/69 (1,4%). The frequency of abscess formation did not differ between the four groups (p=0,851).

All but 3 patients had a clinical follow-up after a median of 31 days (IQR 22-41) and a mean of 42,6 days (SD 52,8). Clinical resolution was achieved in 52/66 (78,8%) whereas complete resolution on conventional x-ray was present in only 26/60 (43,3%) but 7 of the abnormal 34 x-rays showed great improvement. Remaining abnormalities on x-ray were (7 cases with great improvement not included): Brodie's abscess (6/27), sclerotic changes (4/27), periostal reaction (2/27) and avascular necrosis (1/27) for the OM group, scoliosis (2/27), kyphosis (1/27), narrowing of the intervertebral space (5/27) and chronic infection (1/27) in the SD group, avascular necrosis (1/27) and sclerotic changes (4/27) in the SA group and chronic infection (1/27) and sclerotic changes (1/27) for the combined OM and SA group.

In 14/66 (21,2%) patients, clinically relevant sequelae were documented: avascular necrosis (2/14), chronic infection (3/14), limb length differences (1/14), lytic changes near the growth plate (3/14), proprioceptive difficulties (1/14), impaired range of motion (2/14), kyphosis (1/14), hyperlordosis (1/14) and scoliosis (2/14). These patients were diagnosed with OM (4/14), SA (4/14), combined infection (1/14) and SD (5/14). Two patients had a possible relapse.

Discussion

We described a large cohort of paediatric OAI, recruited at a tertiary care hospital. Epidemiological data from our study were consistent with the literature with a male predominance and the majority of patients (49/69, 71%) below the age of 5 years (4,5,9). Symptoms at diagnosis are vague in the SD group which explains the well known delay in diagnosis. CRP was significantly higher in the SA group, in line with what has been described by others (13). In our population, 6/69 (8,7%) had both negative CRP (<5mg/L) and ESR (<20mm/h) and 22/69 (31,9%) had normal WBC count (<10.000/µL) so a high index of suspicion is warranted despite negative inflammatory markers in suspicious cases.

Microbiological diagnosis was confirmed in 43,5%, with blood cultures taken in almost all patients and sampling from the disease location in 34/69 (49,2%; positive in 18/34). As expected, tissue cultures and PCR were an important asset on top of standard blood culture. Samples from the infectious

Table 2: *Imaging tests performed. The test was defined as diagnostic if it was the only diagnosis in the protocol and as suspicious if it was mentioned as part of a differential diagnosis. Other abnormalities were any other abnormalities mentioned without the use of the terms OAI, osteomyelitis, septic arthritis or spondylodiscitis. Other abnormalities assumed to be related to OAI were presence of intra-articular fluid, effusion, abscess, avascular necrosis or lytic changes.*

	Performed	Diagnostic	Suspicious	Other abnormalities	Related to OAI	Normal
X-Ray	63/69 (91,3%)	5/63 (7,9%)	13/63 (20,6%)	7/63 (11,1%)	4/7 (57,1%)	38/63 (60,3%)
Ultrasound	49/69 (71%)	3/49 (6,1%)	6/49 (12,2%)	18/49 (36,7%)	15/18 (83,3%)	22/49 (44,9%)
CT	10/69 (14,5%)	6/10 (60%)	2/10 (20%)	2/10 (20%)	1/2 (50%)	0/10
MRI	26/69 (37,7%)	17/26 (65,4%)	4/26 (15,4%)	5/26 (19,2%)	3/5 (60%)	0/26
Scintigraphy	26/69 (37,7%)	17/26 (65,4%)	4/26 (15,4%)	2/26 (7,7%)	1/2 (50%)	3/26 (11,5%)

site yielded 10 additional microbiological diagnoses and PCR identified 2 organisms that weren't detected by any other method. However, they were only performed in 34 and 6 patients respectively. A clinical study from France with 2308 patients with OAI showed that PCR detected an organism in 9% of the culture-negative joint and bone samples. Systematic use of PCR in culture-negative cases is an important consideration to aim for higher numbers of pathogen identification. Nevertheless, the impossibility of determining the antibiotic susceptibility, the high cost and the detection of contamination with irrelevant germs must be kept in mind (19).

S. aureus was the most commonly identified pathogen, but no MRSA strain nor other multidrug-resistant organisms were isolated. This is in keeping with previous publications on MRSA prevalence and is an important confirmation to set up local algorithms for empiric antibiotic treatment (14). Kingella kingae was identified in only 5 cases, all within the age group 6 months - 4 years. This age group included 48 patients of which 30 had negative cultures. Possibly, some Kingella kingae infections were missed due to its difficulty to grow on regular cultures.

Similar to other studies, MRI was shown to be most useful for definitive diagnosis of OAI. The median waiting time for MRI was rather long with 3 days (IQR 0-7). Even though this was not related to a difference in diagnostic delay, we strongly feel that dedicated slots for paediatric OAI infections would be beneficial. MRI should be feasible within 24-48h, with anaesthesia if necessary, potentially followed by guided biopsies or punctures for microbiological samples before start of antibiotics, if clinically affordable.

There was no clear consistency in antibiotic choice for our population, especially in the group below 5 years of age, partially explained by referred cases who were already started on treatment. Another explanation is the lack of local clear guidelines as all choices except for the combination of ASP with a third generation cephalosporin are valid alternatives according to the guidelines (24,25). In the group > 5 years, most did receive antibiotic treatment according to current guidelines. Duration of IV treatment was longer than suggested in most studies but the retrospective nature of our study makes it difficult to explain this difference. Reason for longer duration of treatment in the S. aureus can be explained by local complications (5/13) and delay in presentation (3/13). We believe that both clinical and biochemical evolution are crucial before stepping down to oral antibiotics.

Follow-up was extended to a maximum of 398 days and was longer than the recommended 1-2 weeks after discharge in most cases (6,29). Most cases had complete resolution of symptoms, but we documented a high incidence of clinically important sequelae (21,2%) which highlights the importance of strict and long-term follow-up. This high number of sequelae could partially be explained by the fact that this cohort-study was performed in a tertiary care centre with more complex cases and therefore more sequelae. More than 1/3 of the cases were referred from other hospitals.

This study has several limitations, the retrospective nature being the most important one. Nevertheless, our cohort distribution seems to be a fair representation of the total population when comparing our findings to the literature. Therefore, we feel that our findings in combination with the literature update is a good starting point for both local and national guidelines and protocols.

Conclusion

Paediatric OAI is an important entity that can cause significant morbidity if not treated promptly and adequately. An increase in tissue culture collection and the use of PCR techniques could greatly improve the microbiological identification of the responsible pathogen and enable directed antimicrobial therapy. Besides, dedicated MRI slots for paediatric OAI could be useful to avoid a delay in diagnosis and plan early bacteriological sample collection before start of antibiotics.

These are important findings to take into consideration when setting up local guidelines and protocols, currently still insufficiently applied for the management of paediatric OAI.

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SARS-CoV-2 infection in children - a review on clinical disease, transmission and school closures

Liselotte Eke Bijker[a], Else Margreet Bijker[b]

[a] Vrije Universiteit Brussel, Brussels, Belgium
[b] Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, United Kingdom

liselottebijker@gmail.com

Keywords

COVID-19; SARS-CoV-2; Children; Transmission

Abstract

Coronavirus Disease 2019 has significant impact on societies and healthcare systems worldwide, but interestingly, children are less affected than adults. Infections with the severe acute respiratory syndrome coronavirus 2 have been reported in all age categories, including neonates, but occur less often in young children compared to adults. Moreover, the vast majority of children has mild disease and mortality is low. Immunocompromised children appear to have a higher risk of being admitted when infected and infection appears more severe in children with combined immunodeficiencies and immune dysregulation, in comparison to other immunodeficiencies such as antibody deficiencies. Children are less susceptible to infection than adults, and infectiousness appears to be either reduced or comparable. Vertical transmission is possible, but the risk hereof is very low. School closures have significant adverse impact on children, and because school outbreaks are relatively uncommon and strongly associated with regional incidence, school closures should be a last resort. Whether new variants of the virus might significantly change transmission dynamics remains unclear, and spread of these variants should be monitored carefully.

Introduction

The first case of Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was detected in Wuhan, China, in December 2019. Since then, the virus has spread rapidly, was characterized as a pandemic by the World Health Organization (WHO) in March 2020 and has caused more than 80 million cases including 1.8 million deaths as of January 1st 2021 (1). In Belgium, 649.453 cases were confirmed in this period, leading to 19.667 deaths (2).

From early on, children were shown to be less affected than adults. However, a number of questions remain, mainly regarding clinical disease in children with underlying immunodeficiencies, and the role of children in transmission. In this narrative review, we discuss the spectrum of clinical disease in children, with specific focus on immunocompromised children. Next, we review the existing literature on transmission in children and discuss the implications of these data on decisions regarding closing of schools.

COVID-19: clinical disease in children

None of the first reported cases were children, and early on in the pandemic, it was found that, although children of all ages were susceptible, clinical disease was much less severe than in adult patients (3). Even though testing strategies have changed significantly with increased availability over time, young children remain underrepresented among COVID-19 cases. The European Centre for Disease Prevention and Control (ECDC) reported that children aged 1-4 years represented only 1.3% of the cases, and that 4.2% of the cases occurred in children aged 5-11 years, while they represent 3.8% and 6.8% of the population, respectively (4). This is different for older children, where the proportion of cases is roughly equal to the proportion of the population they represent (4). However, children of all ages are substantially underrepresented in severe outcomes such as hospitalisation, intensive care unit (ICU) admission, ventilatory support requirement or death (4).

During the first epidemic wave from March 15th to June 28th extensive laboratory, school and hospital surveillance was performed in Belgium, showing a similar pattern (5). For most of the period investigated, schools were closed, especially for secondary school students. Although children made up about 20% of the population, they only constituted 10% of all tests. In addition to the fact that they were tested less frequently than adults, the positivity ratio was lower (1.8% in children versus 6.3% in adults). Moreover, infection with SARS-CoV-2 in children was less often a reason for hospital admission: only 1.6% of hospitalised patients in Belgium was less than 18 years old, whereas 3% of all positive test results were from children. Among hospitalised children, infants less than 1 year were overrepresented. Not only was the admission rate per 100.000 individuals higher in children less than 1 year compared to older children, the admission rate per 100 positive tests was also higher, suggesting that the youngest category of patients is hospitalised more readily in case of infection. The majority of hospitalised children (81%) did not suffer from severe complications and only 3% needed intensive care. Median hospital stay was only 3 days. Of all COVID-19 related deaths in Belgium, only 0,04% was younger than 25 years (8 out of 19.667 in the period December 1st 2019 up to January 1st 2021 while they represented 28% of the population on January 1st 2020 (6).

The proportion of asymptomatic children is estimated to be between 14.6 and 42% (7). A systematic review of 20 studies describing clinical presentation and outcomes in 1810 children showed that the majority (72%) had mild disease, while 21% of children had moderate disease severity and 7% was severely or critically ill. Mortality in these studies was 0.3% (8). Disease severity is probably overestimated in these studies, as most included only hospitalised patients, and are therefore biased towards the more severe spectrum.

Of children presenting with symptoms, fever and cough are most common, occurring in 46% to 64.2% and 32% to 55.9% of children, respectively. Symptoms such as rhinorrhoea, headache, sore throat, fatigue/myalgia and gastrointestinal symptoms including diarrhoea and vomiting can occur as well, but less frequently, in 10% to 20% of children (7, 9). However, fever and cough are indications for testing in many countries, which might have resulted in overestimation of the prevalence of these symptoms. When compared to adults in a study from China, children were found to present more frequently without symptoms (20% versus 5.5%), and less frequently with fever (57.1% versus 72%) (10).

A comparison of children who were admitted to either the general ward or the PICU in a hospital in New York showed that age ≥12 years was associated

with admission to ICU, while comorbidities such as prematurity, respiratory disease, congenital heart disease, diabetes mellitus, immunosuppression or kidney disease were not (11). These data suggest that adolescents are at higher risk of severe disease than younger children. A multinational European study showed that age of less than 1 month was associated with ICU admission (12). In Belgium, however, clinical surveillance during the first epidemic wave showed that infants younger than 1 year had a lower risk of complication (pneumonia, bacterial or fungal superinfection, ICU admission or acute respiratory syndrome) than older children (5). Indeed, neonatal SARS-CoV-2 infection is rare, mortality is low, and short-term prognosis in this group seems favourable (13-16).

Multisystem inflammatory syndrome

In April 2020, clinicians in the United Kingdom (UK) observed increased reports of previously healthy children presenting with a severe inflammatory syndrome in areas with high community transmission, two to four weeks after the initial peak of infections (17). This post-COVID inflammatory syndrome was termed Paediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 (PIMS-TS) in the UK (18) and multisystem inflammatory syndrome in children associated with COVID-19 (MIS- C) in the United States (US) (19).

Children present with prolonged fever and abdominal symptoms such as abdominal pain, vomiting and diarrhoea. Cardiovascular manifestations are present in 50-87% and rash in about half of the patients (20, 21). Clinical presentation is variable, with some children presenting with very high inflammatory markers but relatively mild disease, and others with profound shock. Kawasaki features are present in some children, with 5-22% of children meeting the criteria for complete Kawasaki, and 9-36% developing coronary aneurysms(20, 22, 23). Lymphopenia and high inflammatory markers are common. Median age is 8-11 years, and children from Asian and Afro- Caribbean backgrounds appear to be overrepresented (20, 23).

This syndrome of post-COVID inflammation is rare, estimated at less than two per 10000 COVID-19 cases (24). Although patients are frequently admitted to the ICU, length of stay is usually less than a week, and mortality is low, approximately 2% (22, 23). Most patients are treated with immunoglobulins or steroids, to halt the inflammation. However, effectiveness of these therapies needs to be investigated in ongoing clinical trials (25).

COVID-19 in immunocompromised children

Data from SARS-CoV-2 infection in patients with immunodeficiencies remain scarce. Moreover, patients with immunodeficiencies are a very heterogeneous group, and the course of SARS-CoV-2 infection is probably different depending on the specific part of the immune system that is affected. While a significant proportion of patients with life-threatening COVID-19 pneumonia were shown to have defects in type 1 interferon pathways, and patients with such a defect are clearly at higher risk of severe disease, similar linkages of specific immunodeficiencies to disease severity will be difficult to assess, since most of these conditions are rare (26).

Evidence from adults suggests that patients with both primary and secondary immunodeficiencies experience greater morbidity and mortality (27), although early reports described a favourable outcome in the majority of patients (28). A more recent description of SARS-CoV-2 infections in patients with immunodeficiencies, reported by the UK Primary Immunodeficiency Network registry demonstrated increased morbidity and mortality, with a case fatality rate of 31.6% in patients with primary, and 39.2% in patients with secondary immunodeficiency (29).

Studies reporting infection rates and outcomes of SARS-CoV-2 infection in children with immunodeficiencies are even rarer. A number of case reports with a total of 14 children, including common variable immunodeficiency patients, patients on prednisolone and patients receiving chemotherapy, showed asymptomatic or mild course in all patients, with none requiring admission (30-32). Testing of sera from 485 children with immunocompromising conditions, including oncologic diagnoses, solid organ transplant, bone marrow transplant, primary immunodeficiency, and rheumatologic conditions or inflammatory bowel disease on systemic immunosuppression showed a seroprevalence of 1%, similar as in general paediatric population. Moreover, only one patient was admitted with mild disease (33). Analysis of 21161 paediatric COVID-19 cases in the national registry in Mexico showed that while children with immunodeficiencies were less likely to be diagnosed with SARS-CoV-2 infection (adjusted prevalence ratio 0.773, 95% CI 0.664-0.882), they were more likely to develop pneumonia and be admitted (34). While the reduced infection rate might be the explained by an increased proportion of these patients having shielded, the increased risk of hospitalisation suggests that immunodeficiency might be associated with an increased risk of more severe disease in children.

The largest study reporting COVID-19 in children with immunodeficiencies reported an analysis of 2754 patients with primary immunodeficiencies in Iran, who were tested for SARS-CoV-2 infection if they presented with cough, fever and dyspnoea. They confirmed infection in 19 patients, resulting in an increased incidence of 1:144 compared to 1:178 in the total population (35). Infection appeared more common in children with combined immunodeficiencies and immune dysregulation, as opposed to other immunodeficiencies such as antibody deficiencies. Infection was not observed in patients with innate or complement deficiencies. However, the number of patients was too small to draw definitive conclusions. The mortality in this cohort was high, 8 out of 19 patients (42%) died. The majority of these had combined immunodeficiency and were not treated with haematopoietic stem cell transplantation (HSCT), potentially indicating the importance of cellular immunity. Although medical care was probably not optimal for these patients (the authors mention HSCT is not available), this indicates potential severity of COVID-19 in this subgroup of patients.

SARS-CoV-2 transmission in children

Whether or not children play a significant role in SARS-CoV-2 transmission has been a topic of much debate. As described earlier, clinical disease is less frequent and less severe in children compared to adults. However, whether this is due to reduced susceptibility to infection, or other factors, is not an easy question to answer. Moreover, it soon became clear that asymptomatically infected individuals could transmit the virus, which raised the question to what extent children contribute to spread of the virus, knowing that for many respiratory viruses, e.g. influenza, children are the main drivers of transmission (36). However, accumulating data is now pointing towards a minor role of children in SARS-CoV-2 transmission. In order to unravel the role of children in SARS-CoV-2 transmission, we discuss their susceptibility and infectiousness separately. Hereafter, we review the available information regarding vertical transmission.

Susceptibility of children to infection with SARS-CoV-2

In a seminal study from Iceland, 6% of the population was tested early in the pandemic. The investigators performed both targeted testing of symptomatic people and persons from high-risk areas or individuals with COVID-19 contact (n=9199) and random population screening (n=13080). In the targeted testing, 6.7% of children under the age of 10 tested positive, compared to 13.7% in older individuals. However, children were probably underrepresented in this group because they are more frequently asymptomatic. In the random population screening group, all children under 10 tested negative, while 0.8% of persons 10 years or older tested positive (37). This indicated that children were less susceptible to infection. Moreover, differences in viral load and duration of Polymerase Chain Reaction (PCR) positivity could potentially explain some of the difference between the groups (38, 39).

Instead of testing for presence of the virus by PCR, population-based seroprevalence studies could overcome some of these issues. Several cross-sectional population-based seroprevalence studies have been performed. The majority of these studies found lower seroprevalence rates in children compared to adults, with generally lower seropositivity in young children compared to adolescents (40-43). A large study in the US, using a convenience sample of 16025 serum samples, of which 1203 (7.5%) were obtained from children showed lower seroprevalence in children compared to adults in six states, similar levels in two states and higher levels in two states (44). Weighed mean seropositivity rates, calculated based on the data provided in the paper were 1.8% for children and 3.2% for adults. However, seroprevalence studies have a number of drawbacks. Antibody levels are higher in individuals with

more severe disease, and young children might induce lower levels, thereby underestimating the true rate of previous infection. Moreover, people from different age groups vary significantly in their behaviour and therefore risk of contact with SARS-CoV-2 infected individuals, which will influence the outcome of these studies, making it difficult to estimate the true susceptibility of children for SARS-CoV-2 infection compared to adults.

Household investigations are an elegant way to circumvent some of these hurdles. Because the contacts are well defined, and exposure is assumed to be comparable between adults and children, household contact investigation allows one to compare secondary infection rates between children and adults and therefore their relative susceptibility.

We found sixteen household studies that systematically tested household contacts by PCR and compared secondary infection rates in children versus adults (see table 1). Eight of these studies found a lower secondary infection rate in children and seven found no difference between children and adults. One study found an increased secondary infection rate in children (45). However, in this last study, there was a significant difference between children 0-9 years-old (3 out of 57 contacts tested positive, 5.3%) compared to children 10-19 years-old (43/231 positive, 18.6%). A meta-analysis on this subject confirmed that children younger than 10 to 14 years are less susceptible to infection with SARS-CoV-2 than adolescents and adults with an odds ratio of 0.52 (CI 0.33-0.82) (46).

Table 1. *Susceptibility of children for SARS-CoV-2 infection, compared to adults, based on household investigations.*

Study	Age children (year)	Children Infected/total tested (%)	Adults Infected/total tested (%)	Country
Bi 2020(105)	0-9	11/148 (7.4)	67/837 (8.0)	China
	10-19	6/85 (7.1)		
Grijalva 2020(63)	<12	18/32 (56.3)	70/129 (54.2)	US
	12-17	14/30 (46.7)		
Hu 2020a(64)	0-14	22/936 (2.4)	187/7223 (2.6)	China
Hu 2020b(106)	0-14	10/216 (4.6)	49/1128 (4.3)	China
Hua 2020(107)	<15	43/325 (13.2)	108/510 (21.2)	China
Jing 2020(108)	0-19	9/171 (5.3)	88/599 (15.7)	China
Lewis 2020(109)	<10	3/29 (10.3)	33/120 (27.5)	US
	10-17	16/39 (41.0)		
Li 2020(110)	0-5	1/44 (2.3)	60/292 (20.5)	China
	6-17	3/56 (5.4)		
Park 2020(45)	0-9	3/57 (5.3)	1202/10304 (11.7)	South Korea
	10-19	43/231 (18.6)		
Rosenberg 2020 (111)	0-5	5/25 (20.0)	88/182 (48.4)	US
	5-18	37/131 (28.2)		
Somekh 2020(112)	0-4	2/18 (11.1)	21/36 (58.3)	Israel
	5-17	13/40 (32.5)		
Van der Hoek 2020(113)	1-5	2/19 (10.5)	23/67 (34.3)	The Netherlands
	6-11	7/44 (15.9)		
	12-17	15/44 (34.1)		
Wang 2020a(114)	0-17	13/36(36.1)	64/92 (69.6)	China
Wang 2020b(115)	0-17	2/10 (20.0)	130/201 (59.7)	China
Wu 2020(116)	0-3	4/10 (40.0)	43/112 (38.4)	China
	4-18	1/21(4.8)		
Yousaf 2020(117)	<18	14/69 (20.3)	33/126 (26.2)	US

Although household studies are probably the most robust method to assess susceptibility to infection, there are a number of issues. For example, it is difficult to ascertain whether the person who presented first was indeed the index case, or whether this person was infected by another, asymptomatic or mildly symptomatic, household member. Alternatively, as shown by Kim et al., multiple infected individuals from one household could instead be infected by a common index patient outside the household (47). Indeed, antibody testing in quarantined household contacts of adult COVID-19 cases in Spain showed similar seroconversion rates for children and adults (17.6 and 18.7%, respectively) (48). Another analysis of 30 households with adult COVID-19 index patients also showed similar seroconversion rates in children (28/53, 52.8%) compared to adults (16/27, 59.3%) (49).

People from different age groups differ in their behaviour, and might also differ in their adherence to physical distancing and hygiene measures. This could alter their risk of exposure to SARS-CoV-2, even within households. However, looking at the available evidence to date, it seems highly likely that young children have a reduced susceptibility to SARS-CoV-2 infection compared to adults. This finding is supported by two modelling studies. Fitting of an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada and South Korea demonstrated that susceptibility of infections was approximately half in individuals under 20 years of age, compared to older people (50). Another modelling study on transmission in 14622 individuals who were close contacts of 870 COVID-19 patients showed that susceptibility of children younger than 13 years old was significantly reduced compared to adults (OR 0.41, 95% CI 0.26-0.63) (51). The reason for this reduced susceptibility remains to be elucidated, but reduced expression of the angiotensin-converting enzyme 2 (ACE2) receptor in children younger than 10 years of age could play a role (52).

Infectiousness of children with SARS-CoV-2 infection

Nasopharyngeal samples of children with PCR-confirmed COVID-19 were tested in cell culture and demonstrated culture-competent virus in 12 (52%) of 23 children (53). However, in order to assess the true infectiousness of children compared to adults, it would be important to compare secondary infection rates stratified by age of the index patient. Unfortunately, there are few data available to answer this question.

Children are less often shown to be the index case in household clusters: in an analysis of 4021 households with one or more IgG positive child and one or more IgG positive adult, the first adult and child tested positive at the same time in 55.9%, the adult had the first positive result in 35.7%, and the child had the first positive result in only 8.4% of the households (54). Another study showed that in 31 household transmission clusters, only 3 out of 31 index cases (9.7%) was a child, where this was 30 out of 56 (54%) in H5N1 influenza (55). A similar result was found in another study, where in only 3 out of 39 (8%) of households a child was the first to develop symptoms (56). However, this could be biased due to the higher proportion of infected children presenting asymptomatically.

A study in a Parisian hospital showed a lower attack rate amongst health care workers in the paediatric setting compared to the adult setting (2.3 versus 3.2% respectively, p=0.0022), although this was probably a reflection of the lower number of COVID-19 admitted cases and potentially a difference in adherence to personal protective equipment and physical distancing measures (57). Large-scale comparison of self-reported incidence rates amongst child care providers in the US (within the context of already implemented significant mitigation measures) showed no difference with background transmission rates, therefore suggesting that exposure to child care does not entail an increased risk for COVID-19 (58). This finding is supported by a French seroprevalence study in children and day-care staff, which suggested that intrafamily transmission was more common than transmission in day-care centres (59). The probability of transmission is highest in contacts of the same age, particularly for children up to 14 years old and adults aged 65 years and older (60). However, this might mainly reflect the nature of behaviour and interactions of certain age groups.

In a Korean study, 5320 contacts of 22 children with confirmed COVID-19 were tested, with only two secondary cases detected, and investigation of transmission from paediatric cases in Norwegian primary schools found no secondary cases (61, 62). Analysis of 191 household contacts of 101 index patients in the US showed that if the index case was less than 12 years old, the secondary infection rate was 53% (9/17), and 38% (11/29) if the index case was 12-17 years old. This was not significantly different from adult index cases, where the secondary infection rate was 57% (82/145) (63). Although this study is valuable because of the direct comparison of secondary infection rates between children and adults, the small number of paediatric index patients and the high secondary infection rate suggests some selection bias, impeding extrapolation. A similar study in China showed a secondary infection rate of 1% (2/193; 95% CI 0.1-3.7) if the index patient was a child, compared to 2.6% (207/7966) if the index patient was an adult, which was not significantly different (64). This was supported by a modelling study on transmission in 870 COVID-19 patients and 14622 close contacts, which found no difference between infectiousness of children and adults (51). However, a more recent household study from Israel showed a reduced relative infectivity of children of 63% (95% CI 37-88%), compared to adults (65). Most studies comparing children and adults do not separately assess children <10 years of age, who might be less infectious than older children. In summary, infectiousness of children with SARS-CoV-2 is difficult to establish reliably, but appears to be similar or reduced compared to adults.

Whether or not faecal shedding of virus contributes to transmission remains unclear. There is ample evidence of prolonged viral shedding in stool, with multiple reports describing children who test positive by PCR on faecal samples for up to five weeks after testing negative in samples from the respiratory tract (66-69). However, there are only sporadic reports of replication-competent virus being isolated from stool (70).

Vertical transmission of SARS-CoV-2

The possibility and relevance of vertical transmission is still debated. Although the ACE2 receptor is expressed abundantly in the placenta, it was hypothesized that physiological mechanisms exist to prevent transplacental transmission of SARS-CoV-2 (71). Since the start of the pandemic, the lack of information on this subject has created uncertainty and concern. Presence of SARS-CoV-2 has been confirmed by PCR on placentas, amniotic fluid, umbilical cord blood, vaginal secretions and breast milk (72, 73). Percentages of positive SARS-CoV-2 PCR in neonates born to mothers with COVID-19 vary from 0% to 8% (72-75). However, although there have been cases described where positive test results were reported simultaneously in placental and neonatal samples, indicating that vertical transmission occurs, it cannot be stated unequivocally that confirmed neonatal infections are due to vertical transmission in a majority of cases (73). Congenital malformations related to maternal COVID-19 have not yet been reported. Reviews on the transmission of SARS-CoV-2 in breast milk show that 0% to 13.2% of milk samples tested with PCR were positive (76, 77). However, replication competency of the virus was not confirmed in these samples. In none of the neonates who tested positive it could be established with certainty whether transmission took place through breast milk, through droplets during close contact, during passage of the birth canal or via the placenta. Therefore, it is recommended that mothers with COVID-19 should be encouraged to breastfeed, as the benefits seem to substantially outweigh the potential risk for transmission, especially considering the immunomodulating effects of breast milk (77, 78).

Closing schools in order to reduce transmission: a last resort

School closures have been implemented to reduce transmission, but the negative effect of this measure on children is significant. Here, we discuss the available data on SARS-CoV-2 transmission in educational settings, the impact of school closures on children and on transmission, and the pros and cons of this intervention.

Accumulating data suggest that transmission in schools occurs, but that it is relatively uncommon. Twelve out of 17 countries (71%) who responded to an ECDC survey, reported transmission clusters in educational settings, the majority of which occurred in secondary schools, followed by primary schools and preschools. The number of cases involved in each cluster was usually less than 10, although clusters with up to 80 cases were reported (4). Analysis of notified cases from January until August in Germany showed that

school outbreaks re-occurred after schools reopened, but these were few and small. Out of 8841 COVID-19 outbreaks, 48 (0.5%) occurred in schools, and included 216 cases, of which almost half was older than 21 years old (79). A large prospective epidemiological study in England, analysing national surveillance data from cases occurring in students and staff after reopening of schools after the first lockdown in July showed that infections and outbreaks were uncommon. Importantly, there was a strong association with regional COVID-19 incidence, and measures to mitigate community transmission should be implemented to protect educational settings (80). This notion was confirmed in a modelling study of transmission data from Germany and Scandinavian countries, which showed that school closure caused a visible reduction in on transmission, but that reopening of schools is feasible as long as community transmission levels are low (81).

School surveillance was started in Belgium when schools reopened after the summer holidays (5). Several additional mitigation measures were imposed on population level and schools remained closed after the autumn break for an extended period. During this period of 15 weeks, from all children less than 6 years old, 0.2% tested positive by PCR. This was 2.8% and 4.5% in all children aged more than 12 years and staff, respectively. Similar to other countries, the pattern of confirmed cases in children follows, rather than precedes the pattern of infections in the general population in Belgium.

Secondary infection rates in schools are generally low (82-84). Early data from Ireland, from before schools closed in March 2020 did not show any paediatric transmission, although the overall number of cases was low and the number of paediatric cases was probably underestimated because only symptomatic individuals were tested (89). Epidemiological data from New South Wales, where most schools remained open during the first epidemic wave, showed that the secondary attack rate was low at 1.2%, and schools did not contribute significantly to SARS-CoV-2 transmission (28). However, large school outbreaks are reported occasionally; one such outbreak occurred in Israel just after schools reopened with attack rates of 13.2% in students and 16.6% in staff (85). Belgian data show that less than one fifth of the cases in school are a result of transmission inside the school (5).

It has been challenging to estimate the relative effectiveness of school closures, compared to other mitigation efforts. However, consensus amongst most studies is that closing schools reduces transmission, but is most effective when implemented in combination with other interventions. A modelling study from the Netherlands showed that closing schools for children aged 10-20 years is expected to reduce the reproduction number by 8%, while closing schools for children aged 5-10 years would reduce the reproduction number by 5% and reducing contacts among children aged 0-5 years is expected to have negligible effect (86). This suggests that closing secondary school would have most impact on transmission. Whether new variants of the virus, such as recently identified in the UK and South Africa, might change these dynamics remains unclear, and transmission should therefore be monitored carefully, with appropriate adjustments of policies if necessary, based on evolving evidence. The variant that was first encountered in the UK on 20 September 2020 was designated as Variant of Concern (VOC) on 18 December 2020. Whereas it constituted initially only 1 in 4 tests, the proportion of the new variant increased to almost two thirds in London in only three months' time (87). It was estimated that individuals infected with this VOC 202012/01 transmit the virus to 11% to 15% of contacts, leading to a secondary attack rate that is 10% to 70% higher than in cases with the wild type virus (88). The increased transmissibility does not affect any age group in particular, as was shown by a surveillance study in the UK (89). During an outbreak of COVID-19 in a school in Rotterdam, The Netherlands, students, teachers and household contacts were tested for the new variant. Preliminary results showed that 10% tested positive and approximately 40% of these infections was due to the new variant (90). In Belgium, four possible cases of the VOC 202012/01 were identified, but definite results were not yet available on December 25th (91).

Given the low prevalence and reduced severity of COVID-19 in children, exposure of teachers and other staff should be a major concern. A significant proportion of school employees in the US (39.8-51.4%) was estimated to be at increased risk of severe COVID-19 according to CDC guidelines (92, 93). However, studies from England, Norway, Denmark, Sweden and The Netherlands demonstrated that teachers did not have an increased risk of COVID-19 compared to other professions(4, 94-97).

UNESCO reports that in late April 85% of learners worldwide were affected by school closures due to SARS-CoV-2 (98). Closing schools has significant adverse impact on children, not only because they miss out on important learning opportunities, but also because of reduced interaction with peers, the lack of structure and daily rhythm and for some children school meals, with significant impact on well-being and child protection (99). There is evidence of increased vulnerability and domestic violence for children when schools are closed (100). In The Netherlands an increase of child abuse of 81% was reported by an online assistance tool, and was confirmed by National Prevalence Studies of Abuse in Children and Adolescents where child abuse was estimated to have more than doubled, especially in the category of emotional neglect (101). Children with special needs and from less advantaged backgrounds are more likely to suffer, with the risk of aggravating existing inequalities in society (99). Moreover, the economic costs of schools closures are estimated to be substantial, mainly due to reduced parental economic activity (102).

In order to open schools safely, it is crucial that physical distancing measures are in place in order to prevent crowding, and that children and staff are trained to strictly apply hygiene measures in order to prevent transmission. Concrete advice on these measures, including formation of so-called 'bubbles' is now available from several resources (4, 103). Moreover, efficient testing and tracing should be implemented in order to prevent onward transmission if cases occur. A modelling study estimated that in order to prevent another wave of infections, 75% of individuals with symptomatic infection would need to be tested, assuming that 68% of contacts could be traced, and all positive cases would need to be isolated (104).

In conclusion, schools play a limited role in transmission if mitigation measures are implemented, and should only be closed as a last resort because of significant harm to children's mental health, educational opportunities and social development.

Conclusion

Young children are proportionally less often affected by SARS-CoV-2 infection than adolescents and adults. Moreover, children are underrepresented in admissions, complications and mortality. Asymptomatic infection appears to be common in children and although adolescents and immunocompromised children seem to be at higher risk of severe disease, short-term prognosis for children is favourable, even in the rare and clinically variable entity of multisystem inflammatory syndrome. Evolving evidence shows reduced susceptibility and similar or reduced infectiousness of children compared to adults and a very low risk of vertical transmission. Secondary attack rates in schools are low and patterns of infection in school aged children generally follow population incidence. Educational staff does not appear to have a higher risk of infection with SARS-CoV-2 compared to other professions. On the other hand, children's mental health, educational opportunities and development can be significantly impeded by school closures, which should therefore remain a last resort. Transmission dynamics might change with the spread of new variants and vigilance is required. In the future, less invasive and faster testing methods might contribute to close monitoring of transmission and facilitate health policy decisions.

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Impact of COVID-19 pandemic on paediatric trainees

Tine Alliet [a,b*], Thomas Gestels [a,c*], Siel Daelemans [a,d], Levi Hoste [a,e,f]

[a] Junior Representation of the Flemish Society for Paediatrics (Jong VVK)
[b] Department of Paediatrics, University Hospital of Leuven, Leuven, Belgium
[c] Department of Paediatrics, Antwerp University Hospital, Edegem, Belgium
[d] Department of Paediatrics, University Hospital of Brussels, Brussels, Belgium
[e] Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium
[f] Department of Paediatric Immunology and Pulmonology, Center for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Gent, Belgium
[*] contributed equally

levi.hoste@ugent.be

Keywords

COVID-19, residency, trainees, paediatrics

Abstract

Background and objectives

The COVID-19 pandemic has put strain on the activities and well-being of health care workers. We aimed to measure the direct and indirect impact on a personal and professional level for paediatric trainees in Flanders, Belgium.

Study design

Junior representatives of the Flemish Society for Paediatrics (Jong VVK) conducted a longitudinal study among their fellow paediatric trainees. The impact of COVID-19 on daily tasks, education and emotional well-being for the first (March-April 2020) and second wave (October-November 2020) of the pandemic were studied.

Results

One hundred and nineteen surveys were completed in the first wave, representing data of 51% (119/233) of the total number of paediatric trainees in Flanders. Eighty surveys were completed in the second wave. Educational program changes occurred in 25% (30/119) of trainees and more than half (61%; 72/119) described the pandemic as an impediment for their educational progress. The perception of impaired education persisted for 30% of the responders (24/80) during the second wave. One out of three (30%; 35/119) felt their job was more exhausting than usual and 38% (45/119) perceived more stress at work. These numbers were comparable at both time points. Increases in stress paralleled with increased irritability in daily life and poorer sleep quality.

Conclusions

COVID-19 had an important impact on the daily tasks, education and emotional well-being of the paediatric trainees. Medical training centres should be aware that there is a perception of impediment on the educational program of the paediatric trainee.

Introduction

The novel coronavirus, known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and causing coronavirus disease 2019 (COVID-19), has spread rapidly from a local cluster of severe pneumonia cases in Wuhan (China) in December 2019 to a pandemic crisis. It has led to a massive disruption of individual and societal structures and caused important health care-associated and socioeconomic consequences in all parts of the world in a few weeks' time (1). Entire health care systems were forced to swiftly adapt to this unprecedented scenario to prepare for a massive influx of COVID-19-associated hospital admissions and to prevent collateral damage in patients with alternative or chronic conditions.

During the pandemic, Belgium recorded the highest death rate in the world as a consequence of COVID-19 in March 2020 (84.45 deaths per 100,000 population) and with a rate of 1,735 cases per 100,000 inhabitants in 14 days, it had the highest rate of SARS-CoV-2 infections in Europe in November 2020 (2).

The unprecedented measures that were necessarily taken inside and outside the hospitals have put strain on the personal and professional activities and well-being of health care workers (3). Although COVID-19 mainly presents with (severe) disease in the elderly population with co-morbidities and therefore primarily affects adult care, other specialties were not spared from the consequences of this crisis either. Of all health care work forces, especially trainees in several medical specialties were exposed to COVID-19 patient care and felt an immediate or indirect impact from the crisis (4). This observation has been made by various medical specialties such as cardiology, urology, plastic surgery, neurosurgery, radiology, otolaryngology, ophthalmology, anaesthesiology, cardiothoracic surgery and general surgeons (5-15). COVID-19 also had an impact on the curriculum of (medical) students which was yet described in detail (16).

Medical trainees are a unique group of doctors who are still in a learning process to become a specialist but who, simultaneously, are also responsible for the care of patients. Paediatrics is a specialty that is familiar with infectious diseases and is acquainted to tackle epidemics causing temporary periods of high clinical demands (e.g., respiratory infections in winter months). Nevertheless, it is unlikely that the unseen measures necessary to tackle the challenges associated with the COVID-19 pandemic and the inevitable impact on health care systems, work forces and (lack of adequate) resources would not put significant burden on trainees in paediatrics. Few articles were published on the experiences of paediatric trainees during COVID-19. Sanghavi et al. found that 21% of American paediatric trainees displayed symptoms of a mild depression and 7% of

a moderate depression (17). Babal et al. found anxiousness in 71% of paediatric trainees in the USA, angriness in 53%, sadness in 53%, and detachment in 41% (18).

In this study, we aimed to measure the direct and indirect impact of the COVID-19 crisis on a personal and professional level in Flemish paediatric trainees.

Materials and Methods

An electronic questionnaire was drafted by junior representatives of the Flemish Society for

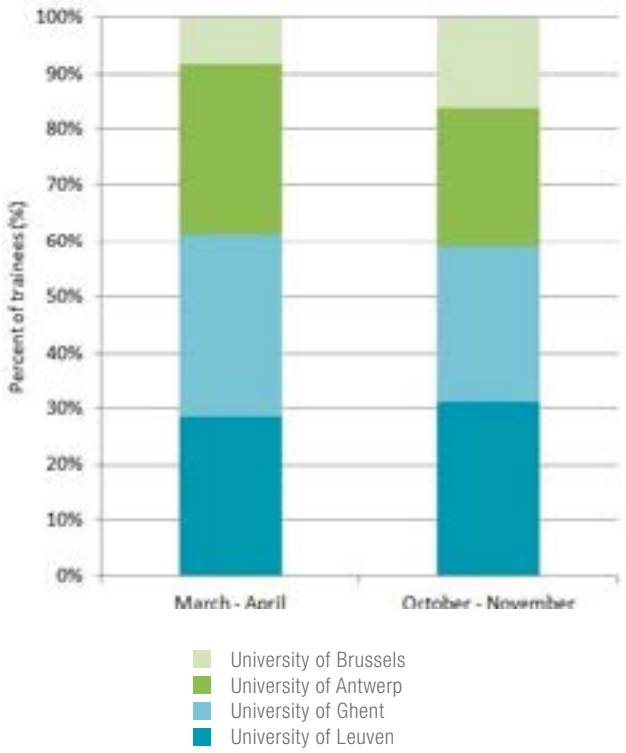
Paediatrics (Jong VVK) and was tested for its technical functionality prior to dissemination. The questionnaire was sent out to fellow trainees in paediatrics at the four Flemish universities (University of Antwerp, Ghent University, Catholic University of Leuven and Free University of Brussels), either by contacting them directly or by e-mail. In the questionnaire, participants were informed about the duration of the survey, the investigators and the purpose of the study. To minimize recall bias, data concerned current opinions and the participants were asked to recollect data on the past two months. Two similar surveys were sent out after each epidemic wave in Belgium: the first at the end of April and the second at the end of November. Trainees that initiated their training in October 2020 were excluded in the second survey because they were not able to answer questions that compared the first and the second wave. Trainees were given a deadline of two weeks to complete the survey. No incentives were offered. The number of questions per page was two to five with a total of seven pages. All questions had to be answered before the questionnaire could be sent to the investigators. The survey consisted of basic demographic data (such as the university training hospital, current hospital and years of training) and three parts regarding the pandemic. The first part mainly addressed changes in daily tasks in the hospital (e.g., care for adult patients, working in other departments, changes in working hours or working from home,…), while the second and third part explored the impact on an educational level (added value or obstruction as a result of the crisis) and psychosocial well-being (e.g., emotional stress, fatigue, irritability,…), respectively. In this final part, trainees were asked to contemplate on 16 different statements and relate to them by answering on a Likert scale (completely agree - rather agree - neutral - rather disagree - completely disagree). The second survey contained multiple comparing questions about differences between the first and second peak. Answers were anonymized for the researchers. Junior trainees were defined as first- or second years. Senior trainees were defined as being at least in their third year of education (standard trajectory in Belgium comprises of five years of full-time education).

Non-parametric statistical tests were used, according to results of normality tests (Shapiro-Wilk). Mann-Whitney U and Kruskal Wallis test were used in the data analysis depending on the number of variables. For statistical analysis, dichotomous variables were created from statements declaring agreement (completely/rather agree = true, neutral/rather/completely disagree = false).

Results

One hundred and nineteen surveys were completed by individual trainees after the first epidemic wave, which consists of 51% (119/233) of the total number of paediatricians currently in training at the four targeted universities (Figure 1). The second questionnaire was filled in by 80 trainees, a lower number that could mainly be attributed to exclusion of the first years in training. Most of the trainees were part of a clinical training program. Only 19 out of the 119 (16%) trainees were involved in a research program. This fraction was slightly higher in the second survey (15/80; 18,8%). There was a homogeneous spread of years in training (seniority), with an expected overrepresentation of second years in the first survey and third years in the second survey, as this year consisted of an almost double cohort due to shortening of the medicine study program from seven years to six years (resulting in two cohorts of medical students graduating at the same time).

Figure 1 : *Response per university for both questionnaires. All four Flemish universities were represented in both questionnaires (March-April and October-November).*



As stated above, first-year trainees were excluded in the second survey. The majority (55%; 65/119 and 59%; 47/80) of respondents was working in a university hospital at the time the questionnaire was sent out. The second largest group (39%; 47/119 and 35%; 28/80) was working in a district hospital. The remaining seven trainees from the first survey were either employed in a research facility (2), a revalidation centre (2), abroad (2) or doing a combination of on calls and working from home (1). In the second survey the remaining responders were either working abroad (2), in a revalidation centre (1) or in a research facility (2) (Figure 2). Two thirds (63%; 50/80) were working in different hospitals during the two epidemic waves.

While most of the paediatric training programs were not directly affected by the COVID-19 pandemic, both during the first and second peak, 1 out of 4 respondents did experience a change in their program. Trainees working in a university centre in the first lockdown (23/65) were significantly more affected compared to trainees in district hospitals (7/47; $P<0.05$). For most of the trainees with a change in program (60%; 18/30 in the first peak and 57%; 12/21 in the second peak), the adjustments of their schedule were implemented for less than or equal to one month. Nevertheless, for the remaining 40% (12/30) and 42% (9/21), more than 1 month of their training was affected.

When analysing the workload and working hours of the first wave, most trainees experienced either no difference or a decrease in both workload and working hours compared to their usual workload and working hours (Figure 3). Only 13% (16/119) felt their workload had increased and 12% (15/119) replied that they had worked more hours. However, an increase in workload was significantly associated with increased working hours ($P<0.001$), feelings of unsafety ($P<0.001$), more stress and exhaustion at work ($P<0.05$), needing to do uncomfortable tasks ($P<0.05$) and worse sleep quality ($P<0.05$).

This was unchanged for the majority of trainees during the second wave, although 29% (23/80) felt their workload had increased when compared to the first wave and 34% (27/80) worked more hours as compared to the first wave (Figure 3).

Figure 2 : *Working environment.*
This figure shows the percentage of trainees working in a university hospital, a district hospital, a revalidation center or abroad for each training year in the first questionnaire (March-April = a) and second questionnaire (October-November = b).

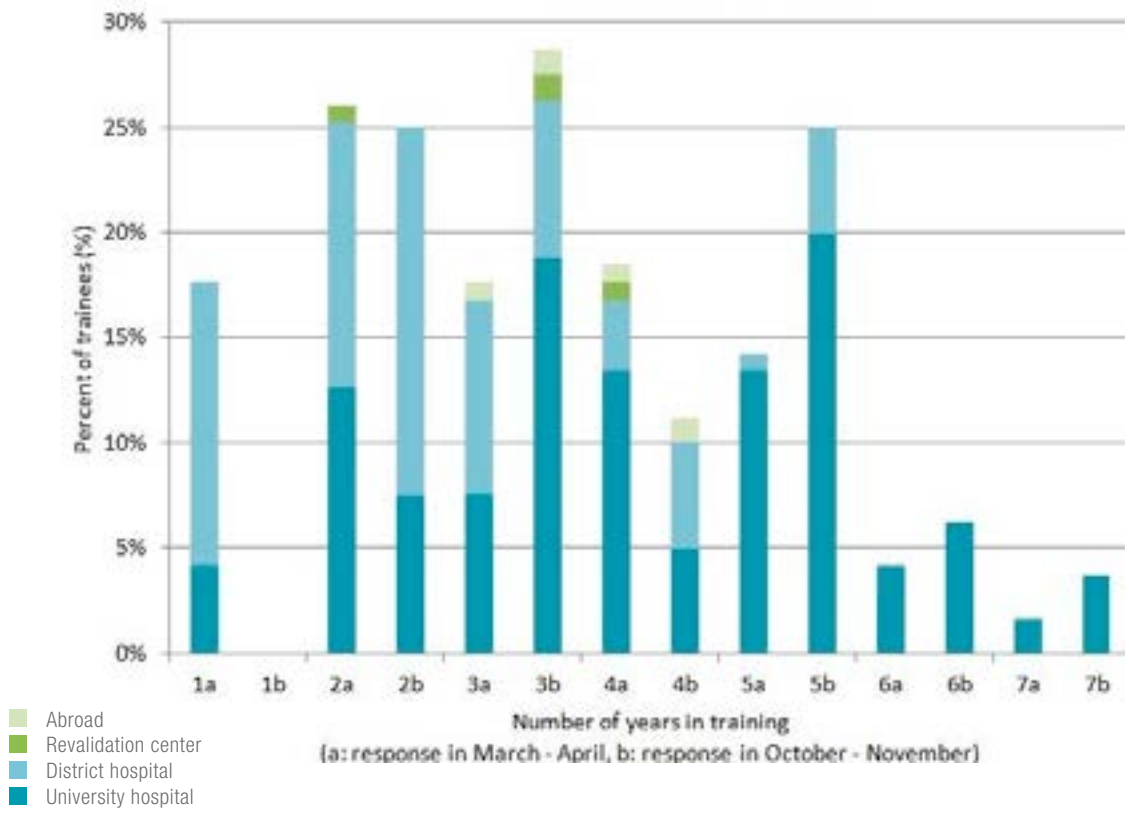


Figure 3 : *Workload and working hours.*
This figure showed the perceived workload (left) and working hours (right) from the first wave (March-April) compared to pre-COVID-times and the second wave (October-November) compared to the first wave.

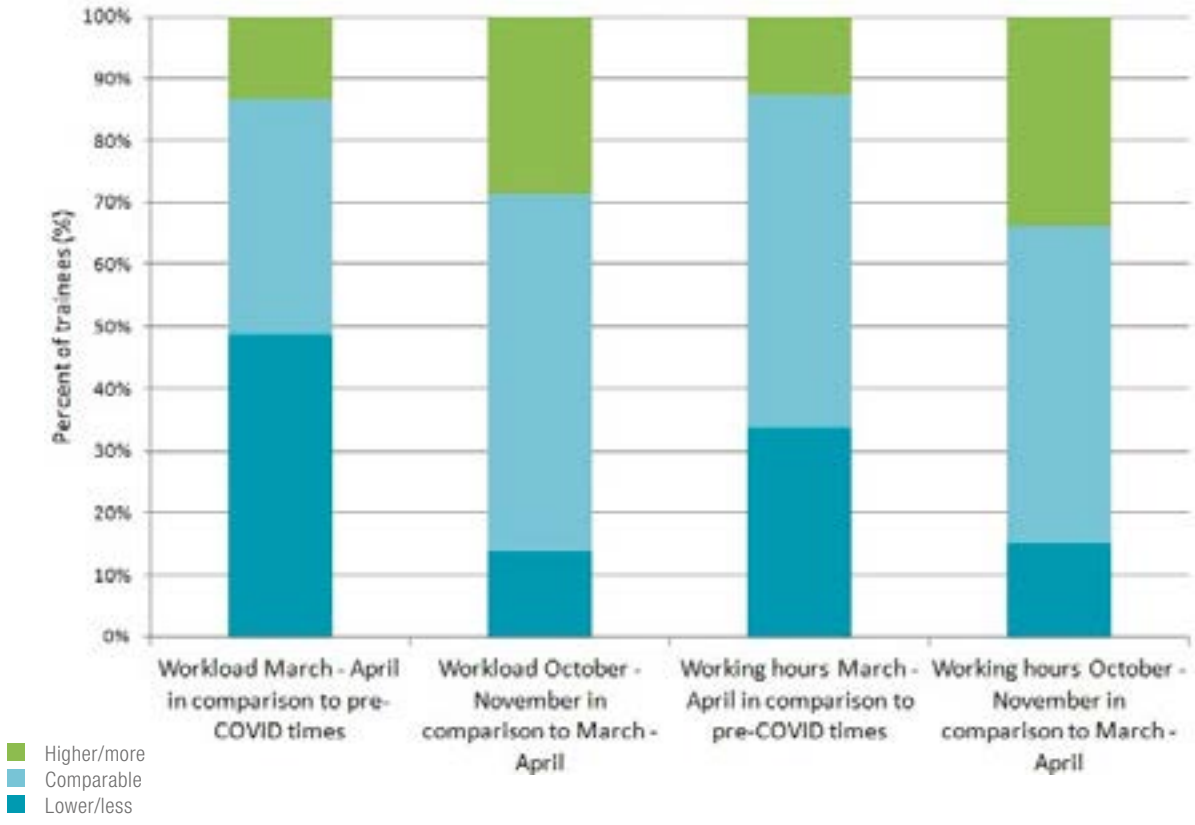
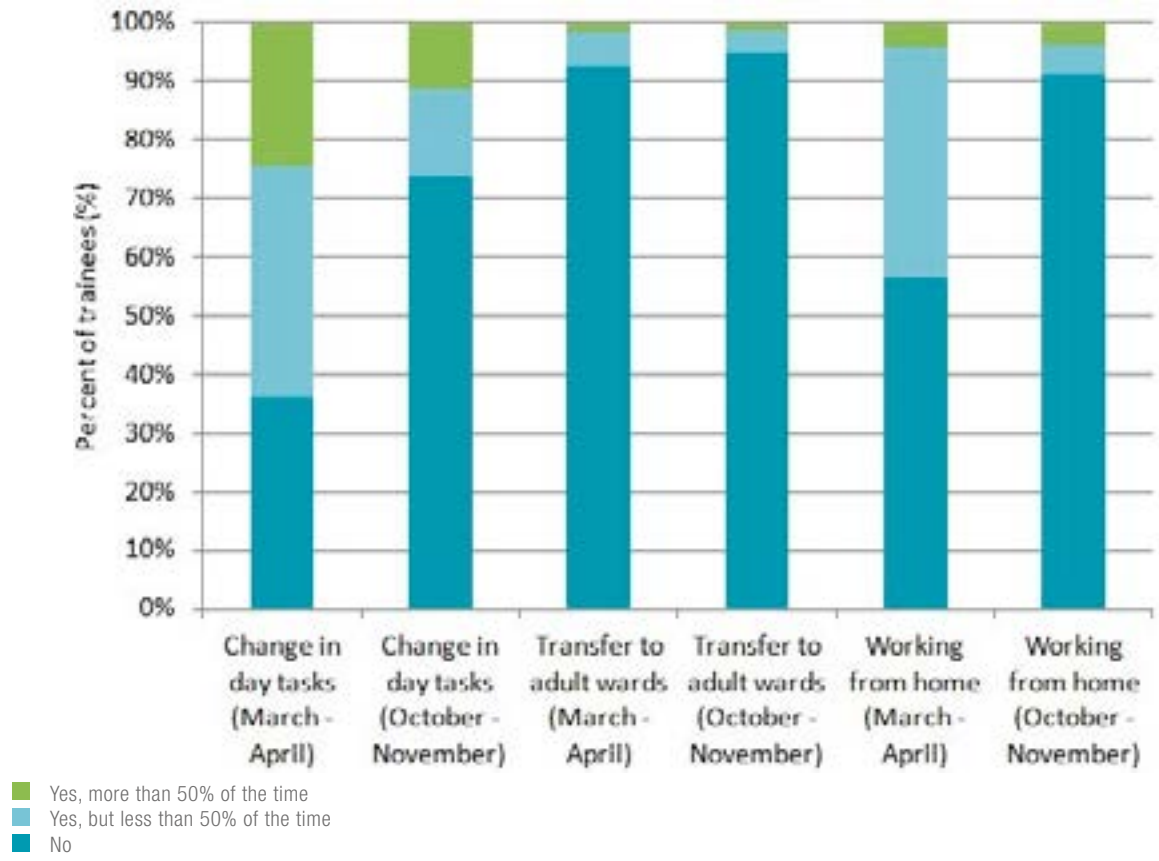


Figure 4 : *Change in content of the working day.*
Proportion of trainees who experienced a change in the day tasks (left), who were transferred to an adult ward (middle) and who were working from home (right) in the first and second questionnaire.



In contrast to workload and hours, the content of the working day did change for most paediatric trainees during the first peak. Only a third of respondents (36%; 43/119) said their daily job had not changed at all. Often this meant doing different tasks within their own department. Only 8% (9/119) were asked to help out on the adult wards and 5% (6/119) were assigned a different function (e.g., nursing care) (Figure 4). Senior trainees were significantly more at risk for having a change in their program (25/67; $P<0.05$) as compared to juniors (7/52). On the other hand, juniors were significantly more at risk of carrying out another function in the hospital (6/52; $P<0.05$), whereas no single senior trainee carried out a non-medical task during the crisis.

During the second COVID-19 wave, working day content was unaffected for 74% (59/80) of the trainees. In contrast to the first wave, only 5% (4/80) were transferred to assist in patient care on adult units (Figure 4).

Remarkable is that almost half of all the trainees who answered the first questionnaire (44%; 52/119) were at least partially working from home (Figure 4), which occurred significantly more in trainees working in university hospitals (45/65) as compared to district centres (3/47; $P<0.001$). Since only 14% (17/119) of participants had to self-isolate due to symptoms, this was not the main reason for the increase in homework. Working from home was most likely initiated to prevent all medical staff to be present at the same time, to ensure physical distancing and thereby preventing the spread of the virus. The proportion of trainees working from home did not declare being more stressed at home, did not feel less part of a team or did not feel useless in the crisis. The number of trainees working from home decreased massively in the second wave (9%; 7/80) (Figure 4). Absence because of health issues due to confirmed or suspected COVID-19 remained rather exceptional (5%; 4/80).

Even though some of the training schedules had fewer working hours compared to the regular working rota, income was unchanged for the large majority (89%; 106/119) of the trainees. For 3 of the 119 responders pay had increased, while 10/119 stated to have lost income. A single trainee even reported an income reduction of more than 25%. Working from home did not result in a higher proportion of trainees with a reduction in income. Juniors however, had a more frequent decrease in payment during the crisis (9/52) as compared to seniors (1/67; $P<0.05$).

Half of the trainees (56%; 67/119) declared having a great interest in paediatric specialties directly related to COVID-19 (respiratory diseases, infectious diseases, epidemiology, immunology, acute paediatrics or intensive care). Only 16% (19/119) showed little interest. Most trainees stated that the pandemic did not change their interest level in these domains. More interest in COVID-19 related specialties did not significantly increase well-being. The pandemic did not influence the choice for paediatrics for the vast majority (71%; 85/119). For 28% (33/119) their career choice was even positively reinforced.

Unfortunately, 61% (72/119) of paediatric trainees experienced this pandemic as an impediment for their educational progress. This remained the case for 70% (56/80) in the second questionnaire, notwithstanding 64% (36/56) stated this had already improved when compared to the first peak.

Despite the fact that a third of the trainees (34%; 40/119) were provided with COVID-19 related courses by their training institute and about 29% (34/119) were able to enjoy COVID-19 related teaching in their training centre, 81% (96/119) felt they mainly had to educate themselves to expand their knowledge about the new coronavirus. This remained unchanged in the second wave, and an even larger proportion stated to mainly have been responsible themselves for their education on COVID-19 (84%; 67/80). Declaring that self-study comprised the largest part of education was found more frequently in trainees employed in district hospitals (42/47), as compared to trainees in university centres (48/65; $P<0.05$).

Figure 5 : *Impact on end terms.*
Trainees' perception of the impact of the COVID-19 crisis in meeting their clinical and technical (left) and administrative (right) end terms.

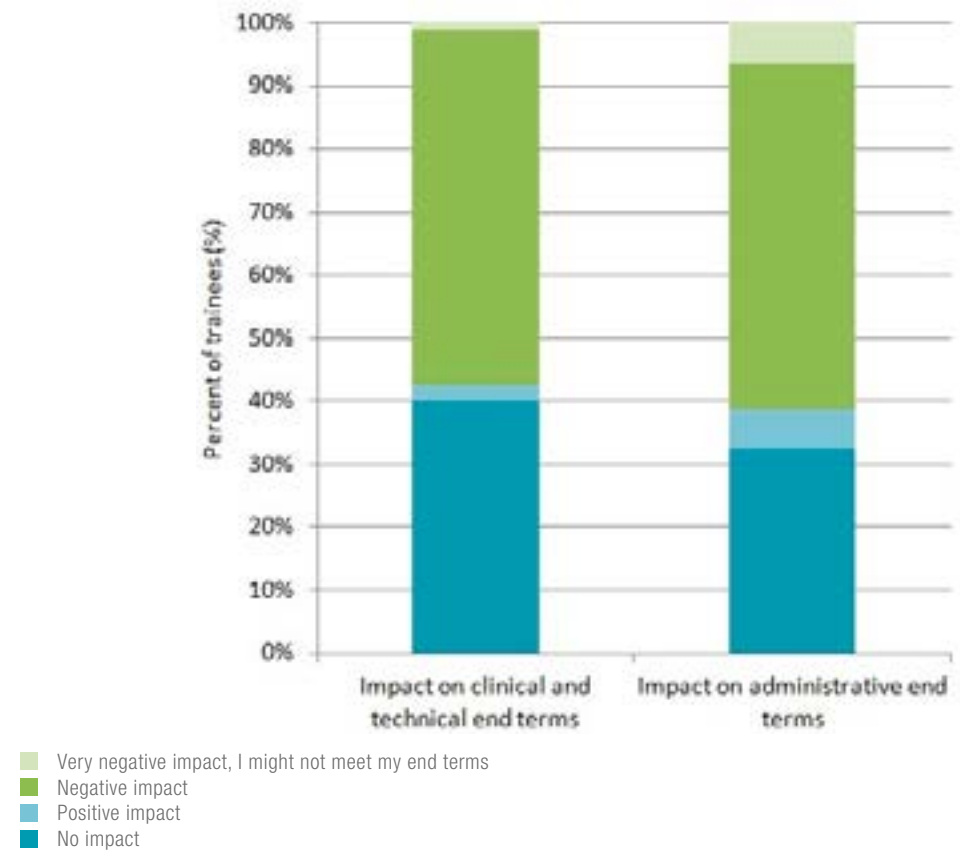
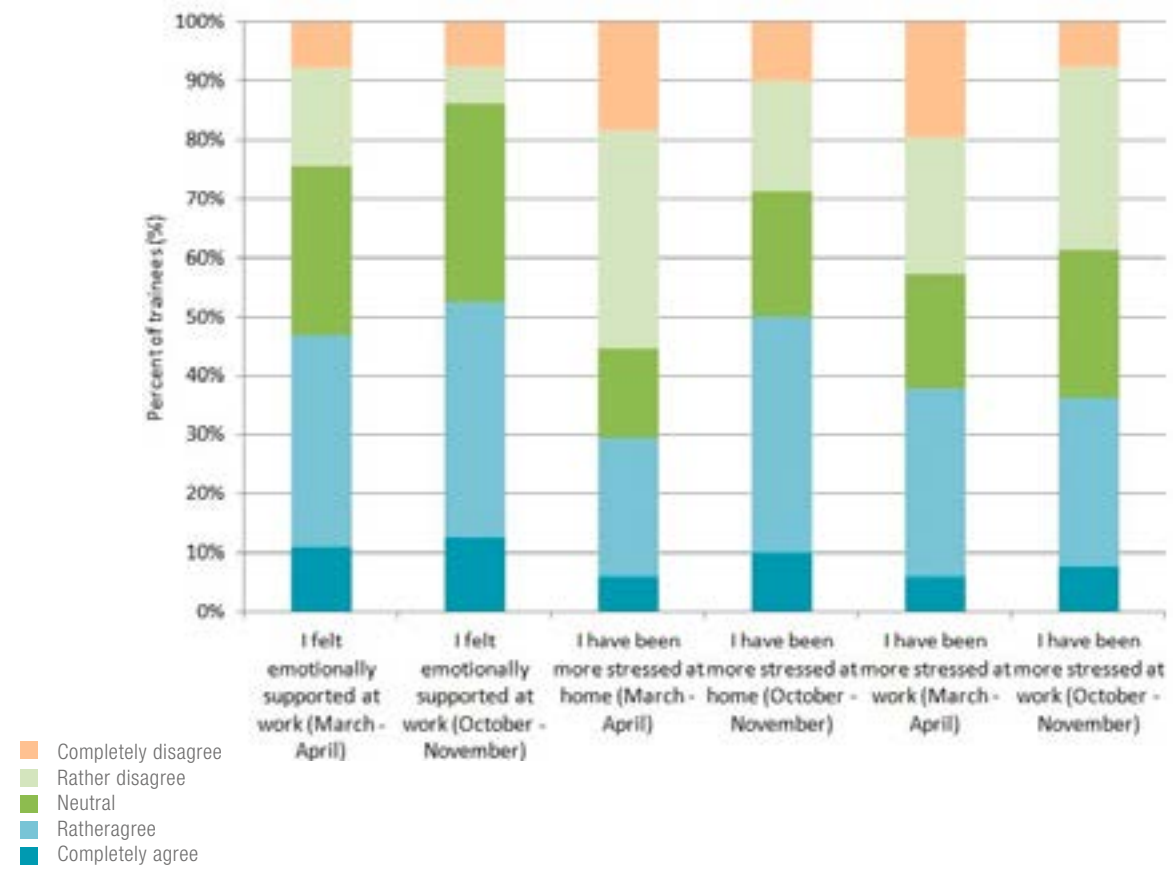


Figure 6 : *Stress and emotional support.*
This figure shows how trainees felt they were supported at work (left) and if they experienced more stress at home (middle) or at work (right) in both waves.



Education in general seems to have improved during this coronavirus pandemic when comparing the educational availabilities at the beginning of the pandemic to the situation by the end of the year, according to 41% (33/80) of the responders. Online teaching and re-introduction of teaching in the hospital were mentioned most often as an explanation for this improvement. Nevertheless, a relevant proportion of trainees did not experience this improvement. Twenty-nine percent (23/80) of the trainees felt little to no change and 30% (24/80) even responded that education was even worse in the second wave when compared to the first one.

Trainees were asked to evaluate the effect of the entire pandemic on their clinical, technical and administrative end terms (Figure 5). Administrative end terms included master papers, other publications and professional recognition criteria. Concerning clinical and technical end terms, 40% (32/80) felt no impact, 3% (2/80) experienced a positive impact but the majority (57%; 46/80) felt a negative impact of which one trainee even stated that this might influence his/her end terms attainment. For the administrative end terms, an even greater proportion declared to have encountered a negative impact (61%; 49/80), of which five trainees feared failure to achieve their end terms.

As reported above, the number of working hours was not greatly affected for most trainees. Nonetheless, one out of three (29%; 35/119) felt their job was more exhausting than usual and 38% (45/119) was more stressed at work (Figure 6). This observation was significantly more frequent in junior trainees (25/52), as compared to seniors (20/67; $P<0.05$). These numbers remained largely unchanged in the second questionnaire. This increase in stress was often present at home too, as 43% (51/119) of the trainees stated their stress levels at home were higher than usual in the first wave with a slight increase in the second wave (50%; 40/80) (Figure 6). A smaller group of 21% (25/119) felt unsafe at work and had concerns for their own health. These concerns were troubling more trainees in the second wave (32%; 25/80). Trainees with feelings of unsafety declared significant higher workload (13/35; $P<0.001$) and working hours (10/35; $P<0.05$), more exhausting work (26/35; $P<0.001$), more stress at work (26/35; $P<0.001$) and worse sleep quality (18/35; $P<0.05$).

The increase in stress resulted into increased irritability in daily life for 26% (31/119) and in poorer sleep quality for 29% (35/119) of the trainees which remained unchanged during the second peak.

Unfortunately, less than half of the trainees answered positively when asked about the provision of emotional support at work (47%; 56/119) (Figure 6). A quarter (24%; 29/119) disagreed when asked whether they were sufficiently supported. Sadly, the availability of emotional support at work did not change during the second wave according to the majority of the responders (69%; 55/80).

When asked whether the trainees felt more part of a team than usual during the pandemic, almost half of them (45%; 53/119) had no opinion about this subject. A third (34%; 41/119) agreed and unfortunately a fifth (21%; 25/119) disagreed. It is worth noting that feeling emotionally supported at work significantly increased the proportion of trainees declaring the crisis as an added value (23/41; $P<0.05$) as compared to not being supported (24/78).

Exactly half of the trainees replied that relaxing outside of work has been more difficult than usual due to the lockdown restrictions. This number was significantly higher in the second wave (88%; 70/80). For another 14% (17/119) relaxation was more difficult due to work or other reasons (e.g., family related). Controversially, almost a quarter (23%; 27/119) stated that relaxing outside of work was easier than usual. Feelings of stress at work correlated with higher proportions of workload ($P<0.05$), needing to do uncomfortable tasks ($P<0.05$), feeling more stress at home ($P<0.05$), having worse sleep ($P<0.05$), feelings of exhaustion and unsafety ($P<0.001$), and feeling less part of a team ($P<0.05$) or less useful in the crisis ($P<0.05$). Even though we know paediatric patients were less severely affected by COVID-19, 15% (18/119) declared that they were confronted more often with severe illness and end-of-life decisions during this pandemic. This number remained high in the second survey (19%; 15/80).

There has been a lot of media attention for medical staff, hospital funding and healthcare organisation due to the current pandemic. A third (34%; 40/119) of trainees however, felt their job should receive more respect after this pandemic. More than half of the respondents (57%; 68/119) declared they did not feel very useful in the battle against SARS-CoV-2 and only a minority (19%; 23/119) confirmed that they felt useful during the pandemic. Contradictory with these results, only 21% (25/119) wished they could have played a different role in the pandemic. These numbers were comparable in the second survey.

Discussion

This longitudinal study, conducted in paediatric trainees in Flanders, Belgium, confirms our research hypothesis that although the paediatric specialty was relatively spared from the direct consequences of the COVID-19 pandemic, its impact was indirectly felt in the daily tasks, education and emotional well-being of the trainees.

Although the majority of trainees in this study saw no reduction in workload or hours in the clinic, the overall appreciation of their education was insufficient and was frequently labelled as obstructive for their training goals. Strikingly, although still in a didactical environment, knowledge concerning COVID-19 was most often gained from self-study. Although the pandemic evidently forced us to swiftly adapt traditional educational activities to an unfamiliar and largely virtual learning environment, the technological tools and skills that we currently employ should from now on pave the way for accessible distance learning to provide sustained educational programs for every trainee.

Thankfully, several actions with the aim to optimize trainees' well-being and education have already been proposed, such as adequate access to personal protective equipment, sufficient support (at the level of both the trainee program and the institutions) and instituting telehealth education programs (6). As the current pandemic forces us to leave the more traditional teaching model of high case volumes and passive learning behind, training centres should embrace these circumstances to deploy resources towards these internet- and video-based learning, simulator training and more individualised educational models. The deployment of such smart-learning technologies in order to limit the impact of the COVID-19 on the learning curves of trainees has already been proposed in other specialty trainings, such as urology, gastroenterology and dermatology (7,19,20). Practical tips for supporting competency-based medical education have already been published (21). If sufficiently offered, these new training methods and technologies may allow for fulfilment of important and individualized educational goals that may not have been met in the past.

Besides medical education, the impact on mental well-being may not be forgotten. In this study, one out of three paediatric trainees were more stressed at work, and this was especially so for junior trainees This increase in stress resulted into increased irritability in daily life and poorer sleep quality. A quarter of the trainees did not feel sufficiently supported at work and the majority of trainees stated that relaxing outside of work was more difficult. Luckily most trainees were, despite this, still positive about their career choice. But, knowing this world crisis is a marathon and not a sprint, a long-lasting combination of these factors can contribute to the development of burnout. Burnout prevalence is known to be high in trainees, also during this pandemic (22,23). It is thus important in such a crisis to install monitoring systems early on and offer psychological support to those in need. Dispatching trainees to perform patient care outside their clinical competencies, such as is reported in this study, is however a risk (24). Feelings of anxiousness and vulnerability have indeed been observed in trainees serving on the pandemic's front lines, which was confirmed by an important share of our cohort (25). Safety concerns in particular were believed to be an important asset to

these feelings. A survey among local residents (263 participants) in China already showed that 52% of participants felt horrified and apprehensive due to the pandemic. An open learning environment and resilience training programs have been suggested to respond to these feelings of hopelessness and burnout (26).

Generally speaking, the COVID-19 pandemic could and should be an important learning opportunity, especially on generic skills such as professionalism, quality and safety in care and tackling ethical dilemmas that have risen during this crisis. Mastering these tools is highly valuable to every paediatrician and should transcend the subspecialty divisions. As such, both trainees with interests directly related to COVID-19 patient care (infectious diseases, immunology, respiratory medicine,...), but also trainees without these specific interests should be in a position to benefit from this period, and subsequently none of them should label this crisis as an obstruction for their educational goals. Taking into account the findings of this survey, prompt and customized action is thus required to meet the presumed educational shortcomings. COVID-19 is one of the many infectious diseases of the past decades and will most certainly not be the last for this generation. These outbreaks will most likely become more common given increasing urbanization rates, the widespread accessibility of air travel, and worsening climate change (27). Therefore, it is of most importance to take appropriate lessons from this period and seize the opportunity to adapt and act relevant in the preparedness for the next crisis. Priority areas central to promoting and maintaining the well-being of health care work forces, including trainees, have already been identified in this crisis and should be used to provide support at both the residency program and institutional or governmental policies (28). A recent publication addressed the well-being of trainees during COVID-19 and proposed a Modified Maslow's Framework to tackle the needs of the trainees' educational program, within and outside their institution (29). Program leaders can take the opportunity to reflect upon their training programs based on this framework and should improve them based on our data.

Besides taking care of patients, trainees are fulfilling an academic training. The COVID-19 pandemic was perceived as an impediment with negative consequences on clinical and technical end terms by the majority of the participants. This was also the case for administrative end terms with some trainees even fearing to fail to achieve their end terms. Medical training centres should be aware of this and should take preventive measurements to obviate the perceived negative impact.

This study has several limitations. The questionnaire is a self-designed questionnaire based on literature and adapted for the local context and was never formally tested for validity and psychometric characteristics. This questionnaire did not have the intention to identify burnout or other psychological conditions, but rather to collect information on the impact of COVID-19 on paediatric trainees. Another limitation is that this study only represents the Flemish paediatric trainees and our educational setting in Flanders may differ from the educational setting elsewhere which can interfere with future comparisons. Because the questionnaire was anonymised, it was not possible to determine how many trainees answered the questionnaire twice.

In the aftermath of COVID-19, it is not unlikely that the burden on paediatrics might be undervalued when essential policy decisions are being taken. Based on the findings described above and without compromising the appreciation for their respective efforts, one should be cautious not to allocate all possible resources solely towards the specialities that were most prominently on the front lines of COVID-19 patient care (e.g., emergency medicine, critical care, internal medicine...). Taking into account that both budgetary and organizational resources will always be limited in health care systems, the post-pandemic period will inescapably require protracted and dire policy decisions to allow for an optimal recovery from the psychosocial and economic harm done by this virus. This survey might contribute to the plea that paediatricians, and their trainees, should not be forgotten in this aftermath.

Conclusion

Paediatric trainees were affected by the SARS-CoV-2 pandemic on essential domains of occupational and educational activities and emotional well-being. The results of this cohort study should be taken into account in policy making and resource distribution in the early aftermath of the pandemic, with the plea that paediatricians and their trainees should not be forgotten when allocating educational and psychosocial support.

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NUTRICIA

Hemoptysis caused by the unilateral absence of a pulmonary artery: a noteworthy diagnosis

Sophie Pohlen [a], Valentine Weber [b], Nicolas Arribard [c], Nasroola Damry [d], Christine Quentin [b]

[a] Pediatric Fellow. Hôpital Universitaire des Enfants Reine Fabiola (HUDERF). Brussels, Belgium.
[b] Pediatric Pulmonology. Hôpital Universitaire des Enfants Reine Fabiola (HUDERF). Brussels, Belgium
[C] Pediatric Cardiology. Hôpital Universitaire des Enfants Reine Fabiola (HUDERF). Brussels, Belgium
[d] Pediatric Radiology. Hôpital Universitaire des Enfants Reine Fabiola (HUDERF). Brussels, Belgium

sophie.pohlen@ulb.be

Keywords

Angiography, children, hemoptysis, unilateral absence of pulmonary artery

Abstract

Unilateral absence of a pulmonary artery is a rare congenital abnormality. The diagnosis is complicated because it remains asymptomatic or exists with non-specific symptoms, unless the abnormality is associated with other cardiac malformations. Hemoptysis is rarely the initial symptom of the malformation, especially in the pediatric population. Computed tomography angiography is the gold standard to confirm the diagnosis. There is no consensus on how the pathology should be managed or treated.

We report a rare clinical case with an initial atypical symptom and review the literature.

Case report

A 13-month-old girl suffering from hemoptysis for two days, during an episode of bronchiolitis was referred to our pediatric service. Clinical examination showed fresh blood in the back of her throat and pulmonary auscultation revealed wheezing. The patient's vital parameters were within normal limits. No other bleeding points were noticed. The anamnesis was able to exclude foreign body aspiration, contact with an irritant product, direct contact with tuberculosis patients and hereditary hemorrhagic diseases prior to the onset of the illness.

The child had been born at full-term by vaginal delivery following a normal pregnancy. Her post-natal adaptation was normal. Upon physical examination at birth three vascular spots were observed on the baby's skin: one on the right knee and two on the left buttock. An ultrasound scan did not reveal any vascular malformation. The patient's medical history mentioned bronchial hyperreactivity treated by inhaled corticosteroids.

Complementary investigations showed hemoglobin to be at 10,4 g/dL (normal value between 13 and 18 g/dL) while platelet and coagulation panel were normal, ruling out the possibility of a systemic hemorrhagic disease. A chest radiograph did not reveal any focus or malformation. Fibroscopy revealed the presence of fresh blood on the vocal cords but no visible active bleeding. Bronchoscopy showed very dilated vessels in the right bronchus, which may have explained the hemoptysis. In addition, a contrast-enhanced computed tomography (CT) of the chest revealed complete absence of the right main pulmonary artery and the presence of collateral circulation arising from the bronchial arteries, intercostal arteries, right internal mammary artery, right subclavian artery and diaphragmatic arteries vascularizing the right lung (fig. 1 and fig. 2). Catheter angiography confirmed the diagnosis of isolated absence of the right pulmonary artery (fig. 3) and showed two important collaterals: a collateral from the right subclavian artery and one originating from the descending aorta. There was no associated heart defect. Pulmonary pressure in the left pulmonary artery was normal (average 18 mmHg).

In summary, only the left lung was involved in oxygenation. The right lung was vascularized by aortic collaterals performing a left-right shunt and, as a result, it only received blood that was already fully saturated. The flow of these aortic collaterals was modest because the child's growth was good. In view of the normal pulmonary pressures and the child's normal growth, the decision was taken to abstain from therapy for the time being. In the event of massive hemoptysis, collateral embolization would have been considered, provided the risk of pulmonary infarct was limited. The child will have to follow a vaccination schedule against pneumococcus and influenza.

One month later, the child returned for recurrence of hemoptysis, caused by an upper respiratory tract infection with influenza. The hemoptysis was limited and did not require any medical intervention.

Discussion

Unilateral absence of a pulmonary artery (UAPA) has been known since 1868 and was first described by Frantzel (1). The malformation is generally associated with other cardiac anomalies and is mostly located on the left side (80 %) (2). Occasionally, the malformation is isolated and in such cases it usually affects the right pulmonary artery (60 %) (2). The prevalence of this rare pathology is estimated at 1/200000 and the mortality can reach 7% caused by massive hemorrhage, right heart failure or respiratory failure (2,3). In case of UAPA, there is an increase in blood flow in the contralateral pulmonary artery resulting in shear stress on the endothelium with subsequent release of vasoconstrictor agents such as endothelin. This results in chronic vasoconstriction of the pulmonary arterioles, leading to remodeling and thus increased resistance in the pulmonary vascular system. The development of pulmonary arterial hypertension leads to right ventricular hypertrophy that can result into right heart failure which can be fatal.

Between 1978 and 2000, Jan Ten Harkel AD et al. have found 108 cases of isolated UAPA that were reported in the literature (4). The authors used the database of the National Library of Medicine. We have used the same database focusing exclusively on the last 10 years, using the key words "isolated absence of pulmonary artery", "children" and "case report". With these search criteria, only 8 cases have been reported over this time period. All cases concerned children under 7 years old, whereas the median age of the cases in Jan Ten Harkel et al. was 14 years (range 0.1 to 58 y), which suggests that this malformation is rarely identified in young children.

When UAPA is associated with other cardiac anomalies, the symptoms may appear early in childhood usually consisting of cyanosis, heart failure, heart murmur or growth retardation. By contrast, isolated UAPA remains

asymptomatic during childhood and goes generally undiagnosed. The median age of diagnosis in the pediatric population is 4 years old (5)range 6 months to 10 years. Most of the cases reported in literature concern adults whose diagnosis is complicated because the symptoms are not very specific: recurrent respiratory infections (37%), dyspnea during exercise (40%) and pulmonary arterial hypertension (25%) (4)diagnostic procedures, and therapeutic strategies of patients with an isolated unilateral absence of a pulmonary artery (UAPA. I.Boudard et al. conducted a retrospective study that included children with UAPA, 75% of them had a symptomatology suggesting asthma, as was the case in our patient (5)range 6 months to 10 years.

Hemoptysis only occurs in 10-20% of cases and is most often seen after observation of systemic collateral vascularization, which has evolved over a number of years (4,6). This explains its absence in the pediatric population. The alveoli are in close contact with the pulmonary arteries, in which pressure is very low, even under stress (20mmHg). In UAPA, vascularization of the lung occurs through collaterals from the systemic circulation, which are subject to higher pressure than normally measured in a pulmonary artery leading to a rupture of their thin walls in case of respiratory tract infection and hemoptysis occurs. To the best of our knowledge, our case report describes the youngest child with hemoptysis as initial symptoms of this pathology reported in the literature to date. We would like to underline the importance of considering pulmonary arterial malformations in the differential diagnosis of hemoptysis in children. In the other few reported cases of infant diagnosis of isolated UAPA reported in literature, the initial signs were cyanosis or murmur (7, 8).

The diagnosis can be suspected on a chest radiograph (3,4)diagnostic procedures, and therapeutic strategies of patients with an isolated unilateral absence of a pulmonary artery (UAPA. This sometimes occurs unintentionally when a different diagnosis was being pursued. The following anomalies can be observed in the adult population: an asymmetry between the two pulmonary fields, a mediastinum shift attracted to the affected side of the lung, an elevation of the ipsilateral diaphragm and a narrowing of the intercostal spaces (2). Differential diagnosis should consider unilateral emphysema, embolism of a pulmonary artery, coarctation of the pulmonary artery and Swyer James syndrome.

Since 1952, angiography has been used as the gold standard to confirm the diagnosis (5). It is the examination method of choice to study the systemic revascularization of the affected lung. Such revascularization is of particular interest in the case of hemoptysis since it directs embolization. Hemoptysis is usually limited, but it can be life threatening when it is substantial. Two approaches are available : embolization and pneumonectomy. Pneumonectomy should be considered in cases of massive hemoptysis, congestive heart failure, bronchiectasis or pulmonary arterial hypertension. In patients having co morbid conditions or for critically ill patients, selective embolization is indicated for the treatment of hemoptysis. This therapeutic approach is safe, effective, well tolerated, minimally invasive and the operation can be repeated. Embolization can also be useful to delay pneumonectomy, as it delays long-term side effects such as scoliosis, thoracic deformity and overdistention of the remaining lung (9). Nonetheless, the embolization procedure can result in complications such as pulmonary infarction, spinal artery embolization, post-embolization syndrome and the procedure has a long-term recurrence rate of 25% (2).

Another promising treatment is the revascularization of the isolated lung at a young age in order to prevent life threatening complications.

The embryologic cause is thought to occur during the involution of the proximal branches of the 6th aortic arch, leading to the absence of the proximal part of the pulmonary artery (7). During embryonic life, there is a distal pulmonary artery which is supplied by an ductus arteriosus. Thanks to this duct, the fetal pulmonary development is normal. At birth, the ductus closes, which leads to homolateral pulmonary hypoplasia and to the development of collateral circulation. A retrospective study has demonstrated that reperfusion of the affected lung before the age of 6 months appears to improve lung growth and to prevent the development of pulmonary hypertension and of collaterals, thus preventing hemoptysis (47%) (10). The techniques that have been used are: persistent ductus arteriosus stenting and the creation of an anastomosis between the main pulmonary artery and the distal part. The retrospective

Figure 1: *Chest CT scan, frontal view.*
Arrows point to an enlarged right internal mammary artery and intercostal arteries.

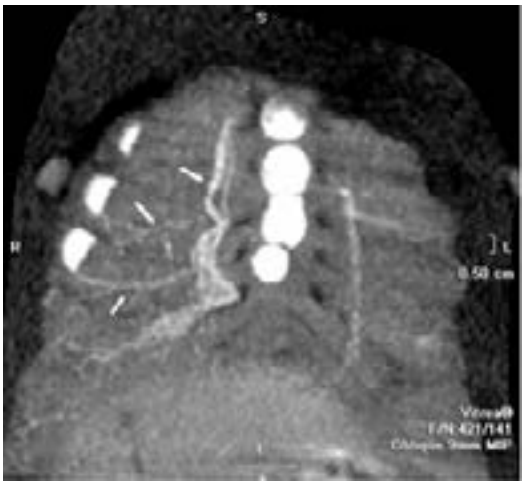


Figure 2: *Frontal CT scan reconstruction shows an unusual collateral vessel (arrows) from the right subclavian artery penetrating the right hilum.*

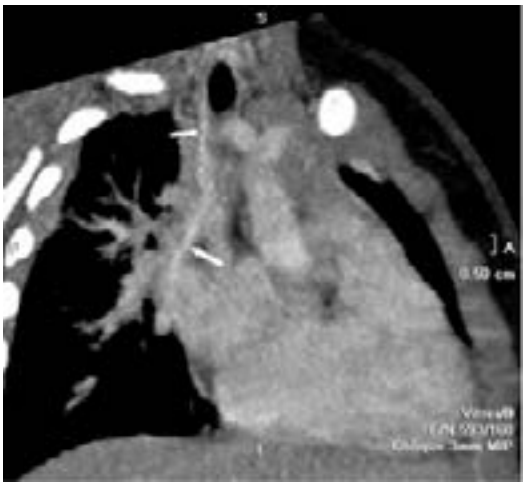
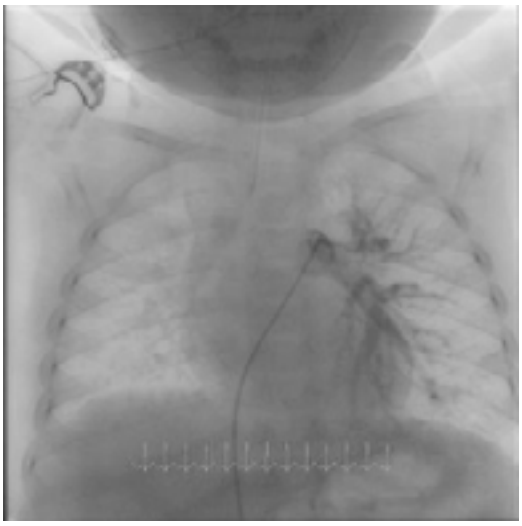


Figure 3: *Catheter angiography showing absence of the right main pulmonary artery.*



study shows that good post-natal lung growth requires adequate pulmonary vascularization.

The youngest case reported in recent literature concerns a 2-day-old child. The baby had a heart murmur on clinical examination, which lead the doctors to perform a cardiac ultrasound with Doppler. On further examination, the doctors discovered the absence of the right pulmonary artery, without any other cardiac defect. No medical or chirurgical intervention was deemed necessary in light of the fact that the malformation was isolated, that the child was asymptomatic and that she had regular growth rates at one week of age. Close monitoring of pressure in the left pulmonary artery was recommended. Three years later, the child is still symptom-free and is growing well (8) dyspnea, chest pain, hemoptysis and recurrent pulmonary infections. As patients may remain asymptomatic or have vague symptoms, the diagnosis of isolated UAPA can be difficult to make in infancy. Indeed, most cases described in literature are adults. Due to the rarity of neonatal presentation, there is no consensus regarding the treatment of this malformation. Case presentation: Herein, the case of a two-day-old term female infant, born after uneventful pregnancy, who required a cardiological assessment for a light murmur, is reported; an echocardiogram demonstrated an isolated unilateral absence of the right pulmonary artery, confirmed by means of magnetic resonance imaging (MRI.

Given the rare cases described in pediatrics, there is no consensus yet on treatment. This will have to be the subject of a multidisciplinary discussion. Any decision should take factors into account such as the child's age, symptoms, growth and cardiopulmonary anatomy (2). A decision to rely on monitoring without immediate intervention can work very well: cardiac ultrasound allows us to detect changes in pulmonary arterial pressure as well as changes in the right ventricular function. Even though the median age of onset of the development of pulmonary arterial hypertension is not known, the literature reports that it occurs early on in life (5). For this reason, close monitoring is even more important. Complications would be discovered early on, allowing for prompt action. The disadvantage of this strategy is that a child may develop comorbidities or insufficient lung reserve and then become inoperable. This should be taken into account in the monitoring program. In all cases, close monitoring is essential.

Conclusion

We report this case to raise awareness of this rare malformation. When faced with a child with hemoptysis, one should consider UAPA in the rare etiologies of hemoptysis. Early recognition of the pathology allows proper management and follow-up, which can prevent the development of associated complications.

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Mycoplasma pneumoniae meningo-encephalitis: a case report

Zoë Casier [a], Sylvie Van Molhem [a], Ann Verschelde [b], Linde De Keyzer [c]

[a] General paediatrics, AZ Damiaan, Oostende
[b] General paediatrics, AZ Sint Jan, Brugge-Oostende
[c] General paediatrics, dept. paediatric pulmonology, AZ Sint Jan, Brugge-Oostende

Zoe.casier@gmail.com

Keywords

case report, children, Mycoplasma pneumoniae, meningo-encephalitis

Abstract

Central nervous system manifestations are a known complication in 0.1% of *Mycoplasma pneumoniae* infections. In this case report we present an 11 year old boy with meningo-encephalitis and pneumonia of the right lower lobe. There is clear seroconversion of *Mycoplasma pneumoniae*. After administration of adequate antibiotic therapy, there was complete clinical recovery. *Mycoplasma pneumoniae* should be taken into consideration when neurological symptoms complicate a respiratory tract infection.

Introduction

Mycoplasma pneumoniae is a known causative agent of meningo-encephalitis in children. It is transmitted by droplets and most frequently causes upper and lower respiratory symptoms (1–4). The central nervous system is only involved in 0.1% of the cases, with (meningo-)encephalitis, aseptic meningitis and myelitis as possible neurological presentations (5). Involvement of the central nervous system can be self-limiting, however early administration of adequate antibiotic therapy may be crucial.

Case report

An 11-year old boy is seen at the emergency department (ED) of a regional hospital with persistent fever for 7 days, aggravating headache and photophobia. He also complains of neck stiffness and nausea. For the last few weeks there have been multiple recurrent episodes of fever, accompanied with headache, conjunctivitis and a sore throat. He was seen by his own paediatrician 5 days prior to the ED visit. At that moment, he had a cough, bilateral conjunctivitis and a hyperaemic pharynx. Auscultation of the lungs is normal. Because of the recurrent febrile episodes, a blood test was done with negative inflammatory parameters (5400 WBC/µL; 4500-13000/µL) and CRP 17.5 mg/L (normal <5mg/L). Serologic analysis was negative for Cytomegalovirus (IgG and IgM) and *Mycoplasma pneumoniae* (IgM index <1.1 and IgG <45 U/mL). Epstein Barr virus serology shows a previous infection (IgM negative, IgG positive). A viral infection was suspected, supportive therapy was continued.

Initial clinical examination in the ED shows a drowsy but alert boy who responds to orders. Vital parameters are normal except for tachycardia (heart rate >120bpm, oxygen saturation 100%, blood pressure 101/74 mmHg). There is severe neck stiffness and photophobia. Further complete neurological examination is normal, Glasgow Coma Scale is 14 (E3M6V5). He has no more complaints of cough, although at lung auscultation diffuse crackles are heard in the right lung without respiratory distress. Ear, nose and throat evaluation is normal. There are no more signs of conjunctivitis.

Laboratory findings show leucocytosis (13000 WBC/µL), predominantly neutrophils (10960 neutrophils/µL; (1800-8000/µL)) , and a slightly elevated CRP of 11.7 mg/L. Radiology of the chest shows an infiltrate of the right lower lobe with bilateral hilar adenopathy. Prior to performing a lumbar puncture, a CT-scan of the brain was done, which showed no abnormalities and no evidence for raised intracranial pressure. Examination of the cerebrospinal fluid (CSF) reveals elevated WBC (930 WBC/µL; <5/µL) with 68% neutrophils and 10% lymphocytes, a low CSF glucose level (54 mg/dL; 60-80mg/dL) in relation to the blood glucose level (101 mg/dL) at the time of puncture and raised protein levels (141 mg/dL; 20-40mg/dL). Culture of the CSF remains sterile. Polymerase chain reaction (PCR) on CSF could not detect any causative agents.

However, serology (performed on day 0, but results on day 2) shows clear seroconversion for *Mycoplasma pneumoniae* with an elevation of both IgM (index 4.2) and IgG (>456U/mL) titres. In the ED as well as at his own paediatrician, the ELISA method was used for detection of antibodies. Nasal swab (PCR method) revealed *Mycoplasma pneumoniae* as well. Magnetic resonance imaging of the brain and electroencephalogram were not performed during initial work-up

The boy was diagnosed with meningo-encephalitis and pneumonia of the right lower lobe and hospitalized. An atypical causative agent was suspected and he was started on ceftriaxone, azithromycin and doxycycline.

Within 72 hours after admission, the boy was afebrile and his symptoms disappeared. Ceftriaxone and doxycycline were both administered for 5 days, azithromycin was given for a total of 10 days. He was discharged after 8 days of hospitalisation. There are no neurological sequels at 6 months follow up. Basic immunologic work-up did not reveal any abnormalities.

Discussion

Definition and pathogenesis

Mycoplasma pneumoniae is a common infectious agent in the paediatric population (5). The highest prevalence is noted among children between 5 and 15 years old (1,3,4,6–9). It is transmitted by droplets. Infections most frequently lead to upper and lower airway symptoms (1–4). However, several extrapulmonary manifestations have been described, with involvement of the central nervous system being the most common (1–3,5). Of all hospitalized patients with *Mycoplasma pneumoniae* infections, the reported incidence of neurological manifestations ranges from 1-10%(1,7–9).

Inflammation of the brain tissue and meninges in meningo-encephalitis causes headache, fever, meningeal signs, convulsions, focal neurological symptoms and an altered mental state (1,3,8–10). When these symptoms are preceded by an upper respiratory tract infection in the previous days to weeks, *Mycoplasma pneumoniae* must be taken into consideration(1,2,8). The interval between onset of respiratory and neurological symptoms ranges from 2 to 14 days (1,3,9). In our patient, onset of neurological symptoms was 1 week later than the respiratory symptoms. However, there is not always a precedent of an upper respiratory tract infection and some studies even state that there is no association with respiratory symptoms (1,3,8,10).

Several hypotheses for extrapulmonary manifestations have been suggested(1,7,9). Recently, the community-acquired respiratory distress syndrome (CARDS) toxin has been discovered (2,4). It is an adenosine 5'-diphosphate-ribosyl transferase and appears to have a significant role in the cellular damage and inflammation seen in

the respiratory epithelium of *Mycoplasma pneumoniae* infected patients (2,4). The extrapulmonary manifestations are now thought to be the result of an auto-immune response of the host (4). This could explain why failure to detect *Mycoplasma pneumoniae* in the CSF, by PCR or direct culture, is not uncommon (3,5,6,8–10). In our case, both PCR and culture on CSF were negative for Mycoplasma pneumoniae. In addition, central nervous system involvement is possible through direct invasion of the pathogen in the central nervous system(5,6). There is some evidence that infection with *Mycoplasma pneumoniae* makes the patient more susceptible to invasion by other pathogens, and vice versa (1,3,4,9,10). Other pathogens, known for their role in causing meningo-encephalitis, should thus be ruled out as co-infections are frequently seen.

Clinical and biochemical findings

On clinical examination, auscultation of the lungs often reveals expiratory wheeze and scattered rhonchi when lower respiratory tract involvement is present (4). Laboratory findings show a normal to elevated leukocyte count and possibly elevated sedimentation rate (2,4,6). On chest X-ray unilateral bronchopneumonia with hilar adenopathy might be observed, as was seen in our patient (2,4). Examination of the CSF in patients with *Mycoplasma pneumoniae* associated meningo-encephalitis often shows pleiocytosis and an elevated protein count with normal glucose levels (3,7–10). In some cases, this is only observed after repeated lumbar puncture (8). Isolation in the CSF of this pathogen is proof of direct invasion and thus establishes the diagnosis of *Mycoplasma pneumoniae* meningo-encephalitis (2,4,6,8,10). Imaging of the brain in suspected meningo-encephalitis patients ranges from normal to focal diffuse oedema, with abnormalities most frequently seen on MRI (3,8,9). Electroencephalogram is frequently abnormal, with focal or diffuse changes (3,9).

Serological methods can be used to detect *Mycoplasma pneumoniae* antibodies (4). Previously *Mycoplasma pneumoniae* infection was confirmed by complement fixation tests, but they lack sensitivity and specificity (6). Enzyme immunoassays (such as the ELISA technique) are more capable of detecting an acute infection than complement fixation tests (2). However, enzyme immunoassays lack sensitivity as cross-reaction with other Mycoplasma species makes them sensitive to false-positive results (2). IgM antibodies appear in the first weeks after onset of symptoms, with peak levels at about 3 weeks (2,4,6,9). Seroconversion with production of IgG occurs at 3 to 8 weeks after infection (2,5,6,9). In adults or immune-compromised patients, the rise of IgM might be less pronounced, since the current episode might be a re-infection, making the diagnosis on serology more difficult (3,9). The rise of IgM in paediatric patients is reliable to confirm ongoing *Mycoplasma pneumoniae* infection (6,8).

In children, the combined use of serology and PCR is recommended to establish the diagnosis of *Mycoplasma pneumoniae* infection (4). PCR is a sensitive detection method, to be used for direct detection on respiratory tract samples or CSF (6,8,9). In combination with serology, it is possible to differentiate colonization from active infection (6,9). Positive PCR does not necessarily indicate acute infection, as it can be detected beyond the death of the pathogen or in healthy asymptomatic carriers (2,3,6,10). However, PCR can be positive before antibody response (4,6).

This indicates that several diagnostic approaches must be used to establish the diagnosis (3).

Treatment

Mycoplasma pneumoniae is a small prokaryote, characterized by the absence of a rigid peptidoglycan cell wall (1,2,4). That is why they are insensitive to the administration of antibiotics that interfere with cell wall construction, such as β-lactam antibiotics (1,2,4,6). Antibiotic agents interacting with DNA-, RNA- or protein synthesis, such as quinolones, macrolides or tetracyclines are the first choice (1,3,5,6,8,9). However, their ability to cross the blood brain barrier is limited (3,7). Doxycycline might be an alternative, but its use is not recommended in children under 8 years old (6,9). In our patient, azithromycin and doxycycline were both associated.

Macrolides are the antibiotics of choice in the paediatric population (2,4,7). Macrolides also appear to have an immunomodulating effect, in addition to their bacteriostatic properties, which makes them even more suitable (2,5,7). Recent studies have shown that there is an emerging share of macrolide resistant mycoplasma strains (2,4). It remains uncertain if the administration of the appropriate antimicrobial therapy changes the course of the disease, since clinical improvement is not reported in all cases and full clinical improvement without administration of adequate therapy has been described (1,3,8,9). However, anti-mycoplasma therapy should always be considered when suspecting *Mycoplasma pneumoniae* (meningo-)encephalitis, because of the possible neurological sequels and even fatal outcomes (5,8,9).

There are no guidelines regarding the duration of the anti-mycoplasma therapy, specifically in patients with neurological manifestations (7). In patients with severe neurological manifestations or radiological abnormalities, the administration of corticosteroids or immunoglobulin should be considered given the possible immune-mediated pathogenesis (1,2,7–9).

Prognosis

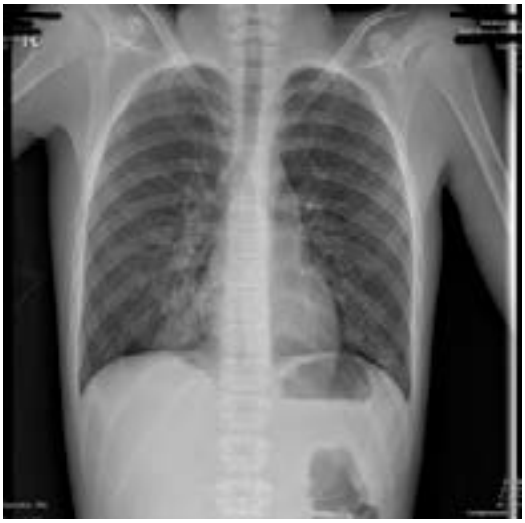
Neurological sequels have been described in 10 to 50% of patients with *Mycoplasma pneumoniae* associated meningo-encephalitis (1,8). These sequels range from mental retardation, epilepsy and cerebellar ataxia to mild cognitive impairments and might be permanent in 30% of patients (1,9).

Mycoplasma pneumoniae as the causative agent of meningo-encephalitis is associated with a worse prognosis in comparison to other pathogens and has a mortality rate of 5 to 10% (8,9).

Conclusion

We report the case of an 11 year old boy with meningo-encephalitis caused by Mycoplasma pneumoniae. Although this is rare, it is important to think of this pathogen in the differential diagnosis given that *Mycoplasma pneumoniae* needs specific antibiotic treatment and can have serious neurologic outcomes. Further research is indicated to establish guidelines for the treatment of *Mycoplasma pneumoniae* associated central nervous system manifestations.

Figure : *Bilateral hilar adenopathy and infiltrate of the right lower lobe*



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Phenotypic variability within *PIK3CA*-Related Overgrowth Spectrum, illustrated by two cases.

Willem Van Hoe [a], Hannelore De Maeseneer [b], Quentin Jordens [b], Dirk Van Gysel [b]

[a] Medical student, Faculty of Medicine, KU Leuven, Belgium
[b] Department of Pediatrics, O.L.Vrouw Hospital Aalst, Belgium

dirk.van.gysel@olvz-aalst.be

Keywords

PIK3CA gene; PIK3CA-Related Overgrowth Spectrum (PROS); CLAPO syndrome; Macrodactyly; somatic mosaicism

Abstract

PIK3CA-related overgrowth spectrum refers to a heterogeneous group of disorders caused by somatic pathogenic variants in the *PIK3CA* gene. Starting from two cases we recently diagnosed in our practice, 'Progressive Macrodactyly' and 'Capillary and Lymphatic malformation, Asymmetry of face and limbs, Partial or generalized Overgrowth', we illustrate the broad phenotypic variability possible within *PIK3CA*-related overgrowth spectrum. Current literature suggests the absence of a genotype-phenotype correlation. Further research is needed to establish a more adequate classification and a more accurate treatment.

Introduction

The term *PIK3CA*-related overgrowth spectrum (PROS) was first used by Keppler-Noreuil et al. to define a phenotypic spectrum of heterogeneous, rare entities, clinically characterized by asymmetric overgrowth and vascular malformations, and caused by somatic pathogenic variants in the gene *PIK3CA* (1,2).

Originally, PROS included the following syndromes with overlapping phenotypic features.

Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal Nevi, and Spinal abnormalities (CLOVES), Fibroadipose Hyperplasia or Overgrowth (FAO), Hemihyperplasia Multiple Lipomatosis (HHML), Dysplastic Megalencephaly (DMEG)/ Hemi Megalencephaly (HMEG), Megalencephaly-capillary Malformation (MCAP), Isolated Large Lymphatic Malformation (ILM), Facial Infiltrating Lipomatosis, Epidermal Naevi, Macrodactyly, Seborrheic Keratosis and Benign Lichenoid Keratosis (1,2).

However, over the years, multiple syndromes have been proposed to be included in PROS, such as Klippel-Trenaunay syndrome (proposed by Vahidnezhad in 2016) and CLAPO syndrome (Capillary and Lymphatic malformation, Asymmetry of face and limbs, Partial or generalized Overgrowth) (proposed by Rodriguez in 2018) (3,4).

The current identification of new syndromes linked to *PIK3CA* indicates the need for a reclassification in the near future when the spectrum of PROS will be more accurately documented and genotype-phenotype correlations will be better understood.

The *PIK3CA* gene encodes p110α, the catalytic subunit of phosphatidylinositide-3-kinase (PI3K) which is part of the complex PI3K-AKT-mTOR signaling pathway. PI3K catalyzes the conversion of phosphatidylinositol 4,5- bisphosphate (PIP2) to phosphatidylinositol 3, 4,5- trisphosphate (PIP3) which in its turn activates phosphoinositide-dependent kinase-1 (PDK1) which phosphorylates AKT (also known as protein kinase B). Activated AKT further phosphorylates downstream molecules like GSK-3, FoxO, and mTOR (figure 1).

This pathway plays a critical role in most cells by regulating biological processes such as cell proliferation and growth, apoptosis, metabolism and angiogenesis. Furthermore, it is linked to the pathogenesis of cerebrovascular and neurodegenerative diseases, diabetes mellitus and malignant tumours.

Heterozygous somatic gain-of-function variants in a mosaic pattern have been found in the above-mentioned PROS syndromes, explaining their clinical findings and the possible significant overlap (1,5,6).

In this article, we further illustrate the heterogeneity of PROS with two cases recently diagnosed in our department. The first case report describes an infant with a capillary malformation of the lower lip suggestive for CLAPO (7). In the second case report, a congenital enlargement of toes and later progressive enlargement of toes, foot and lower leg, in the context of Progressive Macrodactyly is described (8).

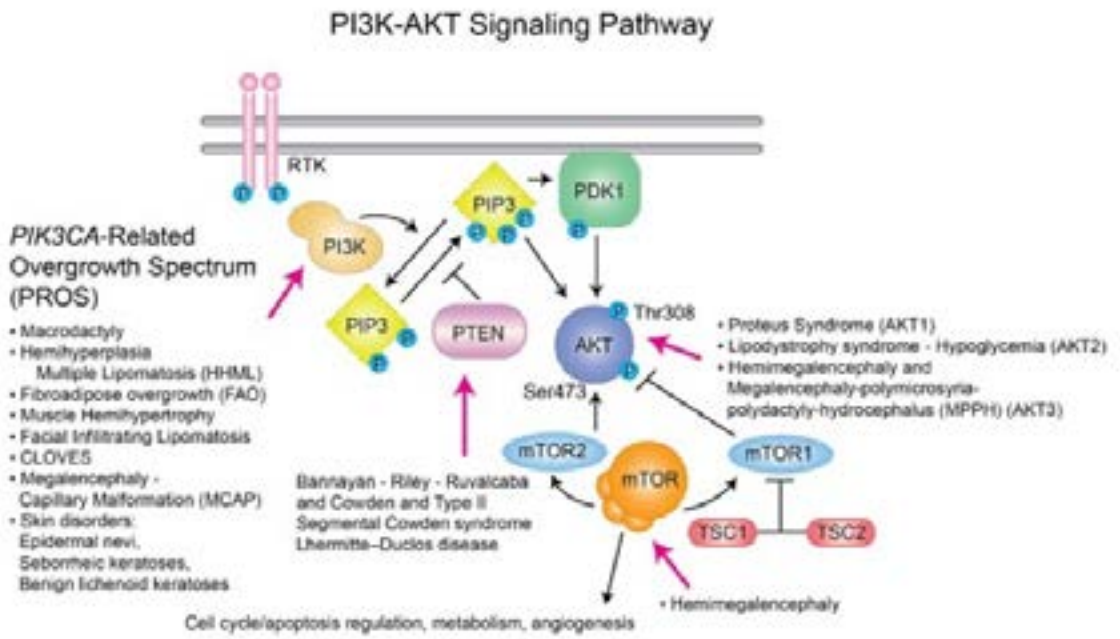
Case reports

The first case is a male newborn delivered after an uncomplicated pregnancy who presented at birth with skin lesions on the lower lip, face, head, and neck. Clinical examination showed a flat, red, blanchable, symmetrical zone on the lower lip with well-defined ragged edges that surrounded the entire lower lip vermillion and even surpassed it (figure 2). Additionally, a capillary malformation on the tip of the tongue was found, which is not shown on figure 2. Furthermore, diffuse reticulate patches of red to purple skin discoloration with underneath prominent veins located on the jaw, scalp, and neck were found (figure 3). No partial or generalized overgrowth was visible up to the age of 4 years. Psychomotor and neurological development were normal. No other vascular or cutaneous malformations were found on magnetic resonance imaging (MRI) of the head and neck. Further molecular investigation through skin biopsy was refused.

The final clinical diagnosis was CLAPO, a syndrome characterized by Capillary malformation of the lower lip, Lymphatic malformation of the face and neck, Asymmetry of the face and limbs, Partial or generalized Overgrowth. Overgrowth has been found only in a rare number of cases and is currently being doubted as clinical criterion. Lymphatic malformations can be present at birth, but may as well become evident after the neonatal period.

The second case is a girl who presented at birth with an enlargement of the first and second left toe (figure 4). The girl was born otherwise healthy after an uncomplicated vaginal delivery. Physical examination revealed a bigger size of the left foot compared to the right with a noticeable increase in circumference and length of the first and second toe. Conventional radiography and MRI of the left foot showed cortical thickening and an increased amount of fibrofatty tissue around the phalanges of the first and second toe. Histopathological examination of a biopsy specimen of the dermis and hypodermis confirmed the presence of abundant fatty tissue infiltrating the dermal connective tissue. Further genetic screening for *PIK3CA* variants was performed on cultured fibroblasts using Next Generation Sequencing on a MiSeq platform with two

Figure 1: *PI3K-AKT Pathway and associated clinical overgrowth disorders. Reprinted with permission from Keppler-Noreuil K, Rios J, Parker V, Semple R, Lindhurst M, Sapp J, et al. PIK3CA-related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. Am J Med Genet A. 2015;167A(2):287-95.*



panels, Tumor Hotspot MASTR Plus (Multiplicom) and Somatic 2 MASTR Plus (Multiplicom). A heterozygote c.1624G>A (p.Glu542Lys) missense variant in the *PIK3CA* gene was found in 69% of the cells of the affected tissue.

During the next months a further enlargement of the involved toes and foot was noticeable, and unfortunately also of the ipsilateral lower limb (figure 5). For this reason, an off-label treatment with sirolimus was started which halted further asymmetric overgrowth. The effect of sirolimus is being monitored by repeated measurements of the circumference of the feet, lower legs, knees, and upper legs, and the length of both lower legs. At the age of two, the aim is to switch sirolimus to a *PIK3CA*-inhibitor, for example BYL719.

These findings supported the diagnosis of a progressive form of Macrodactyly which is thus part of the *PIK3CA*-related overgrowth spectrum (PROS).

Discussion

In this paper, we describe two cases, respectively diagnosed as CLAPO and Progressive Macrodactyly, that belong to the *PIK3CA*-related overgrowth spectrum. The most common gain-of-function variants in the *PIK3CA* gene are the p.His1047Arg (found in 54% of cases), p.His1047Leu ((23%), p.Glu545Lys in (11%), p.Glu542Lys in (8%), and p.Cys420Arg (3%) (1).

However, multiple studies highlight the heterogeneity in variants found in multiple clinical phenotypes, supporting the absence of a genotype-phenotype correlation and so supporting the concept of *PIK3CA*-related syndromes as a single spectrum (1,6).

Keppler-Noreuil et al. hinted the possibility of a genotype-phenotype correlation with p.His1047Arg and p.His1047Leu as most common variants found in Macrodactyly cases. In our case of Progressive Macrodactyly, a p.Glu542Lys variant was found, providing further, even if limited, evidence for the lack of a genotype-phenotype correlation.

PROS needs to be suspected if early childhood-onset overgrowth, sporadic occurrence, and mosaic distribution are present. Vascular malformations and an epidermal naevus are also common findings. Patients suspected of having PROS should be tested for *PIK3CA* variants using a biopsy sample of the affected tissue. However, *PIK3CA* variants are sometimes also detectable in blood and buccal samples of patients with MCAP. Nonetheless, skin and other affected tissues have higher diagnostic rates and are therefore recommended as primary sample for diagnosis of all PROS phenotypes. Not finding any variants doesn't necessarily rule out PROS due to the possibility of accidental low-quality biopsies from non-affected regions. Multiple assays for testing PIK3CA variants are available with ultradeep next generation sequencing

Figure 2: *case 1 showing a flat, red, blanchable, symmetrical zone with well-defined edges that surround and surpass the entire lower lip vermillion.*

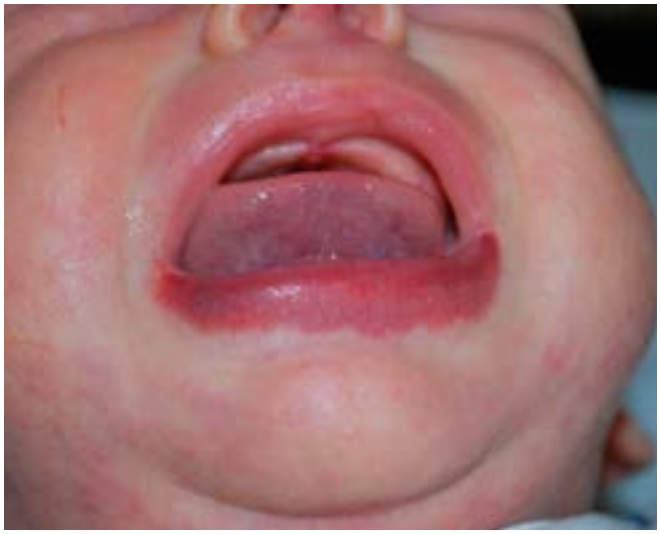
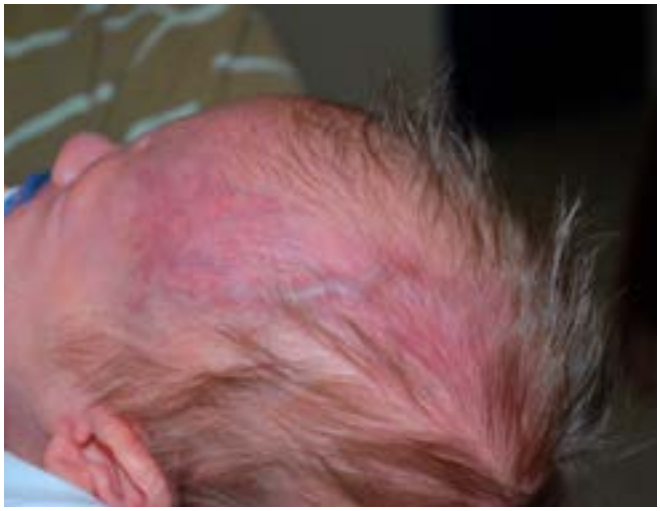


Figure 3: *case 1 showing diffuse reticulate zones of red to purple skin discoloration with underneath prominent veins located on the scalp, jaw and neck.*



being regarded as the most sensitive having a diagnostic rate of 66.7% in one study (2,6).

The current treatment options are inadequate and consist mainly of supportive care, including debulking and orthopedic surgery, amputation, sclerotherapy, and psychological and nutritional support. Relapse of overgrowth following surgery is common and often leads to re-intervention. Multiple pharmacological inhibitors of PI3K, APK, and mTOR are under development (examples are: BYL719, sirolimus, and metformin). These medical therapies, which are currently under evaluation in clinical trials, may suppress the overgrowth, resulting in modest reduction or relative stabilization, but aren't considered to be curative (9-13). A recent study on the efficacy and safety of low dose sirolimus suggests that it can slow down overgrowth but also has a high rate of discontinuation due to significant side effects. A case-by-case approach is so warranted (11).

Follow-up of patients is important since most of the phenotypes can be progressive, as is the case in our patient with Progressive Macrodactyly.

Conclusion

Our two cases are an illustration of the fact that multiple variants in a single gene can result in completely different phenotypes. An absence of a genotype-phenotype correlation has been suggested in recent literature. Our case of Macrodactyly is further supporting this concept since the variant in our patient differs from the variants most commonly described.

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Figure 4: *case 2 at birth showing an enlargement of the first and second left toe*

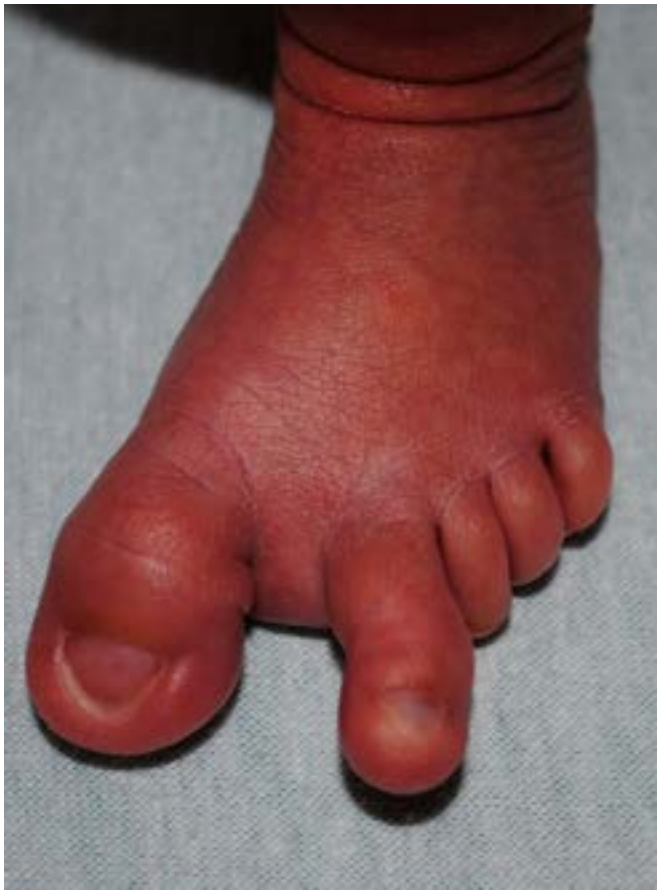
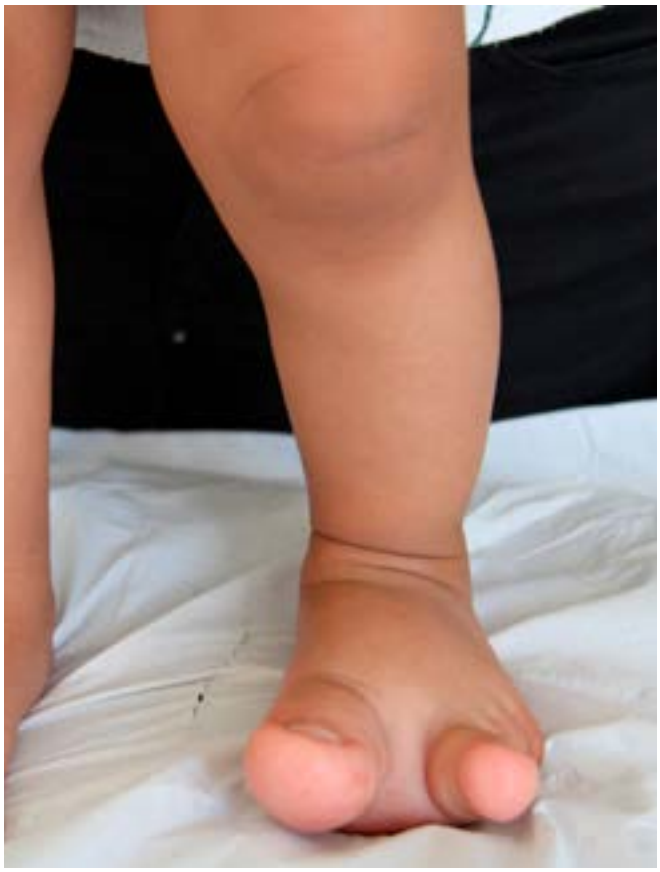


Figure 5: *case 2 at the age of 9 months showing a further enlargement of the involved toes and foot and also of the ipsilateral lower limb.*



*Disponible maintenant pour traiter la constipation chronique chez les enfants dès 1 an

Dénomination du médicament: MOVICOL® Junior Neutral 6,9 g sachet, poudre pour solution buvable Composition qualitative et quantitative: Chaque sachet de Movicol Junior Neutral contient les ingrédients actifs suivants: Macrogol 3350: 6,563 g, Chlorure de sodium: 0,1754 g, Bicarbonate de sodium: 0,0893 g, Chlorure de potassium: 0,0251 g. Après dissolution d'un sachet dans 62,5 ml d'eau, la solution contient les électrolytes suivants: Sodium: 65 mmol/l, Chlorure: 53 mmol/l, Potassium: 5,4 mmol/l, Bicarbonate: 17 mmol/l. **Forme pharmaceutique:** Poudre pour solution buvable. Poudre blanche, fluide. **Indications thérapeutiques:** Pour le traitement de la constipation chronique chez les enfants âgés de 1 à 11 ans. Pour le traitement de l'impaction fécale (définie comme une constipation opiniâtre avec accumulation des selles dans le rectum et/ou le côlon) chez les enfants à partir de 5 ans. **Posologie et mode d'administration:** Posologie: Constipation chronique: Chez les enfants âgés de 1 à 6 ans, la posologie initiale habituelle est de 1 sachet par jour. Chez les enfants âgés de 7 à 11 ans, elle est de 2 sachets par jour. Il faut augmenter ou diminuer la posologie selon le cas afin d'obtenir des selles molles et régulières. S'il faut augmenter la posologie, il est préférable de le faire par paliers, tous les deux jours. Pour les enfants de moins de 2 ans, la posologie maximale recommandée ne doit pas dépasser 2 sachets par jour. Pour les enfants âgés de 2 à 11 ans, la posologie maximale recommandée ne doit normalement pas dépasser 4 sachets par jour. Le traitement des enfants atteints de constipation chronique s'effectue généralement sur une longue période (minimum 6 à 12 mois). La sécurité et l'efficacité du Movicol Junior Neutral sont uniquement démontrées pour une période de maximum 3 mois. Il faut arrêter le traitement de manière progressive et le réinstaurer en cas de récidive de la constipation. Impaction fécale: En cas d'impaction fécale, suivre le schéma d'administration ci-dessous allant jusqu'à 7 jours de traitement: Schéma posologique journalier: Age: 5-11 ans; Nombre de sachets de Movicol Junior Neutral: Jour 1: 4, Jour 2: 6, Jour 3: 8, Jour 4: 10, Jour 5: 12, Jour 6: 12, Jour 7: 12. Les sachets à prendre par jour doivent être administrés en doses séparées et doivent tous être pris sur une période de 12 heures. Le schéma d'administration ci-dessus doit être arrêté dès que survient la fin de la coprostase. Le passage d'un grand volume de selles est un signe de la fin de la coprostase. Après la fin de l'impaction, il est recommandé de faire suivre à l'enfant un entraînement adéquat à la défécation, afin de prévenir le retour de l'impaction (pour prévenir le retour de l'impaction fécale, la posologie devrait être la même qu'en cas de constipation chronique; voir ci-dessus). L'utilisation de Movicol Junior Neutral est déconseillée pour traiter l'impaction fécale des enfants de moins de 5 ans OU pour traiter la constipation chronique des enfants de moins de 1 ans. Chez les patients âgés d'au moins 12 ans, il est conseillé d'utiliser Movicol. *Patients présentant une diminution de la fonction cardiovasculaire:* Il n'y a pas de données cliniques pour ce groupe de patients. Movicol Junior Neutral n'est donc pas recommandé pour traiter l'impaction fécale chez les enfants présentant une diminution de la fonction cardiovasculaire. *Patients présentant une insuffisance rénale:* Il n'y a pas de données cliniques pour ce groupe de patients. Movicol Junior Neutral n'est donc pas recommandé pour traiter l'impaction fécale chez des enfants présentant une diminution de la fonction rénale. Mode d'administration: Chaque sachet doit être dissous dans 62,5 ml d'eau (un quart de verre). Le nombre exact de sachets peut être préparé à l'avance et conservé dans un récipient fermé au frigo pendant 24 heures maximum. En cas d'un traitement d'impaction fécale, on peut, par exemple, préparer 12 sachets dans 750 ml d'eau. **Contre-indications:** Perforation ou obstruction intestinale suite à une affection anatomique ou fonctionnelle de la paroi intestinale, un iléus, des maladies inflammatoires intestinales graves telles qu'une maladie de Crohn, une colite ulcéreuse ou un mégacôlon toxique. Hypersensibilité aux substances actives. **Effets indésirables:** Les réactions les plus fréquentes sont liées au tractus gastrointestinal. Ces réactions peuvent survenir suite à un accroissement du volume du contenu gastrointestinal et à une augmentation de la motilité liée à l'action pharmacologique de Movicol Junior Neutral. Dans le traitement de la constipation chronique, la diarrhée et les selles fréquentes répondent généralement à une réduction de la dose. Des diarrhées, des distensions abdominales, des gênes ano-rectales et de légers vomissements sont souvent observés pendant le traitement du fécalome. Les vomissements peuvent se dissiper lorsque la dose est réduite ou retardée. La fréquence des événements indésirables ci-dessous est définie selon la convention suivante: très fréquent (≥1/10), fréquent (≥1/100, <1/10), peu fréquent (≥1/1.000, <1/100), rare (≥1/10.000, <1/1.000) et très rare (<1/10.000); fréquence indéterminée (ne peut être estimée sur la base des données disponibles). Classe de systèmes d'organes - *Fréquence* - Effet indésirable: Affections du système immunitaire: *Rare:* Réactions allergiques incluant réaction anaphylactique. *Indéterminée:* Dyspnée et réactions cutanées (voir ci-dessous). Affections de la peau et du tissu sous-cutané: *Indéterminée:* Réactions allergiques de type cutané incluant angio-œdème, urticaire, prurit, rash, érythème. Troubles du métabolisme et de la nutrition: *Indéterminée:* Déséquilibres électrolytiques, notamment hyperkaliémie et hypokaliémie. Affections du système nerveux: *Indéterminée:* Céphalée. Affections gastro-intestinales: *Très fréquent:* Douleur abdominale, borborygmes. *Fréquent:* Diarrhée, vomissements, nausée et gênes ano-rectales. *Peu fréquent:* Distension abdominale, flatulences *Indéterminée:* Dyspepsie et inflammation péri-anale. Troubles généraux et anomalies au site d'administration: *Indéterminée:* Œdème périphérique. Déclaration des effets indésirables suspectés: La déclaration des effets indésirables suspectés après autorisation du médicament est importante. Elle permet une surveillance continue du rapport bénéfice/risque du médicament. Les professionnels de santé déclarent tout effet indésirable suspecté via: ***Belgique:*** Agence fédérale des médicaments et des produits de santé, Division Vigilance, EUROSTATION II, Place Victor Horta, 40/40, B-1060 Bruxelles ou Boîte Postale 97, B-1000 Bruxelles Madou, Site internet: www.afmps.be, e-mail: adversedrugreactions@fagg-afmps.be. ***Luxembourg:*** Centre Régional de Pharmacovigilance de Nancy, E-mail: crpv@chru-nancy.fr, Tél: (+33) 3 83 65 60 85 / 87, ou Division de la Pharmacie et des Médicaments, Direction de la Santé à Luxembourg, E-mail: pharmacovigilance@ms.etat.lu, Tél.: (+352) 2478 5592 **Titulaire de l'autorisation de mise sur le marché:** Norgine SA, Romeinsestraat 10, B-3001 Heverlee **Numéro d'autorisation de mise sur le marché:** BE278643 **Mode de délivrance:** Sur prescription médicale. **Date de mise à jour du texte:** 03/2021. Les textes complets des caractéristiques du produit sont disponibles sur demande.

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Benign coccygeal dimple or dermal sinus tract: a big difference

Marcelien Verjans [a], Jansen Katrien [b], Frank Van Calenbergh [c], Philippe De Vloo [c], Marijke Proesmans [d]

[a] Faculty of Medicine, KU Leuven, Leuven, Belgium
[b] Department of Development and Regeneration, KU Leuven, Leuven, Belgium
[c] Department of Neurosurgery, University Hospitals Leuven, KU Leuven, Leuven, Belgium
[d] Department of Pediatric Pulmonology, University Hospitals Leuven, Leuven, Belgium

marcelien.verjans@student.kuleuven.be

Keywords

dermal sinus tract; benign coccygeal dimple; meningitis; case report

Abstract

Dermal sinus tracts are a type of closed spinal dysraphism occurring with an estimated incidence of 1/2500. They are often misdiagnosed as a benign coccygeal dimple, thereby increasing the risk of meningitis and tethering of the spinal cord. This case report describes a 3-month old infant with bacterial meningitis due to a dermal sinus tract in the lumbosacral region. After appropriate treatment with antibiotics she underwent surgical excision of the tract with intradural exploration and untethering of the cord.

Introduction

Dermal sinus tracts are a form of spinal dysraphism present at birth at the dorsal midline with an estimated incidence of 1/2500 and most frequently occurring in the lumbosacral region. Failure to separate the neural ectoderm and cutaneous ectoderm (non-disjunction) between the 3rd and 5th week of embryonic life creates an epithelial-lined tract between the skin and underlying spinal cord. Dermal sinus tracts can end intradurally (60%) or in the epidural space (10-20%). When extending into the dura, they are frequently associated with thickened fatty filum (40%), intradural inclusion tumors like dermoid or epidermoid tumors (50%), tethered cord (79%), myelomeningocele, lipomyelomeningocele or diastematomyelia. This is in contrast to benign coccygeal dimples that occur in 4% of the population and are not associated with dysraphisms. Children with dermal sinus tracts are at risk of infection. Older children can present with tethered cord syndrome (1–4).

Case presentation

A 3-month old girl was referred to our emergency department with suspected meningitis. She presented with acute-onset irritability, fever up to 38.5°C, vomiting and subsequent lethargy. Clinical investigation revealed a pale, moaning and hypertonic infant, with a sacral dimple. The mother mentioned that the sacral dimple was noticed at birth but no further investigations were undertaken. Vital parameters were stable.

White blood cell count (WBC) was elevated to 27,6000/µL but C-reactive protein was low (1.6 mg/dL). Hemoculture was positive for Escherichia coli. Lumbar puncture showed WBC of 4371/µL, protein 1374 mg/L and decreased glucose (<2mg/dL). Cerebrospinal fluid cultures were positive for Escherichia coli, Bacteroides ovatus and Bifidobacterium breve (all commensals of the gut).

The diagnosis of a bacterial sepsis and meningitis was made. Broad spectrum antibiotics were started empirically. During her stay at the hospital clinical neurological examination was normal, except for initial but self-limiting axial hypotonia and head lag with pull-to-sit, likely secondary to the sepsis/meningitis. Neurological deficit of the lower limbs was never observed. The sacral dimple was located above the gluteal cleft, with no visible base. At presentation there was erythema around the sacral dimple with a small tuft of hair (Figure 1).

Imaging of the sacral dimple was performed because the clinical appearance suggested a dermal sinus tract. Ultrasound revealed a hypoechogenic trajectory reaching the spinal canal and suspicion of a low-reaching conus

Figure 1 : *Photograph of the lumbosacral region of the patient showing the ostium of the dermal sinus tract lying just above the gluteal cleft. This dermal sinus tract was associated with cutaneous stigmata; erythema and a small amount of hair. The bottom could not be clearly seen.*

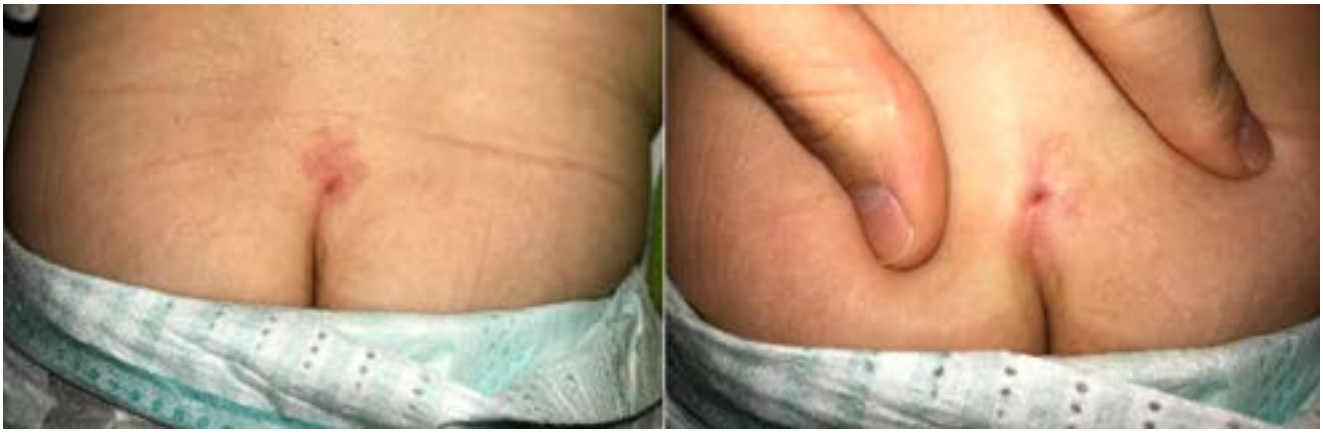
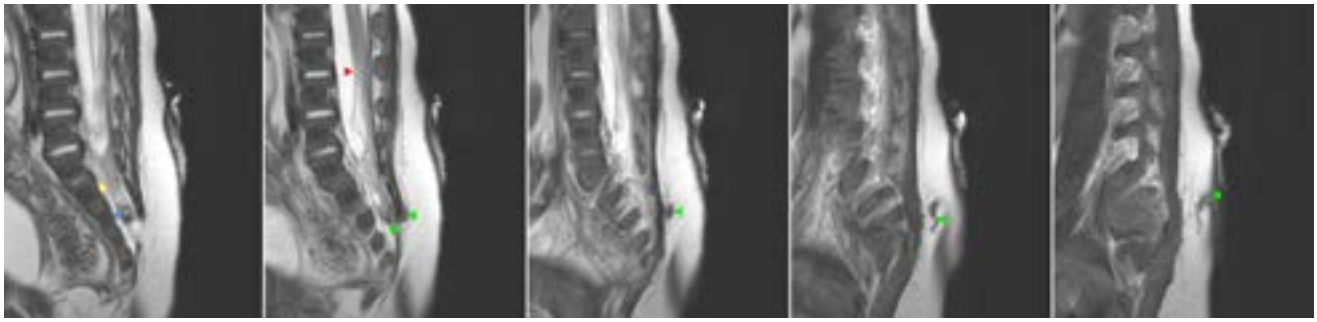


Figure 2 : *Radiological findings. Adjacent T2-weighted (para)median sagittal images of the lumbosacral spine reveal the cutaneous opening (green arrowhead), which leads to a dermal sinus tract (green arrowheads), initially following a caudal course through the spina bifida of S3-5 just underneath the intact lamina of S2. There appears to be a dermoid tumor (blue arrowhead) at the junction of the dermal sinus tract with the thickened filum terminale (yellow arrowhead). There is a low-lying conus medullaris (L3-4 disc space; red arrowhead).*



medullaris with tethered cord. Additional magnetic resonance imaging (MRI) confirmed spina bifida of S3, S4 and S5, a dorsal dermal sinus with a cutaneous entry at the level of S3, with a typical U-shape on sagittal images, ending intradurally at level S3-4, likely on a thickened filum terminale. Along the intradural course of the tract, there was a dermal inclusion cyst. There was radiological tethering of the spinal cord, ending at level L3-4, but otherwise no central nervous system abnormalities (Figure 2). Further, there was a duplicated ureter with small kidneys.

After antibiotic treatment for the meningitis, she underwent surgical excision of the dermal sinus tract with intradural exploration, excision of the inclusion cyst, sectioning of the thickened filum and untethering of the cord (Figure 3). This procedure was performed under neuromonitoring (direct electromyogram with monitoring of the m. gastrocnemius (S1), abductor hallucis brevis (S2) and sphincter ani (S3-4)).

The abnormal skin opening, along with the dermal sinus tract, dermoid tumor and the thickened filum were excised. Pathologically, an epithelial lined lumen was detected, confirming the diagnosis of a dermal sinus tract (Figure 4).

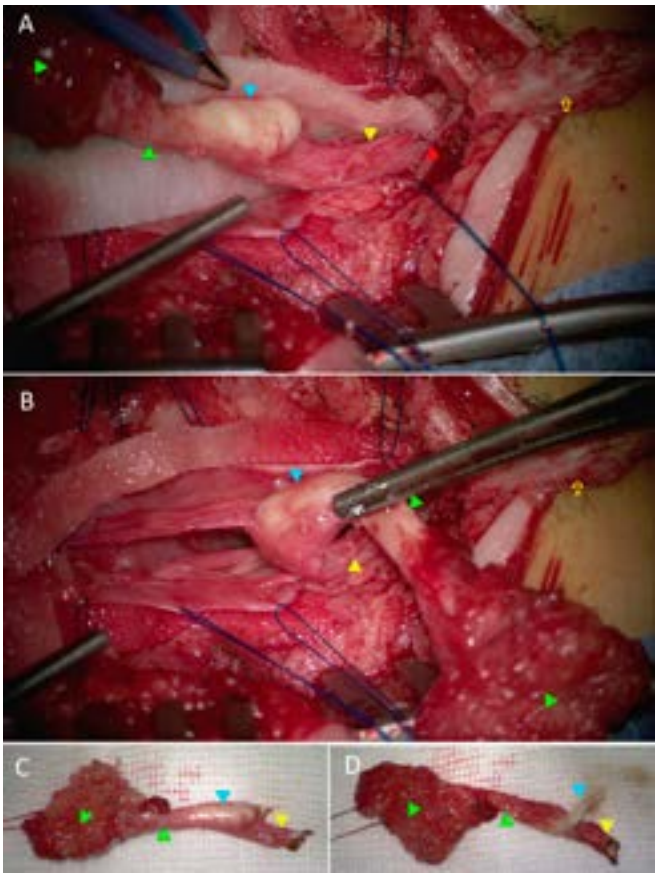
Discussion

Dermal sinus tracts can usually be distinguished from a benign coccygeal dimple on pure clinical grounds. Figure 5 show a benign coccygeal dimple of a newborn. Table 1 lists the differences. Benign coccygeal dimples are located within the gluteal cleft (1,2,4). Only atypical dimples (i.e. larger than 5 mm diameter, located more than 2.5 cm from the anus, not located on the midline and those whose base is not visible) are associated with a high risk of spinal dysraphism (5,6). Dermal sinus tracts are located above the gluteal cleft and are often associated with cutaneous stigmata such as erythema, skin tags, a small skin opening, pigmentation changes, hair or hypertrichosis, angiomata, subcutaneous masses, a human tail, local infection or inflammation (1,2,4).

Non-saccular limited dorsal myeloschizis (LDM) resemble dermal sinus tracts and they must therefore be distinguished from each other. A nonsaccular LDM has a tract without an epithelial lined lumen, consisting of mesodermal tissues. In contrast to dermal sinus tracts, non-saccular LDM are not associated with dermoid or epidermoid tumors. The patients are mostly older at diagnosis and do not have a history of meningitis. Non-saccular LDM are also associated with cutaneous stigmata different from those seen with dermal sinus tracts. The most common are pori and craters. Non-saccular LDM have a risk of tethering and in principle one could postpone surgery until these children are older. With a dermal sinus tract there is a risk of infection and later of tethering, so these children should be treated as soon as possible. Clinically and, radiologically, it is difficult to make a definitive distinction between both entities. Hence, we and others propose immediate surgery upon diagnosis (7–9).

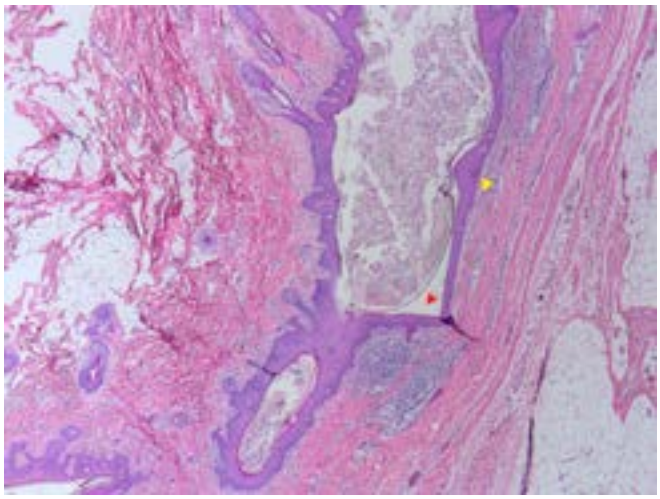
Definitive diagnosis of a dermal sinus tract or non-saccular LDM requires spinal MRI. When these are suspected, an ultrasound can already be performed. Ultrasound has a low sensitivity but high specificity (1,2). A retrospective study of 74 patients, who underwent an MRI preoperatively followed by surgery with intradural exploration, found that MRI even underreported intradural tracts and intraspinal inclusion cysts. MRI is therefore not sensitive enough to exclude these entities (10).

Figure 3 : *Intra-operative photographs. (A) and (B): The skin, subcutis and muscle are spread. The upper sacral and lowest lumbar laminae are deflected upwards (yellow open arrow). The dura is opened with blue-coloured tack-up sutures. The dermal sinus tract (green arrowheads) connects the skin (green arrowhead) with the thickened filum terminale (yellow arrowhead). At the junction between the latter, a small dermoid tumor can be seen as a pale cyst (blue arrowhead). The filum connects to the conus medullaris (red arrowhead). Several lumbar and sacral nerve roots are tightly attached to the thickened filum, likely due to preoperative infection. (C): The resected specimen includes the skin, dermal sinus tract, pale dermoid tumor and thickened filum terminale (same annotations as in (A) and (B)). (D): Upon incision of the dermoid tumor, keratin and a dark hair evacuate.*



Spinal dermal sinus tracts are noticed due to the presence of cutaneous abnormalities, an infection, a neurological deficit and/or orthopedic abnormalities. Children can be asymptomatic or may present with an infection for example meningitis, spinal or brain abscess. Patients can also present with recurrent meningitis or aseptic meningitis. Leakage of cerebrospinal fluid can also occur, increasing the risk of meningitis (11). The median age of infectious presentation is 2.5 years. The most frequent non-infectious presentation are neurological deficits (30%) such as abnormal reflexes, sensory changes, gait changes, altered bladder or bowel function or motor weakness of the lower

Figure 4 : *Photograph of a transverse section through the dermal sinus tract. The lumen of the dermal sinus tract (red arrowhead) surrounded by squamous epithelium (yellow arrowhead) is shown.*



limbs. Almost all children have normal neurological function at birth. With aging, neurological deterioration is more frequent due to increased tethering (1,2,4). Approximately 60-70% of adult patients with closed spinal dysraphism have urological symptoms (12). Orthopedic abnormalities including pes cavus, pes planus, clubfoot or scoliosis are also described later in life.

An infection, neurological deficits and orthopedic abnormalities can be prevented by referring children early for further investigation and treatment (1,2,4). Therefore it is important to make a correct diagnosis as soon as possible to avoid morbidity.

The most important risk associated with a dermal sinus tract is infection. When the diagnosis of a dermal sinus tract is made, urgent surgery is needed because of the increased risk of infection (2). In this case, the infant presented with a bacterial meningitis due to Escherichia coli, Bacteroides ovatus and Bifidobacterium breve. These are all commensals of the gut. Therefore there was a strong suspicion that the lumbosacral dimple was responsible for the infection.

Dermal sinus tracts can be associated with tethered cord syndrome. Traction induced neurological dysfunction is caused by mechanical tension or vascular stress on the spinal cord through growth and repetitive strain. This is the second most common presentation of a dermal sinus tract (1,2,4). In this case, the infant showed no symptoms of the tethered cord syndrome. A lumbar puncture before MRI should be avoided because of the risk of injuring the spinal cord.

Children with a dermal sinus tract have an increased risk of neurogenic bladder dysfunction. Therefore urological evaluation should be performed in all children. A retrospective study of 35 children who were treated for spinal dermal sinus tract reported that 77% had abnormal urological results. Urodynamic studies can detect urinary tract dysfunction before structural damage has occurred and is recommended (2).

We strongly recommend to always consider the possibility of a dermal sinus tract during postnatal clinical examination, during clinical examination of a child with recurrent meningitis, aseptic meningitis and a child with a neurological deficit of the lower limbs or orthopedic abnormalities. When characteristics are consistent with a dermal sinus tract (Table 1), the infant should be referred for further investigation.

Table I: *Distinction between dermal sinus tracts and benign coccygeal dimples*

Dermal sinus tract	Benign coccygeal dimple
Above gluteal cleft	Within gluteal cleft
Base not visible	Base visible
Associated cutaneous stigmata	No associated cutaneous stigmata
Can be associated with intradural pathology	Not associated with intradural pathology

Conclusion

Dermal sinus tracts are a type of closed spinal dysraphism involving significant morbidity if not diagnosed early. Often they are misdiagnosed as a benign coccygeal dimple. They occur most frequently in the lumbosacral region and are often associated with anomalies of the spinal cord. Dermal sinus tracts are located above the gluteal cleft, associated with cutaneous stigmata, the base of the tract is not visible and can be associated with intradural pathology. They can present as an infection, neurological deficit of the lower limbs or orthopedic abnormalities and should therefore be diagnosed and treated early.

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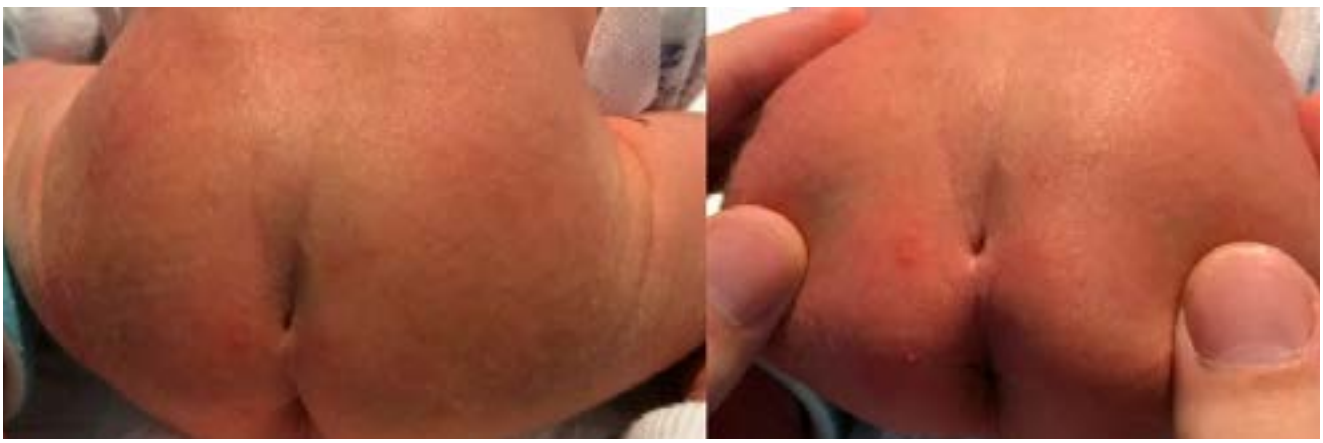
Figure 5 : *Photograph of the lumbosacral region of a newborn showing a benign coccygeal dimple. The dimple is located in the gluteal cleft and is not associated with cutaneous stigmata.*



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Pica as a cause of iron deficiency anemia or the other way around? A look at the cause of iron deficiency anemia in young children.

Simone Van de Velde[a], Linde De Keyzer[b], Ann Verschelde[b]

[a] Department of Pediatrics, Ghent University Hospital, Ghent, Belgium
[b] Department of Pediatrics, AZ Sint-Jan, Bruges, Belgium

simone.vandevelde@ugent.be

Keywords

pica, anemia, iron deficiency

Abstract

We describe a young boy with the unusual habit of eating his own clothes and a severe form of iron deficiency anemia. Both phenomena have been mentioned in the same sentence for ages, but their exact relationship has never been shown. In this case report we will review the current literature on the etiology of pica and iron deficiency anemia and we will clarify the existing hypothesis. We want to raise awareness on the potential dangerous consequences of pica behavior because the diagnosis is still often missed.

Introduction

Pica is typically defined as an unusual craving for and ingestion of inedible substances (1). The term "pica" is derived from "pica pica" which is the Latin word for the brown-billed magpie. This bird is known for collecting and hoarding unusual objects to satisfy its hunger and curiosity (2). It is a complex behavior that can be classified according to the substance ingested (table 1) (2).

Table 1: *Common subtypes of pica*

Subtypes of pica	Substance ingested
Acuphagia	Sharp objects
Coniophagia	Dust
Coprophagia	Faeces
Emetophagia	Vomit
Geophagia	Clay
Hyalophagia	Glass
Lithophagia	Stones
Pagophagia	Ice
Plumbophagia	Lead
Tricophagia	Hair, wool, or other fibres
Xylophagia	Paper

Pica occurs worldwide but the frequency varies by location. Studies have shown that about 20 to 30% of children under the age of six have practiced pica (3). The prevalence might be even higher than documented because it is often overlooked by physicians or under-reported by patients or parents (2). Pica in children is mostly seen in children 18 months to 6 years and is more prevalent in lower socioeconomic classes (2).

Pica may be benign in children with normal intelligence but can also be associated with serious health problems such as electrolyte and metabolic disorders, lead and mercury poisoning, parasitic infections, destructed tooth enamel and various problems of the gastrointestinal tract (1). When associated with iron deficiency (ID), some believe that pica is a consequence rather than a cause. The discussion of this association has been of the chicken-or egg variety: which comes first?

Iron deficiency, with or without anemia, is a major health problem affecting more than 2 billion people around the world (4). Children and adolescents, who have an increased requirement of iron during periods of rapid growth, have the highest risk to develop a shortage (5). Recent numbers from the United States estimates the prevalence of iron deficiency in toddlers at 9,2% and the prevalence of iron deficiency anemia (IDA) at 2,1% (6).

Anemia is defined as a hemoglobin level that is two standard deviations below the mean for age. In IDA there typically is hypochromia and microcytosis. The diagnosis of IDA is only certain when serum ferritin is low or the percent transferrin saturation is low with an elevated total iron binding capacity (4).

With this case report we want to raise awareness for IDA in children and its consequences. We will also try to shine a light on the association of pica with IDA.

Case report

A two and a half year old African boy without prior medical history was brought to our outpatient clinic by his mother with the complaint of her son "eating his clothes and diapers". This behavior began six months ago and escalated to the point of almost completely rejecting normal foods. He does drink large amounts of cow's milk, more than 1 liter a day. There were no other complaints. Especially no abdominal pain or extreme fatigue.

At consultation we saw an odd little boy who was actively playing but was not good at making social contact. He appeared pale and fatigued. Clinical examination revealed pale conjunctiva and gums. He was diagnosed with pica. Diagnostic work-up showed an important IDA with a hemoglobin level (Hb) of 6,2 g/dl (reference range 11,5-14,5), mean corpuscular volume (MCV) of 55 fl (reference range 75-87) and serum ferritin of 2,7 µg/L (reference range 15-150) He was started on oral iron therapy and we suggested limiting the amount of cow's milk.

Due to the COVID-19 pandemic he was lost to follow-up and we only saw him again after four months. We learned that the pica behavior almost resolved completely. Mama told us she kept giving the iron therapy daily and that the boy now only drinks 400ml of cow's milk a day. Control blood tests were performed. Hb was 11,5 g/dl, MCV 70,9 fl and serum ferritin 29.4 µg/l. Iron supplementation was continued.

After another four weeks we saw the boy again. Pica behavior had now completely resolved and he resumed normal eating habits. Blood control showed a normal Hb of 13.3 g/dl.

Discussion

Children mostly depend on their diet to provide around 30% of the daily iron need (7). These dietary factors play a major role in the development of IDA in children. Prolonged breastfeeding without iron supplementation, as well as a vegetarian diet, are risk factors. The ingestion of large volumes of unmodified cow's milk (CM) leads to IDA by either the low iron content of CM, the inhibition of iron absorption by components of CM or the risk of occult intestinal blood loss. Celiac disease, Crohn's disease and giardiasis are important etiologies as well because they influence the absorption of iron throughout the intestine. Inflammatory bowel disease and cow's milk protein induced colitis lead to increased gastrointestinal loss and are thereby also associated with ID (7,4,8).

ID is not just anemia. Anemia is only one of the manifestations of ID. It is the most known clinical feature and is mostly asymptomatic. Pallor is used to estimate the grade of anemia but is often an unreliable sign. Consequences of the anemic state are lethargy, fatigability, tachycardia, irritability and poor appetite (9).

ID at a young age can result in impaired psychomotor and mental development. Iron is required for proper myelinization of neurons, neurogenesis, and differentiation of brain cells that can affect learning, memory and behavior. It's also a cofactor for enzymes that synthesize neurotransmitters. Some of these effects may not be reversible which makes ID a really important topic in pediatrics (10).

And what about pica and IDA? There are a lot of articles written on their possible association. A recent meta-analysis of 83 studies from Miao et al. including more than 6.000 individuals with pica stated that pica was associated with a 2.35 times greater odds of anemia and lower zinc concentrations (11). But how are these two related? Is pica responsible for iron deficiency or is iron deficiency responsible for pica? Despite the knowledge about this phenomenon for centuries, there is still no explanation of the pathophysiology of it. There do exist a number of hypotheses that we will try to clarify.

Some authors suggest that pica could induce iron deficiency by the binding of pica materials on the mucosal layer of the gut and thereby preventing the absorption of micronutrients. This is described in the literature as the first adaptive hypothesis or the 'protection hypothesis'. These materials may also absorb micronutrients in ingested food, which prevents them from being metabolized (12). In a recent study, Seim et al. refuted this hypothesis, stating that geophagic substances do not bind to bioavailable iron and are therefore not responsible for reduced iron absorption. With their study they proposed an in vivo model for assessing the impact of geophagic earth on iron status. A group of broiler chickens were force-fed daily with varying dosages of geophagic material or pure clay mineral. At the end of a 4 weeks period they detected only a minimal impact on the iron status and on the transcript levels of divalent metal transporter 1 (DMT1) of the animals (13). The protection hypothesis suggests that pica-materials are ingested as medication. Pica may be protective by either reducing the permeability of the gut wall to toxins and pathogens or by binding directly to the toxins (12). In this hypothesis questions about the strong association between pica and anemia continue to exist. Pentice et al. suggest in their interpretation of the protective hypothesis that anemia might be a response to infections, whereby the sequestration of certain nutrients can protect against pathogenic agents. Many bacteria need iron to reproduce and so iron sequestration would reduce bacterial growth rates. By accepting this hypothesis, the relationship between anemia and pica would rather be correlational than causal (14,15).

More often it is said that iron deficiency itself induces pica. Young et al. explain this in their second adaptive hypothesis, claiming that consuming micronutrients like calcium, sodium, zinc, and iron is an attempt to compensate for their shortage. They actually rejected this hypothesis in their 2016 paper about geophagy when they said that the timing of geophagy does not parallel the timing of changes in nutrient needs through the lifespan. Furthermore, the irregular presence and low bioavailability of iron in geophagic earth, as well as experimental data indicating that micronutrient absorption is limited after earth consumption, raises doubts on their hypothesis (15).

The last and most plausible explanation is the neurological based or non-adaptive one. Pica cravings could be an epiphenomenon of nutrient deficiencies that affect appetite-regulating brain enzymes or taste sensitivity (15). Recent experiments in rats have shown that iron deficiency can modify olfactory behavior and that DMT1 levels are significantly higher in the olfactory bulbs of iron-deficient rats. The gustatory function might also involve DTM1 and therefore be influenced by body iron repletion. It is be possible that the iron content of the hippocampus influences the expression of pica in humans (12). Another possible explanation is that iron deficiency is responsible for a decrease in dopaminergic transmission, leading to pica. This is suggested because of a clear exacerbation of pica behavior under therapy with neuroleptics (8). The decreased iron levels in the central nervous system would therefore be the pathophysiological basis of pica (12).

Conclusion

Pica and its association with IDA have been known for centuries but its precise pathophysiology remains a mystery. Its cause keeps being the source of speculation and no study results have been unanimous. Even in this case, it is not sure whether the pica behavior disappeared because of the oral iron treatment or because of the dietary changes and how big the impact of his autistic behavior was. It is important to treat the possible underlying ID and therefore oral iron therapy is the first choice because it is readily available, inexpensive, effective and safe.

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Febrile cholestasis with mucocutaneous signs in a 13-year old during COVID-19 pandemic: a forgotten intravenous immune globulin response.

Eline Lambert [a], Koen Kaïret [b], Liesbet Vercammen [c], Bert Suys [d], Luc Pattyn [c]

[a] Department of Pediatrics, University Hospitals Leuven, Belgium
[b] Department of Pediatrics, AZ Sint-Jozef Malle, Malle, Belgium
[c] Department of Pediatrics, AZ Turnhout, Turnhout, Belgium
[d] Department of Pediatric Cardiology, GZA, Antwerp

eline.lambert1@student.kuleuven.be

Keywords

Coronavirus disease 2019; incomplete Kawasaki disease; intravenous immune globulin; febrile cholestasis

Abstract

Intravenous immune globulins (IVIG) are increasingly used in Kawasaki-like cases possibly related to coronavirus disease 2019 (COVID-19), generally with striking clinical response. We describe a teenager presenting febrile cholestasis, along with coronary aneurysm and other criteria fulfilling incomplete Kawasaki disease. The girl was treated with high dose acetylsalicylic acid and IVIG transfusion. Laboratory work-up revealed hepatitis antibodies. However, this result was obtained after IVIG and is considered as passively transferred IgG's from blood donors. Especially during COVID-19 pandemic, clinicians should be familiar with unusual Kawasaki presentations as febrile cholestasis, as well as inconclusive serology after the desired IVIG therapy.

Introduction

Kawasaki disease (KD) is the most common pediatric systemic vasculitis, mostly affecting children under five years (1). KD typically presents as a self-limited condition, with fever and other acute inflammatory manifestations. Coronary arteritis leading to coronary artery aneurysm is the most important complication. The frequency of aneurysm development and mortality of KD has dramatically decreased with intravenous immune globulin (IVIG) therapy. Etiology of KD remains unknown, although some infectious agents are considered as triggers in genetically predisposed individuals (1). During the COVID-19 pandemic, in April 2020, clinicians in the United Kingdom noted an increasing number of previously healthy children presenting with a severe inflammatory syndrome with Kawasaki features (2). All 8 reported cases tested positive for SARS-Cov-2 antibodies. On May 14th, the Centers for Disease Control and Prevention (CDC) issued a public health advisory and case definition, terming it Multisystem Inflammatory Syndrome in Children (MIS-C) associated with COVID-19 (3). Other authors refer to the entity as Pediatric Inflammatory Multisystem Syndrome Temporally associated with SARS-CoV-2 infection (3).

Case report

On May 16th, a 13-year-old girl was admitted to our pediatric department with protracted fever for five days. She complained of swollen fingers and generalized pruritus. In the past week, she experienced two episodes of presyncope when standing up. Her medical history included prematurity, short bowel resection secondary to fulminant necrotizing enterocolitis and yearly iron infusion for iron deficiency anemia. She took weekly vitamin D supplementation as only medication. She was in general good health and had no known contacts with SARS-Cov-2 virus. Clinical examination revealed a moderately sick teenager with diffuse polymorphous exanthema, icteric sclerae, strawberry tongue and crackled lips. Extremities showed mild edema, but no desquamation. Neither lymphadenopathies nor enlarged liver were palpated. Upon presentation, she was hemodynamically stable with a blood pressure of 100/56 mmHg, body temperature 38.0°C. Laboratory examination showed elevated inflammatory parameters: erythrocyte sedimentation rate 54 mm/h (ref. range < 20 mm/h) , C-reactive protein 23.2 mg/L (ref.range <5 mg/L), leucocyte count 11.4 x10E9/L (ref. range 4.3-11.0 x 10E9/L), with decreased lymphocyte count 0.4 x10E9/L (ref. range 0.97-3.96 x 10E9L). Thrombocyte count was normal, ferritin levels were at 110 µg/L (ref. range 13-78 µg/L). We noted discrete hypo-albuminemia 34 g/L (ref. range 35-55 g/L). Prothrombin time was prolonged (INR 1.2) with elevated fibrinogen and D-dimers. Liver enzymes aspartate aminotransferase and alanine aminotransferase were only mildly elevated, contrasting with marked elevation of total bilirubin up to 87.2 umol/L (ref. range <17.1 umol/L) and gamma-glutamyl transferase 227 U/L (ref. range <21 U/L). Alkaline phosphatase remained within the reference range.

Throat swab was negative for streptococcal infection. Urine sample showed a moderate sterile pyuria. Abdominal ultrasound revealed no hepatic or biliary abnormalities. Echocardiography showed inflammation of the left coronary artery with proximal fusiform aneurysm. (Fig1). We considered this case as strongly suspicious for MIS-C, although CDC definition was not fulfilled because of negative SARS-Cov-2 polymerase chain reaction (PCR) on nasopharyngeal swab. The patient was hospitalized and intravenous immunoglobulins (IVIG, Nanogam®) were administered at dose regimen 2g/kg. Respecting coronary aneurysm, acetylsalicylic acid was started at anti-inflammatory dose (50 mg/kg daily). After initiation of IVIG, rapid clinical improvement was seen with gradual normalization of all clinical as well as biochemical anomalies. Vital signs remained stable during hospitalization. Considering differential diagnosis for jaundice, viral hepatitis serology was investigated on a second blood sample. It revealed hepatitis B surface antibodies along with hepatitis B core antibodies and positive hepatitis E IgG antibodies. All hepatitis IgM antibodies were negative. Given that she was vaccinated following the Belgian scheme and had no history of hepatitis infection, this was a particular result. Retrospective analysis of the blood sample prior to IVIG administration, however, showed absence of any hepatitis antibodies. SARS-Cov-2 antibodies turned out to be negative as well.

Repeated echocardiography showed slightly decreased coronary abnormalities. The patient was discharged after five days with continuation of acetylsalicylic acid at antithrombotic dose (2 mg/kg daily). Ambulatory follow up, including pediatric cardiology and hepatology, was provided.

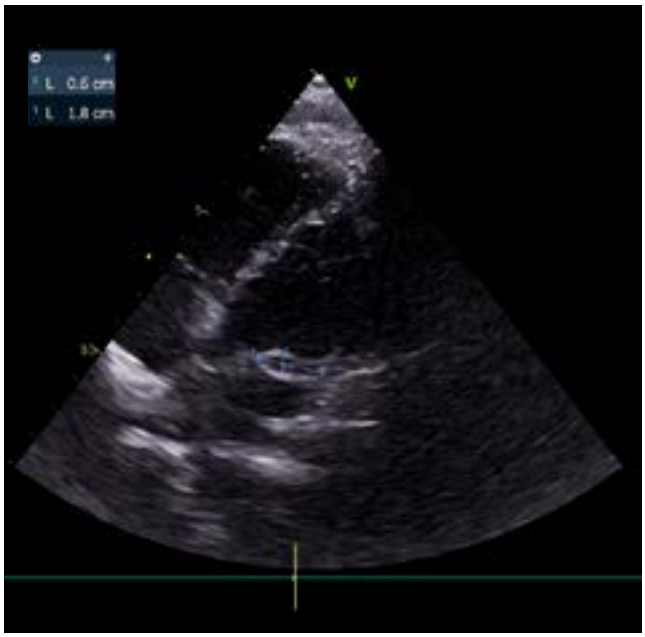
Discussion

This case broaches two important observations. Firstly, we describe a Belgian teenager presenting with Kawasaki-like disease during COVID-19 pandemic. Presenting with fever lasting for five days and presence of 3/5 major clinical signs of KD, diagnosis of incomplete Kawasaki disease can be established (1). Laboratory parameters (hypo-albuminemia, coagulopathy, pyuria) as well as echocardiographic abnormalities support this diagnosis. On the other hand, clinical as well as biological course is largely parallel to other reported cases of multisystem inflammatory syndrome associated with COVID-19 (2,3). Contrasting with many others, our patient did not need intensive care. We believe prompt recognition and initiation of IVIG treatment might be a partial explanation, but also MIS-C likely representing a spectrum of disease (3). Our case meets most criteria for MIS-C following CDC definition: individual aged <21 years presenting with fever, laboratory evidence of inflammation, clinical severe illness requiring hospitalization, multisystem organ involvement (cardiac, hematological, dermatological and hepatic) and no other plausible diagnosis. There was no evidence for current or recent SARS-Cov-2 infection by PCR nor serology. Nonetheless, we believe our case to be related to COVID-19 considering Belgian epidemiological situation at time of diagnosis, characteristic lymphocytopenia and the -otherwise rarely- KD in a teenager (1,4). Negative serology is noted in some other suspected reports as well (3). As expected in MIS-C, the girl responded stunningly to IVIG therapy.

Secondly, our patient presented cholestasis with conjugated hyperbilirubinemia up to 87 umol/L at time of diagnosis. Although not widely recognized among clinicians, acute febrile cholestasis is associated with Kawasaki disease in up to 20% of the cases (5). To exclude viral origin, we performed hepatitis serology which showed hepatitis B and E IgG-antibodies. We note that this result was obtained after initiation of IVIG therapy. Initial blood sample being negative for all hepatitis antibodies, cholestasis in our patient is presumably related to KD. This hypothesis was reinforced by gradually declining cholestatic parameters during hospital stay.

Human immune globulins are antibody-containing products purified from large pools of human plasma (6). The WHO has published minimum standards for manufacturing IVIG preparations. Preparation should contain highly purified polyvalent IgG from at least 1000 individual donors, undergoing viral inactivation processes among many others. Following European guidelines, Belgian blood services use triplet HIV/HBV/ HCV nucleic acid testing in blood product donors (7). Consequently, subjects with prior hepatitis B infection (negative hepatitis B surface antigen, no HBV DNA but anti-hepatitis B surface and anti-hepatitis B core IgG) are eligible donors.

Figure 1 : *Left coronary artery inflammation with proximal fusiform aneurysm at diagnosis in our patient. Measurements: 1.8 x0.6 cm (May 16th, 2020)*



Hepatitis E (HEV) on the other hand is a fecal- orally transmitted RNA-virus. Seroprevalence in blood donors in European countries varies from 2 to 49% and is rising during the past 10 years (8,9). After acute infection, hepatitis E IgG's are probably lifelong detectable but do not protect against re-infection. HEV transmission with blood transfusion is described, but not with IVIG. HEV RNA is currently not tested in blood donors in Belgium, although recent data support this practice (9). In conclusion, hepatitis epidemiology and blood donor screening strategy in Belgium, can explain the presence of hepatitis B as well as hepatitis E IgG's in IVIG preparations.

As illustrated, IgG serologic studies can become falsely positive after IVIG therapy due to passively transferred antibodies (6). Considering IgG's half-life of 21 to 28 days, these antibodies should not persist beyond 60 days. Indeed, in our case, there was absence of hepatitis B core and hepatitis E IgG on laboratory testing a few months later. Quantification of hepatitis B surfaces antibodies was at 5 IU/L (ref. range after vaccination >10 IU/L). We conclude that our patient is a non-responder to routine vaccination, therefore we planned a hepatitis B booster vaccination.

Conclusion

During the first months of COVID-19 pandemic pediatricians worldwide noticed a rising number of Kawasaki-like cases, some exhibiting severe multisystem inflammation requiring intensive care. We faced the case of a teenager also suffering from acute cholestasis and coronary aneurysm. All clinical criteria as defined by the CDC for Multisystem Inflammatory Syndrome in Children (MIS-C) were met. Following timely recognition and initiation of IVIG therapy, the girl demonstrated a rapid and complete recovery. Through diagnostic work-up, we encountered positive hepatitis B and E antibodies that were passively transferred by IVIG and had no clinical impact.

This case thus highlights two important learning points:

- Febrile cholestasis as a presentation of Kawasaki disease in up to 20% of cases.
- The importance of diagnostic antibody testing prior to IVIG administration. We warn clinicians for drawing incorrect serologic conclusions thereafter due to passive transfer of IgG's.

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Treatment-resistant papilledema in a boy with homocystinuria

Lisa Neven [a], Ingele Casteels [a], Peter Witters [b], Katrien Jansen [b], Catherine Cassiman [a]

[a] Department of Ophthalmology, University Hospitals Leuven, Leuven, Belgium
[b] Department of Pediatrics, University Hospitals Leuven, Leuven, Belgium

lisa.neven@uzleuven.be

Keywords

Betaine, homocystinuria, hypermethioninemia, cerebral edema

Abstract

We report an 8-year old boy with the diagnosis of pyridoxine non-responsive cystathione beta-synthase deficiency. At a routine ophthalmological examination bilateral papilledema was detected on fundoscopy. Urgent brain imaging showed the typical signs of elevated intracranial pressure and cerebral edema. Laboratory results revealed high plasma methionine levels, secondary to treatment with betaine and a catabolic state because of a low calorie intake. Methionine excess is usually reversible with discontinuation of betaine together with a methionine restricted diet. In our patient however, a ventriculoperitoneal shunt placement was required to lower intracranial pressure and resolve the bilateral papilledema.

Introduction

An 8-year old boy, diagnosed with autism spectrum disorder, was referred to our ophthalmology department because of a suboptimal visual acuity with his current spectacle correction. At presentation a suboptimal visual acuity of LogMar 0.35 was measured in the right eye and LogMar 0.45 in the left eye. Retinoscopy revealed myopic astigmatism of -4 (-3x180°) on the right and -2.5 (-1.75x10°) on the left eye. Biomicroscopic examination of the anterior segment revealed a bilateral lens subluxation. To exclude systemic disease associated with lens luxation, our patient was referred for metabolic screening. The biochemical investigations matched with the diagnosis of cystathione beta-synthase deficiency or classical homocystinuria. The plasma homocysteine and methionine concentration at diagnosis were respectively 120µmol/L (normal 7-15µmol/L) and 176µmol/L (normal 10-45µmol/L). Molecular genetic analysis confirmed the biochemical diagnosis. First-line treatment with pyridoxine (vitamin B6) was not successful in correcting the metabolic disturbances. Betaine was started in a low dose (100mg/kg/day), in combination with a moderate protein restriction of 2.4 g of natural protein per kg per day to reduce homocysteine and methionine levels. The plasma levels of methionine were routinely monitored after the introduction of Betaine. In the first six months after betaine introduction the plasma methionine concentration ranged between 834 µmol/L and 1004 µmol/L.

On routine ophthalmological examination, six months after the introduction of betaine, fundoscopy revealed bilateral papilledema (figure 1A). Early morning vomiting, an important neurological sign of increased intracranial pressure, was reported since one month with an increased frequency in the last week. Caloric intake in the last few weeks was low. Due to the autism of the child, headaches were not reported. The plasma methionine concentration was 1257 µmol/L (normal ≤45µmol/L) and urgent brain computed tomography showed crowding of the sulci and gyri with white matter edema, consistent with the diagnosis of elevated intracranial pressure (figure 2). In homocystinuria there is a well-known risk of thrombosis, but clinical or radiographically signs of a cerebral vein thrombosis were absent. A magnetic resonance venography to exclude a thrombosis, was not performed.

Betaine was discontinued and acetazolamide (dose 3x250mg) was started, but without significant improvement of the intracranial abnormalities or laboratory results after several days. A high calorie diet with more rigorous protein restriction was started to prevent a catabolic state that would aggravate the hypermethioninemia. Evacuating lumbar punctures to lower intracranial pressure, were not performed because of the cerebral edema. Unfortunately, ophthalmological follow-up on day 10 showed a bilateral decrease in visual acuity with persistent papilledema and beginning signs of optic disc pallor (figure 1B). Placement of a ventriculoperitoneal shunt to lower the intracranial pressure was decided. Hence, the bilateral papilledema resolved quickly. In the following months, there was no recurrence of the papilledema. Because of progressive astigmatism, bilateral lensectomy with intraocular lens implantation was performed. At a follow-up visit, two years after the acute episode of papilledema, the best-corrected visual acuity was LogMar 0.15 in the right eye and 0.05 in the left eye. Unfortunately the optic discs remained partially atrophic because of the episode of persistent intracranial hypertension (figure 1C).

Discussion

Classical homocystinuria, the most common type of homocystinuria, is an autosomal recessive disorder of the metabolism of homocysteine due to deficiency of cystathionine beta synthase. This leads to an accumulation of homocysteine and methionine, leading to adverse effects on the ocular, skeletal, cardiovascular and central nervous system (1). Early signs and symptoms of homocystinuria can be subtle in infants, leading to a diagnostic delay; visual problems can give a clue to the diagnosis of homocystinuria. The major ocular manifestation is a high and rapidly progressive myopia at young age. The presence of a suboptimal vision with full correction of myopia and astigmatism should suggest the presence of ectopia lentis. Less frequently reported ophthalmological findings are iridodonesis, glaucoma, optic atrophy, retinal detachment and central retinal artery occlusion. Systemic neurological findings include intellectual deficits, developmental delays, seizures and psychiatric disorders. Due to elevated levels of homocysteine, patients have an increased risk for premature atherosclerosis and venous thromboembolism (1). Early recognition and treatment of homocystinuria is important because symptoms at an early stage can be reversible (2). First-line treatment consists of high doses of vitamin B6 (pyridoxine). Insufficient lowering of homocysteine in pyridoxine-unresponsive patients requires the start of a methionine restricted diet in combination with betaine (trimethylglycine). Betaine lowers homocysteine levels by promoting the conversion of homocysteine to methionine (2).

The first case of cerebral edema in a patients with homocystinuria was

reported in 2002 in a 10-year old girl who recently was put on betaine therapy. After withdrawal of betaine and with a strict diet, the cerebral edema resolved (3). This timeline strongly suggests that betaine can be responsible for the elevated intracranial hypertension. Almost all reported cases of intracranial hypertension, including our case, started after introduction or dose raise of betaine. However, the incidence of brain edema in patients receiving betaine therapy is low and most patients tolerate betaine without apparent complications. The safe dose range of betaine is not yet established, but research suggests that the additional benefit of betaine dose above 150 mg/kg/day is low (4). Also, most cases of brain edema occur at levels above 150 mg/kg/day. Schwahn et al. reported only one case of intracranial hypertension when taking only 107 mg/kg/day of betaine, but in our patient the dose of betaine was also low (100 mg/kg/day)(5). In cases of excessive hypermethioninemia in patients taking a relative low dose of betaine, a bad adherence to the diet or a catabolic state due to a low calorie intake should be suspected.

Two hypothesis are currently proposed in literature to explain the development of brain edema in patients on betaine treatment. The first hypothesis suggests a direct effect of betaine on the brain. Betaine has been described as being an intracellular osmolyte and osmoregulator in the brain, which could lead to the accumulation of intracerebral fluid (6). There are few data regarding plasma and cerebrospinal fluid concentrations of betaine during an acute episode of brain edema. Devlin et al. reported a case with plasma levels of betaine of 98µmol/L (normal range for subjects without betaine intake of 18-73µmol/L) and cerebrospinal fluid levels of 6.6µmol/L (no normal range provided)(7). Schwahn et al. presented a case of cerebral edema in a patient with plasma betaine levels of 131µmol/L (5). Considering these available relatively low concentrations of betaine in plasma and in cerebrospinal fluid, they assumed the hypothesis of an accumulation of betaine was less likely. In contrast, the measured levels of methionine in plasma and cerebrospinal fluid were excessively increased when compared to normal levels (5). This finding could match with the second hypothesis, which states that the hypermethioninemia itself is responsible of the acute brain edema. Elevated methionine concentrations have a well-known toxic effect on cells of the brain (8). The intake of betaine only enhances the hypermethioninemia because of its working mechanism in converting homocysteine to methionine. This hypothesis is supported by reports of patients with cerebral edema and hypermethioninemia without intake of betaine. Mudd et al. described two healthy infants with methionine excess due to a high methionine intake who developed cerebral edema (9). Allen et al. reported a single patient not on betaine treatment in a group of 35 homocystinuria patients with hypermethioninemia and encephalopathy (10).

In patients with homocystinuria, plasma methionine levels should be monitored routinely. Schwahn et al. collected the methionine levels of all published case reports of acute encephalopathy. This revealed that the lowest plasma level of methionine at the time

Figure 1 : *Fundus photographs of the optic nerves. (*
A) Papilledema at presentation.
(B) Sectorial optic atrophy, day 10 after diagnosis of intracranial hypertension. The arrows delineate the optic nerve atrophic areas.
(C) Atrophic discs at the two year follow-up visit.

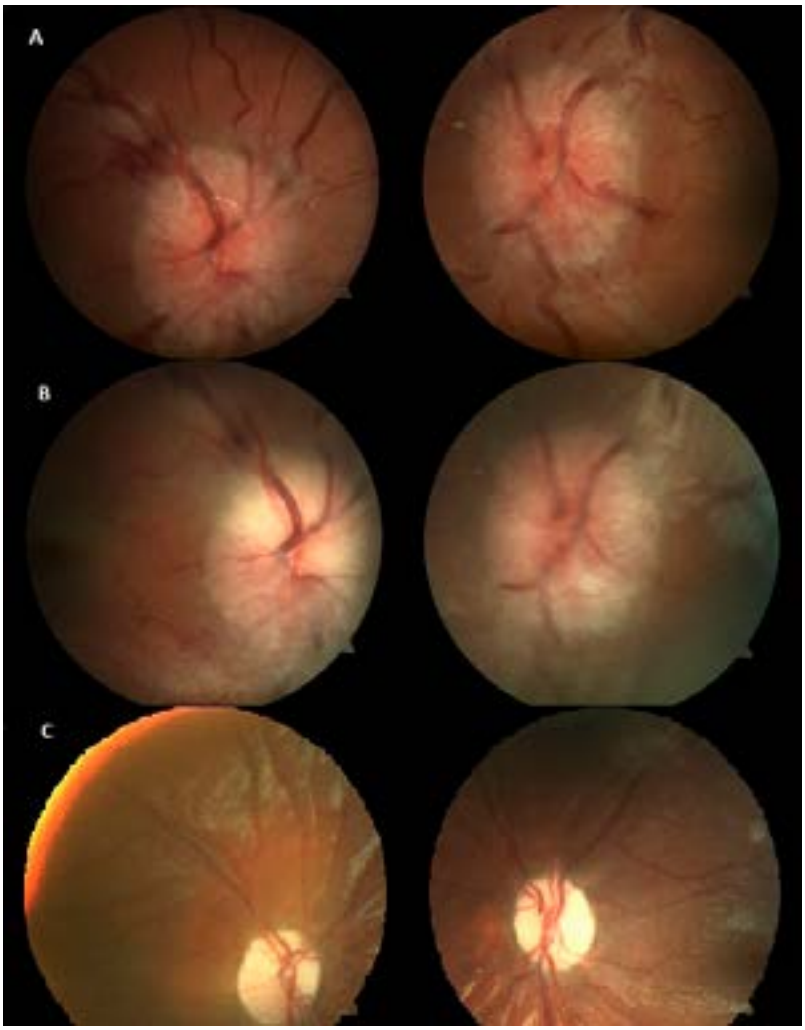
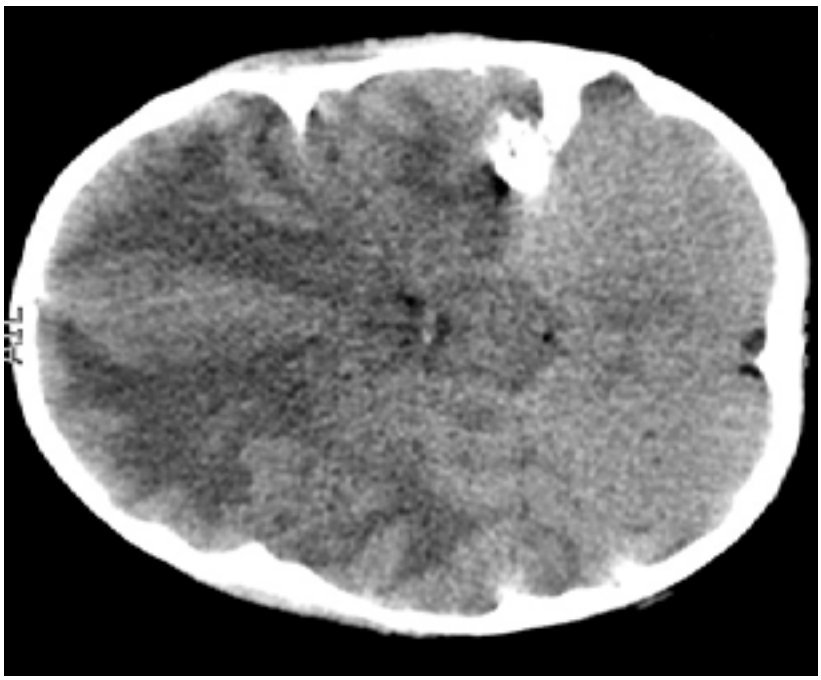


Figure 2 : *Diffuse white matter edema on brain CT.*



of elevated intracranial pressure was 559 µmol/L. They concluded that methionine levels below 500 µmol/L can be considered safe (5). Most cases of cerebral edema developed at levels close to or above 1000 µmol/L, analogous to our case.

The approach of hypermethioninemia in the context of signs or symptoms of intracranial hypertension varies in literature, but if methionine is prompt and successfully lowered, the prognosis is good. Ismayilova et al. reported a case of reversible white matter edema after tightening control of dietary methionine intake without reducing or stopping betaine treatment (11). Vatanavicharn et al. started enteral feeding in their case and continued betaine in a low dose (1 g/day)(12). In most cases however, treatment with betaine was stopped. Only in exceptionally cases, additional treatment was necessary to reduce intracranial pressure. Devlin et al. reported a case of acute hypertension, bradycardia and loss of consciousness due to the diffuse brain swelling. Bilateral frontotemporal decompressive craniotomies were performed (7). In our patient, the hypermethioninemia persisted 10 days after stopping betaine. Ophthalmological follow-up showed a bilateral decrease in visual acuity with persistent papilledema and beginning signs of optic disc pallor, leading to the decision to place a ventriculoperitoneal shunt to lower intracranial pressure.

Conclusion

We present a case of treatment-resistant papilledema associated with high methionine levels in a boy with cystathione beta-synthase deficiency on betaine treatment. The underlying pathophysiology of the cerebral edema and the susceptibility of some patients to this complication, is not clear. In patients receiving betaine, attention must be paid to signs and symptoms of intracranial hypertension. Ophthalmological follow-up is essential in the early detection and monitoring. Strict adherence to a methionine restricted diet and dose adjustment or discontinuation of betaine should be considered if methionine levels rise above 1000 µmol/L. In most cases of cerebral edema, the neurological symptoms disappear and the cerebral edema resolves. In selected cases, additional neurosurgical interventions are necessary to lower the intracranial pressure.

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Pulmonary Embolism complicated Acute Chest Syndrome and suspected SARS-CoV-2 infection in adolescents with Sickle Cell Disease.

Milena Demey [a], Laurence Dedeken [b], Pierre Smeesters [a,c], Anne Tilmanne [c], Alina Ferster [b]

[a] Department of Pediatrics –Hôpital Universitaire des Enfants Reine Fabiola (HUDERF) – Université Libre de Bruxelles (ULB) - Brussels – Belgium
[b] Hematology-Oncology Unit– Hôpital Universitaire des Enfants Reine Fabiola (HUDERF) – Université Libre de Bruxelles (ULB) - Brussels – Belgium
[c] Infectious Disease Unit – Hôpital Universitaire des Enfants Reine Fabiola (HUDERF) – Université Libre de Bruxelles (ULB) - Brussels – Belgium

milena.demey@ulb.be

Keywords

Sickle cell disease, COVID-19, Acute Chest Syndrome, Thromboembolic Events

Abstract

SARS-CoV-2 causes a hypercoagulable state that predisposes patients to thromboembolic events. We report two adolescents with sickle cell disease who developed pulmonary embolism during an acute chest syndrome episode associated with a possible SARS-CoV-2 infection. Both sickle cell disease and SARS-CoV-2 infection predispose to thromboembolic disease. Thromboprophylaxis with low molecular weight heparin should be considered in adolescent with acute chest syndrome, related or not to COVID-19 disease.

Introduction

Acute chest syndrome (ACS) can be a severe life-threatening condition and is defined as an acute illness characterized by fever and/or respiratory symptoms, with a new pulmonary infiltrate on chest X-ray (1). In addition to an infectious cause, microvascular injury, fat embolism, fluid overload and/or hypoventilation may trigger or worsen ACS. In adults with sickle cell disease (SCD), ACS is the main cause of death and may be complicated by pulmonary embolism (PE) (2).

On January 01, 2021, a total of 82 745 324 COVID-19 confirmed cases have been reported in the world with 1 805 521 deaths. In Belgium, 644 242 confirmed cases were associated with 19 441 deaths. SARS-CoV-2 virus mainly causes a respiratory distress syndrome but can also affect other organs and has been associated with cardiovascular complications (3).

SARS-CoV-2 binds to the cells expressing angiotensin-converting enzyme 2 (ACE-2) which is mainly expressed in alveolar cells but also in cardiac epithelial cells as well as in intestine, kidney and blood vessels (4). Through this binding, ACE-2 is less active and angiotensin II increases, provoking vasoconstriction, inflammation, and oxidative organ damage.

People over 65 years-old or with co-morbidities (such as obesity and high blood pressure) are more at risk of having a serious illness when they are infected by SARS-CoV-2 (4).

In SCD, SARS-CoV-2 (as other viruses) can trigger vaso-occlusive crises (VOC) and/or ACS through a major inflammatory cascade. SCD can probably be considered as an additional risk of having complications, but evidence is needed to confirm this hypothesis (5).

SARS-CoV-2 disease favors hypercoagulable status by endothelial inflammation, hypoxia, immobilization and diffuse intravascular coagulation that puts patients at a significant risk of venous thromboembolic events (VTE) (6).

We report here two Adolescents and Young Adults (AYA) with SCD who developed PE during ACS in a possible context of SARS-CoV-2 infection.

Case report 1

On April 04, 2020, a 17-years-old boy with SCD and autism chronically treated with hydroxyurea, folic acid, aripiprazole and zinc was hospitalized for ACS and managed accordingly (Table 1). He presented low oxygen saturation on pulse oximetry with hypoxia (partial pressure of arterial oxygen of 65mmHg). Oxygen support through non-rebreather mask was needed from day 1 to day 13. In addition, 2 top-up transfusions were required. SARS-CoV-2 infection was confirmed on day 1 by polymerase chain reaction (PCR) on nasopharyngeal swab (no serologies have been performed). No other pathogen was found in blood cultures and the film array respiratory panel on the nasopharyngeal swab was negative. On day 12, respiratory distress worsened, and the biological inflammatory syndrome increased. Computerized tomography (CT) pulmonary angiogram revealed right postero-basal segmental PE (as well as an infiltrate in the basal fields) (Fig. 1A and 1B). Treatment with low molecular weight heparin (LMWH) was started and the patient could be discharged on day 19. LMWH treatment was scheduled for 3 months. When last seen in June 2020, the adolescent was well.

Case report 2

On April 24, 2020, an 18-year-old boy with SCD chronically treated with hydroxyurea and folic acid was hospitalized for ACS and managed accordingly (Table1). He didn't present hypoxia at admission. Oxygen saturation and hypoxemia worsened at day 6, and non-invasive ventilation was required until day 9 in the Pediatric Intensive Care Unit. At admission, pulmonary CT-scan revealed ground glass opacities in both lungs (suggestive of COVID-19 disease). In addition to ventilation support, two top-up transfusions followed by one exchange transfusion for persistent hypoxemia were decided. Prophylactic LMWH was administered from day 9 to day 12 when information about the risk of thromboembolism associated with COVID-19 had emerged, but it was stopped after 4 negative SARS-CoV-2 PCRs on nasopharyngeal swabs, and due to unavailability of guidelines for the thromboprophylaxis in COVID-19 patients at this time. On day 15, the patient became dyspneic, febrile again and the biological inflammatory syndrome increased. PE in the lower left segment (Figs. 2A and 2B) was found on CT pulmonary angiogram. After initiation of therapeutic LMWH, the patient improved and could be discharged on day 21 with LMWH scheduled for 3 months. On day 19, IgG-antibodies for SARS-CoV2 were positive which suggested a possible COVID-19 disease. Other microorganisms could not be identified on blood cultures or with the film array respiratory panel on the nasopharyngeal swab. When last seen in August 2020, the patient was well.

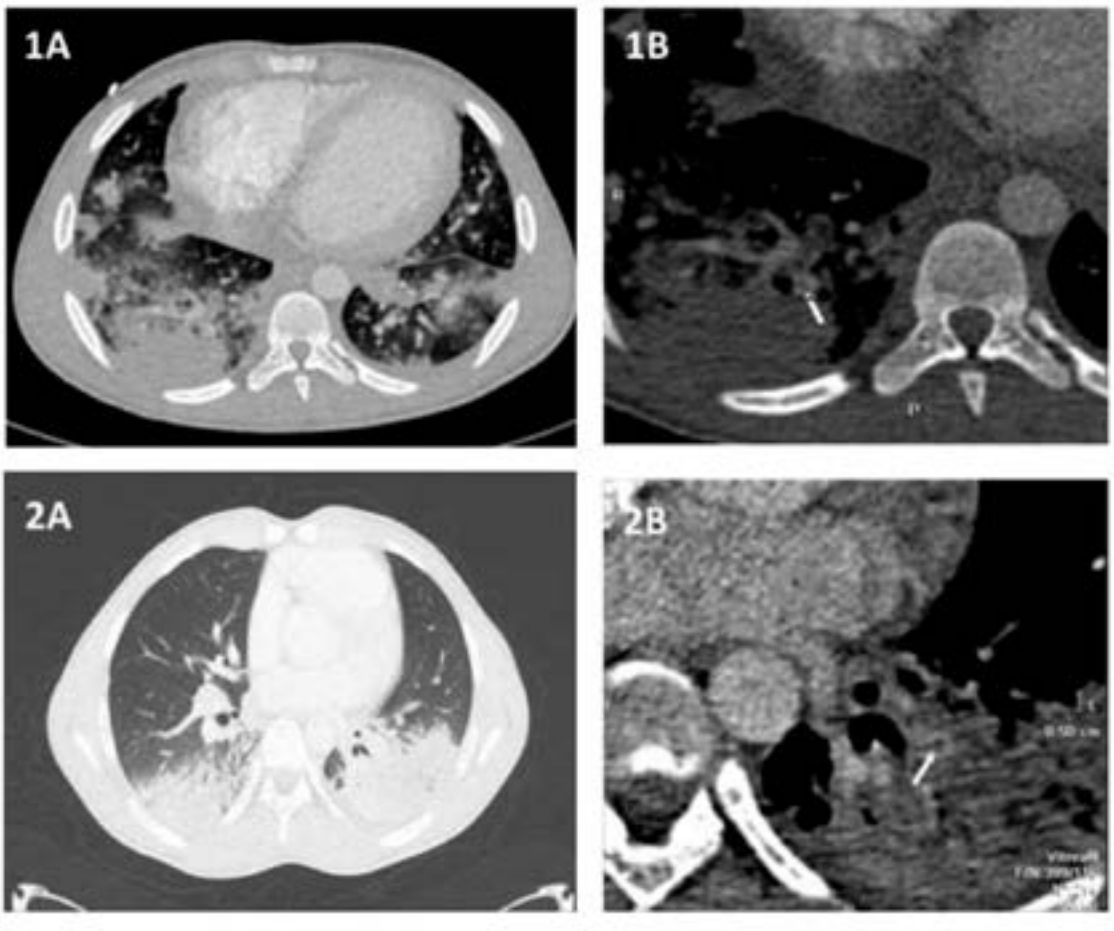
Discussion

The risk of VTE in the SCD adult population is high. In a cohort of 1523 SCD patients aged over 15 years, the Cooperative Study of SCD calculates a VTE

Table 1. *Patient characteristic*

	Patient 1	Patient 2
Sex	Male	Male
Age (years)	17	18
Body mass index	21.2	23.5
Medical History	Sickle Cell Anemia Autism spectrum disorder	Sickle Cell Anemia
Symptoms	Fever (39°C), cough, vomiting, fatigue, tachypnea (45 breath/minute)	Chest pain, chills, fever (38,5°C), tachypnea (40 breath/minute)
Laboratory values at admission Hemoglobin (g/l) White blood cell count (10E9/l) Lymphocytes (10E9/l) Neutrophils (10E9/l) Platelet Count (10 E9/l) CRP (mg/l)	 8.7 13.2 3.3 7.8 279 100	 7.4 18.9 2.2 14.9 300 150
Laboratory values at deterioration Hemoglobin (g/l) White blood cell count (10E9/l) Lymphocytes (10E9/l) Neutrophils (10E9/l) Platelet Count (10 E9/l) CRP (mg/l)	 8.2 12.5 1.6 7.8 800 340	 9.5 24.4 1.5 19.5 920 122
Respiratory support	Non-Rebreather-Mask (10L/min) for 13 days (day 1 to day 13)	Non-Invasive Ventilation for 4 days (day 6 to day 9)
Days in Pediatric Intensive Care Unit	0	3
Central venous catheter	No	No
Exchange transfusion	0	1 (day 8)
Prophylactic anticoagulation	None	Enoxaparin 3 days (day 9 to day 12)
Signs of deep venous thrombosis of the limbs	No	No
PCR on rhinopharyngeal swabs	Positive (day 1)	Negative (day 1,2, 8, 11)
Serology for SARS-CoV2	Not done	IgG 42UI/L – IgM 0 UI/L

Figure 1 : *CT pulmonary angiogram performed in Patient 1 on day 12 revealed consolidations and ground glass opacities in both lungs (Fig 1A) and right postero-basal segmental pulmonary embolism (Fig A2). In patient 2, CT pulmonary angiogram performed on day 15 confirmed the presence of consolidations in the lower lobes (Fig 2A) and right postero-basal segmental pulmonary embolism (Fig 2B).*



rate of 5.2 per 1000 person-years and the incidence of VTE was 11,3% by age of 40 years (7).

The American College of Chest Physicians recommends thromboprophylaxis for all SCD adults (> 18 years) who are admitted for an acute medical condition. There are no such recommendations for children. Our two patients were nearly adults and should have been treated as such. Recommendations for VTE prophylaxis in adults are usually not appropriate in children as their incidence of thrombosis is much lower. However certain factors are clearly associated with an increased risk of thrombosis: intensive care unit admission, the presence of central venous catheters, mechanical ventilation, postpubertal age, obesity, inflammatory disease. Our two patients had respectively 2 and 3 risk factors associated with an increased risk of VTE as indicated in the Branchford risk model which suggest pharmacological intervention in the presence of ≥ 3 risk factors (8).

The exact incidence and pathophysiology of PE in COVID-19 disease is not yet well known, but scientific data is increasing on this topic. SARS-CoV-2 causes an inflammatory cascade and a dysfunctional hemostatic system with high fibrinogen and D-dimers, leading to a hypercoagulable state and a risk for VTE. Hypoxemia further promotes vascular occlusion by decreasing blood flow by vasoconstriction (6).

On May 21, 2020, The American Society of Hematology recommended a pharmacologic thromboprophylaxis in all hospitalized adults with COVID-19, unless it is contraindicated. If this is the case, mechanical VTE prophylaxis (such as compression stockings) should be proposed (9). The Belgian Society on Thrombosis and Hemostasis (BSTH) adhered to this guideline in early June 2020. Our two patients were not treated according these recommendations due to their hospitalization in April 2020 and May 2020.

Compared to adults, SARS-CoV2 infections in pediatric population is less severe with frequent milder clinical courses or asymptomatic cases (10). Nevertheless, Feldstein reported presence of DVT/PE in children with multisystem inflammatory syndrome (MIS-C) (11).

Heilbronner and colleagues presented 12 SCD children (aged 5–17.5 years) admitted to the Pediatric Intensive Care Unit of the Necker Hospital in Paris for an ACS (12). All of them received thromboprophylaxis with Enoxaparin. Four patients had a PCR positive for SARS-CoV2 and they all required respiratory support with noninvasive ventilation. One of the patients aged 16 had a PE even under thromboprophylaxis. This data suggests that even pediatric SCD patients are at risk of PE and should be given antithrombotic prophylaxis. We tend to think that adolescents are more at risk than young children to evolve like adults, as is the case with our two patients.

Sars-CoV-2 infection in our second patient is suggested by the positive single point IgG serology but cannot be proven given the multiple negative PCRs on nasopharyngeal swabs. It could have been a previous exposure with no contribution to the existing respiratory illness.

Conclusion

Particular attention should be given to children and adolescents with SCD who are hospitalized during the COVID-19 epidemic and thromboprophylaxis with LMWH should be considered in adolescent with ACS in a context of COVID-19 disease or not. A high suspicion for PE should be kept in all circumstances in patient with SCD, and particularly in COVID-19 severe cases.

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BEXSERO

Vaccin tegen meningokokken van groep B
(rDNA, component, geadsorbeerd)

Het **eerste** vaccin tegen meningokokken van **serogroep B**.[1]

Het **enige** geïndiceerd vanaf **2 maanden**.[1,2]

2+1

voor zuigelingen vanaf de leeftijd van **2 maanden**.[1]

VERKORTE SAMENVATTING VAN DE PRODUCTKENMERKEN Gelieve de Samenvatting van de Productkenmerken te raadplegen voor de volledige informatie over het gebruik van dit geneesmiddel. **NAAM VAN HET GENEESMIDDEL** Bexsero suspensie voor injectie in voorgevulde spuit Meningokokken groep Bvaccin (rDNA, component, geadsorbeerd) EU/1/12/812/001, EU/1/12/812/002, EU/1/12/812/003, EU/1/12/812/004 Farmacotherapeutische categorie: meningokokkenvaccins, ATCcode: J07AH09 **KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING** Een dosis (0,5 ml) bevat: Recombinant *Neisseria meningitidis* groep B NHBAfusieeiwit [1, 2, 3] 50 microgram Recombinant *Neisseria meningitidis* groep B NadAeiwit [1, 2, 3] 50 microgram Recombinant *Neisseria meningitidis* groep B fHbpfusieeiwit [1, 2, 3] 50 microgram Buitenmembraanvesikels (BMV) van *Neisseria meningitidis* groep Bstam NZ98/254, gemeten als hoeveelheid totaal eiwit dat PorA P1.4 bevat [2] 25 microgram [1] Geproduceerd in *E. coli*cellen door recombinantDNAtechnologie [2] Geadsorbeerd aan aluminiumhydroxide (0,5 mg Al^{3+}) [3] NHBA (Neisseria heparinebindend antigeen), NadA (Neisseriaadhesine A), fHbp (factor Hbindend eiwit) **Therapeutische indicaties** Bexsero is geïndiceerd voor de actieve immunisatie van personen van 2 maanden en ouder tegen invasieve meningokokkenziekte veroorzaakt door *Neisseria meningitidis* groep B. Bij het vaccineren moet rekening worden gehouden met het effect van invasieve ziekte bij verschillende leeftijdsgroepen, evenals met de variabiliteit van de epidemiologie van antigenen voor groep Bstammen in verschillende geografische gebieden. Zie rubriek 5.1 van de volledige SPK voor informatie over bescherming tegen specifieke groep Bstammen. Dit vaccin dient te worden gebruikt in overeenstemming met officiële aanbevelingen. **Dosering en wijze van toediening** Dosering **Tabel 1. Samenvatting van de dosering**

Leeftijd bij eerste dosis	Primaire immunisatie	Intervallen tussen primaire doses	Booster
Zuigelingen van 2 tot en met 5 maanden [a]	Drie doses, elk van 0,5 ml	Niet minder dan 1 maand	Ja, één dosis tussen 12 en 15 maanden oud met een interval van ten minste 6 maanden tussen de primaire serie en de boosterdosis[b, c]
	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	
Zuigelingen van 6 tot en met 11 maanden	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	Ja, één dosis in het tweede levensjaar met een interval van minimaal 2 maanden tussen de primaire serie en de boosterdosis[c]
Kinderen van 12 tot en met 23 maanden	Twee doses, elk van 0,5 ml	Niet minder dan 2 maanden	Ja, één dosis met een interval van 12 tot en met 23 maanden tussen de primaire serie en de boosterdosis[c]
Kinderen van 2 tot en met 10 jaar **Adolescenten (11 jaar of ouder) en volwassenen***	Twee doses, elk van 0,5 ml	Niet minder dan 1 maand	Een boosterdosis dient overwogen te worden bij personen met een blijvend risico op blootstelling aan meningokokkenziekte, op basis van officiële aanbevelingen[d]

[a] De eerste dosis moet niet worden gegeven op de leeftijd jonger dan 2 maanden. De veiligheid en werkzaamheid van Bexsero bij zuigelingen jonger dan 8 weken zijn nog niet vastgesteld. Er zijn geen gegevens beschikbaar. [b] In geval van uitstel mag de booster niet later dan op een leeftijd van 24 maanden worden gegeven. [c] Zie rubriek 5.1 van de volledige SPK. De noodzaak voor en tijdsplanning van een boosterdosis na dit vaccinatieschema is niet vastgesteld [d] Zie rubriek 5.1 van de volledige SPK. * Gegevens over volwassenen ouder dan 50 jaar ontbreken. Wijze van toediening Het vaccin wordt toegediend via een diepe intramusculaire injectie, bij voorkeur in het anterolaterale gedeelte van de dij bij zuigelingen, of in de streek van de deltaspier van de bovenarm bij oudere personen. Als meer dan één vaccin tegelijk wordt toegediend, moeten afzonderlijke injectieplaatsen worden gebruikt. Het vaccin mag niet intraveneus, subcutaan of intradermaal worden toegediend, en mag niet worden gemengd met andere vaccins in dezelfde spuit. Voor instructies over het hanteren van het vaccin voorafgaand aan toediening, zie rubriek 6.6 van de volledige SPK. **Contraindicaties** Overgevoeligheid voor de werkzame stof(fen) of voor een van de in rubriek 6.1 van de volledige SPK vermelde hulpstof(fen). **Bijzondere waarschuwingen en voorzorgen bij gebruik** Zoals dat voor alle vaccins geldt, dient ook toediening van Bexsero te worden uitgesteld bij personen die lijden aan een acute, ernstige, met koorts gepaard gaande ziekte. De aanwezigheid van een lichte infectie, zoals verkoudheid, mag echter niet leiden tot uitstel van vaccinatie. Niet intravasculair injecteren. Zoals dat voor alle injecteerbare vaccins geldt, dienen passende medische behandeling en toezicht altijd direct beschikbaar te zijn voor het geval zich na toediening van het vaccin een anafylactische reactie voordoet. Reacties die verband houden met angst, waaronder vasovagale reacties (syncope), hyperventilatie of stressgerelateerde reacties, kunnen in relatie met vaccinatie voorkomen als psychogene reactie op de naaldinjectie (zie rubriek "Bijwerkingen"). Het is belangrijk dat er passende procedures zijn om letsel als gevolg van flauwvallen te voorkomen. Dit vaccin mag niet worden toegediend aan personen met trombocytopenie of een bloedstollingsstoornis die een contraindicatie voor intramusculaire injectie vormt, tenzij het mogelijke voordeel duidelijk opweegt tegen het risico van toediening. Zoals dat voor alle vaccins geldt, beschermt vaccinatie met Bexsero mogelijk niet alle gevaccineerden. Bexsero wordt niet geacht bescherming te bieden tegen alle circulerende meningokokken Bstammen. Zoals dat voor veel vaccins geldt, moet het medisch personeel zich ervan bewust zijn dat een temperatuursstijging kan optreden na vaccinatie van zuigelingen en kinderen (jonger dan 2 jaar). Profylactische toediening van antipyretica gelijktijdig met en meteen na vaccinatie kan de incidentie en intensiteit van koortsreacties na vaccinatie verminderen. Antipyretische medicatie dient te worden gestart volgens de lokale richtlijnen bij zuigelingen en kinderen (jonger dan 2 jaar). Personen met een immunodeficiëntie, door het gebruik van immunosupressieve therapie, een genetische stoornis, of door een andere oorzaak, kunnen een verlaagde antilichaamrespons hebben bij actieve immunisatie. Immunogeniciteitsgegevens zijn beschikbaar van personen met complementdeficiëntie, asplenie of miltdisfunctie. Personen met familiale complementdeficiënties (bijvoorbeeld C3- of C5-deficiënties) en personen die behandelingen ondergaan die de terminale complementactivatie remmen (bijvoorbeeld eculizumab) hebben een hoger risico op een invasieve ziekte veroorzaakt door *Neisseria meningitidis* groep B, zelfs als deze personen antilichamen ontwikkelen na vaccinatie met Bexsero. Er zijn geen gegevens over het gebruik van Bexsero bij personen ouder dan 50 jaar en beperkte gegevens bij patiënten met chronische medische aandoeningen. Wanneer de primaire immunisatieserie aan zeer premature zuigelingen (geboren na ≤ 28 weken zwangerschap) wordt toegediend, moet rekening worden gehouden met een potentieel risico op apneu en de noodzaak van controle van de ademhaling gedurende 4872 uur, vooral bij zuigelingen met een voorgeschiedenis van onvolgroeide longen. Aangezien het voordeel van vaccinatie groot is bij deze groep zuigelingen, moet vaccinatie niet worden onthouden of uitgesteld. De dop van de injectiespuit bevat mogelijk natuurlijk rubber (latex). Hoewel het risico op het ontwikkelen van allergische reacties zeer klein is, moet het medisch personeel de voor en nadelen goed afwegen voordat dit vaccin wordt toegediend aan personen met een bekende voorgeschiedenis van overgevoeligheid voor latex. Kanamycine wordt aan het begin van het productieproces gebruikt en wordt in latere productiestadia verwijderd. Indien aanwezig, bedraagt het kanamycineniveau in het uiteindelijke vaccin minder dan 0,01 microgram per dosis. Veilig gebruik van Bexsero bij personen die gevoelig zijn voor kanamycine is niet vastgesteld. Terugvinden herkomst Om het terugvinden van de herkomst van biologicals te verbeteren moeten de naam en het batchnummer van het toegediende product goed geregistreerd worden. Overzicht van het veiligheidsprofiel De veiligheid van Bexsero is geëvalueerd in 17 onderzoeken, inclusief 10 gerandomiseerde gecontroleerde klinische studies met 10.565 proefpersonen (vanaf de leeftijd van 2 maanden) die minimaal één dosis Bexsero toegediend kregen. Van de personen die Bexsero toegediend kregen, waren 6.837 zuigelingen en kinderen (jonger dan 2 jaar), 1.051 kinderen (van 2 tot 10 jaar) en 2.677 adolescenten en volwassenen. Van de proefpersonen die de primaire immunisatieserie voor zuigelingen van Bexsero toegediend kregen, kregen 3.285 een boosterdosis in het tweede levensjaar. De meest voorkomende lokale en systemische bijwerkingen bij zuigelingen en kinderen (jonger dan 2 jaar) die in klinische studies zijn waargenomen, waren gevoeligheid en erytheem op de injectieplaats, koorts en prikkelbaarheid. In klinische onderzoeken bij zuigelingen gevaccineerd op de leeftijd van 2, 4 en 6 maanden, is bij 69% tot 79% van de proefpersonen melding gemaakt van koorts (≥ 38°C) wanneer Bexsero gelijktijdig werd toegediend met standaardvaccins (die de volgende antigenen bevatten: 7valent pneumokokkenconjugaat, difterie, tetanus, acellulair pertussis, hepatitis B, geïnactiveerde poliomyelitis en *Haemophilus influenzae* type b) in vergelijking met 44% tot 59% van de proefpersonen die alleen de standaardvaccins kregen toegediend. Bij zuigelingen die Bexsero en standaardvaccins toegediend kregen, is ook vaker melding gemaakt van het gebruik van antipyretica. Wanneer alleen Bexsero werd toegediend, kwam koorts bij zuigelingen even vaak voor als bij standaardzuigelingenvaccins die tijdens klinische studies werden toegediend. Eventuele koorts volgde in het algemeen een voorspelbaar patroon, waarbij de meeste koortsgevallen de dag na de vaccinatie over waren. De meest voorkomende lokale en systemische bijwerkingen waargenomen bij adolescenten en volwassenen waren pijn op de injectieplaats, malaise en hoofdpijn. Er is geen toename waargenomen in de incidentie of ernst van bijwerkingen bij opeenvolgende doses in de vaccinatiereeks. Tabel met bijwerkingen Bijwerkingen (na primaire immunisatie of boosterdosis) die ten minste als mogelijk gerelateerd aan de vaccinatie kunnen worden beschouwd, zijn naar frequentie ingedeeld. De frequentie is als volgt geclassificeerd: Zeer vaak: (≥1/10) Vaak: (≥1/100, <1/10) Soms: (≥1/1.000, <1/100) Zelden: (≥1/10.000, <1/1.000) Zeer zelden: (<1/10.000) Niet bekend: (kan met de beschikbare gegevens niet worden bepaald) De bijwerkingen worden binnen elke frequentiegroep gerangschikt in aflopende volgorde van ernst. Naast de meldingen uit klinische onderzoeken, zijn ook de wereldwijd ontvangen vrijwillige meldingen over bijwerkingen van Bexsero sinds de introductie op de markt in de volgende lijst opgenomen. Aangezien deze bijwerkingen vrijwillig zijn gemeld door een populatie van onbekende omvang, is het niet altijd mogelijk om een betrouwbare schatting van de frequentie te geven en worden ze daarom hier vermeld met de frequentie Niet bekend. **Zuigelingen en kinderen (tot en met 10 jaar)** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Voedings en stofwisselingsstoornissen Zeer vaak: eetstoornissen Zenuwstelselaandoeningen Zeer vaak: slaperigheid, ongewoon huilen, hoofdpijn Soms: insulten (inclusief febriele insulten) Niet bekend: hypotoon-hyporesponsieve episode, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Bloedvataandoeningen Soms: bleekheid (zelden na booster) Zelden: ziekte van Kawasaki Maagdarmstelselaandoeningen Zeer vaak: diarree, braken (soms na booster) Huid en onderhuidaandoeningen Zeer vaak: huiduitslag (kinderen van 12 tot en met 23 maanden) (soms na booster) Vaak: huiduitslag (zuigelingen en kinderen van 2 tot en met 10 jaar) Soms: eczeem Zelden: urticaria Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: koorts (≥38°C), gevoeligheid op de injectieplaats (inclusief ernstige gevoeligheid op de injectieplaats, gedefinieerd als huilen wanneer de geïnjecteerde ledemaat wordt bewogen), erytheem op de injectieplaats, zwelling op de injectieplaats, verharding op de injectieplaats, prikkelbaarheid Soms: koorts (≥40°C) Niet bekend: injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) **Adolescenten (van 11 jaar en ouder) en volwassenen** Immuunsysteemaandoeningen Niet bekend: allergische reacties (waaronder anafylactische reacties) Zenuwstelselaandoeningen Zeer vaak: hoofdpijn Niet bekend: syncope of vasovagale reacties op een injectie, meningeale prikkeling (tekenen van meningeale prikkeling zoals stijfheid van de nek of fotofobie zijn kort na de vaccinatie sporadisch gemeld. Deze symptomen waren mild en van voorbijgaande aard). Maagdarmstelselaandoeningen Zeer vaak: misselijkheid Huid en onderhuidaandoeningen Niet bekend: huiduitslag Skeletspierstelsel en bindweefselaandoeningen Zeer vaak: myalgie, artralgie Algemene aandoeningen en toedieningsplaatsstoornissen Zeer vaak: pijn op de injectieplaats (inclusief ernstige pijn op de injectieplaats, gedefinieerd als niet in staat normale dagelijkse activiteiten uit te voeren), zwelling op de injectieplaats, verharding op de injectieplaats, erytheem op de injectieplaats, malaise Niet bekend: koorts, injectieplaatsreacties (inclusief uitgebreide zwelling van de gevaccineerde ledemaat, blaren op of rondom de injectieplaats en een nodus op de injectieplaats die meer dan een maand kan aanhouden) Melding van vermoedelijke bijwerkingen Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via het nationale meldsysteem: **België** Federaal agentschap voor geneesmiddelen en gezondheidsproducten Afdeling Vigilantie Postbus 97 B-1000 Brussel Madou Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be **Luxemburg** Centre Régional de Pharmacovigilance de Nancy Bâtiment de Biologie Moléculaire et de Biopathologie (BBB) CHRU de Nancy – Hôpitaux de Brabois Rue du Morvan 54 511 VANDOEUVRE LES NANCY CEDEX Tél. : (+33) 3 83 65 60 85 / 87 Fax : (+33) 3 83 65 61 33 E-mail : crpv@chru-nancy.fr ou Direction de la Santé Division de la Pharmacie et des Médicaments Allée Marconi - Villa Louvigny L-2120 Luxembourg Tél. : (+352) 2478 5592 Fax : (+352) 2479 5615 E-mail : pharmacovigilance@ms.etat.lu Link pour le formulaire : http://www.sante.public.lu/fr/politique-sante/ministere-sante/direction-sante/div-pharmacie-medicaments/index.html **HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN** GSK Vaccines S.r.l, Via Fiorentina 1, 53100 Siena, Italië **DATUM VAN DE GOEDKEURING VAN DE TEKST** 07/2020 (V11) **AFLEVERINGSWIJZE** Op medisch voorschrift.

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An atypical neonatal hypoxic ischemic encephalopathy treated by hypothermia may hide a spinal cord lesion

Hortense Hubinont [a], Daniela Avino [a], Grammatina Boitsios [b], Aline Vuckovic [a], Anne-Britt Johansson [a]

[a] Department of neonatology, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium
[b] Department of pediatric radiology, Hôpital Universitaire des Enfants Reine Fabiola, Université Libre de Bruxelles, Brussels, Belgium

hortense.hubinont@gmail.com

Keywords

spinal cord injury, therapeutic hypothermia, cooling, hypoxic ischemic encephalopathy, magnetic resonance imaging

Abstract

Neonatal spinal cord injury is a rare condition and its diagnostic might be delayed by concurrent hypoxic ischemic encephalopathy. Herein we describe a new-born presenting with hypotonia and respiratory failure after a traumatic delivery. After being treated for hypoxic ischemic encephalopathy by therapeutic hypothermia, her neurological evolution led to perform an magnetic resonance imaging which revealed an ischemic spinal cord injury at the level of C1-C2. Therapeutic hypothermia use is anecdotal in neonatal spinal cord injury but could have promising effects. Therapeutic hypothermia did not prevent the fatal outcome in this case. Recognizing risk factors and clinical features of spinal cord injury is crucial. A magnetic resonance imaging examination should be performed following the completion of therapeutic hypothermia.

Introduction

Neonatal spinal cord injury (SCI) is an extremely rare and serious complication. The estimated incidence ranges between 1/29,000 and 1/80,000 of live births (1,2). The diagnosis of neonatal SCI could be delayed by concurrent hypoxic ischemic encephalopathy (HIE) (2). Albeit widely recommended for HIE, therapeutic hypothermia (TH) is still experimental in SCI but could have promising effects. Indeed, TH slows down the cell metabolism and attenuates secondary processes of injury by vascular and biochemical modifications (3). To date, two cases of neonatal SCI were successfully treated by TH applied for 72 hours (2,4). When neonatal SCI is clinically suspected in patients with HIE treated by hypothermia, performing spine imaging is of paramount importance. Magnetic resonance imaging (MRI) provides the most accurate images of spinal cord. Hereafter, we describe a case of neonatal HIE requiring TH, during which SCI was clinically suspected.

Unfortunately in our case, TH was not sufficient to improve the medical condition of this new-born. Nevertheless, this sad clinical situation points out two different reflections. Firstly, the optimal window of MRI will be discussed in the light of the maintenance of TH for 72 hours while shortly delaying the diagnosis of SCI. Secondly, we will highlight the neurological findings that could lead to an earlier diagnosis of SCI.

Case Report

A female infant was born at 39 weeks of gestation with a birth weight of 3,000 g. She is the first child of healthy and unrelated parents with no family history of any neurological disease. The pregnancy was unremarkable. The foetus presented in occiput posterior position, without any evidence of head hyperextension during labour. Due to foetal distress the delivery was initially assisted by a vacuum device and then by forceps associated with a Mac Roberts manoeuvre. At birth, endotracheal intubation was required for respiratory failure and hypotonia. Apgar scores were 1 at 1 minute, 3 at 5 minutes and 4 at 10 minutes. The infant was then admitted to the neonatal intensive care unit. All criteria of severe HIE were present including profound metabolic acidosis (i.e. pH value of 6.88), low Apgar score (i.e. less than 5 at 10 minutes), mechanical ventilation needs after 10 minutes of life, and the short-term electroencephalogram (EEG) registered in the first hour of life showed *major abnormalities* according to the Pressler classification (5). Therefore, whole-body TH was started one hour after admission and planned for 72 hours. After 24 hours, biological parameters normalized. At 20 hours of life, the EEG shows a continuous activity with *mild abnormalities* according to Pressler. Despite EEG improvement, the neurological evolution was still a concern. No spontaneous breathing appeared. Flaccid quadriplegia was obvious with areflexia: no patellar, Achilles neither biceps reflex. Only facial movements were present with normal pupillary light reflex. This clinical picture motivated the realization of a brain and cervical spine computed tomography (CT)-scan at 36 hours of life, which ruled out intracranial and spinal haemorrhage (figure 1). After 72 hours of TH, no clinical improvement occurred. Brain and cervical spine MRI were subsequently obtained at 120 hours of life. While brain MRI showed no signs of encephalic ischemic lesions, cervical spine MRI revealed a high signal lesion in T2 and a low signal in T1 weighted images. The diffusion was restricted in the medulla at the C1-C2 level (figure 2). Given the severity of the lesion and no respiratory recovery, palliative care was initiated and the infant died at 9 days old.

Discussion

New-borns' spinal cord is typically less elastic than the cartilaginous vertebral column and is therefore more vulnerable to rotational forces, explaining why a history of difficult delivery is often reported. Cephalic deliveries are more often associated with upper cervical spine lesions by torsion forces, while breech deliveries are related to lower cervical and upper thoracic lesions by traction forces (1,6). Mechanisms of SCI include compression, ischemia and traumatism or tearing of the spinal cord (1,7). Tearing is the most common cause of neonatal SCI as opposed to the compression injuries which mainly occur in adult patients (6). As the spinal cord contains capillaries in the grey and white matters, it makes it vulnerable to hypoxic ischemic lesions, explaining why SCI is often associated with HIE (1).

In addition to those primary lesions, after a few hours or days, a wide range of secondary injury mechanisms might develop. According to experimental studies, TH would act on the secondary injury process. Those mechanisms include haemorrhage, ischemia-reperfusion, excitotoxicity and inflammation leading to apoptosis (3, 8).

In neonates with HIE, the diagnosis of SCI should be ruled out in the case of respiratory failure and severe hypotonia, while EEG and biological parameters improve unexpectedly, particularly in an assisted, breech or difficult deliveries. The other neurological findings that could lead to the diagnosis are areflexia, sensory level, distended bladder and atonic anal sphincter. The clinical manifestations depend on the level and extend of the lesion. Spasticity can occur later (6).

A careful neurological exam can suggest the diagnosis, but complementary imaging is necessary. CT-scan of the cervical spine allows early detection of haemorrhagic compressive lesions and bone injuries, which rarely occur due to the cartilaginous skeleton of neonates. Yet almost 15% of spinal injuries are missed on CT-scan (9).

MRI is the gold standard for assessment of tissue damage in SCI. Spinal MRI informs on the type, localization and extent of the lesion and contributes to the prognosis. Lower cervical and upper thoracic lesions are associated with better outcomes than upper cervical ones (1,6). Spinal cord haemorrhage has the poorest outcome, while compression and ischemia of the spinal cord are less severe and more reversible (1,10). In adults, a first MRI assessment is recommended between 24-72 hours post trauma (9). The diagnosis of SCI could be missed if MRI is performed too early, as sensitivity to detect haemorrhage increases with time as well as the extent of oedema in spinal cord (10). Therefore, performing MRI after TH completion may be judicious for a better accuracy of detection.

In some patients SCI can co-occur with HIE and meet the criteria of TH. Cooling must be performed to reduce mortality and major neurodevelopmental disability in newborns with moderate to severe HIE. TH is mostly beneficial when initiated before 6 hours of life and lasting for 72 hours. The neuroprotective effect of hypothermia has been demonstrated in adults with SCI but there are still doubts that prevent from its general use. In neonates, TH applied for 72 hours has been reported in only three cases of SCI among which one death occurred (2,4,8). No clinical trial about TH in neonatal SCI has ever been conducted. In adult's series, cooling was applied for up to 48 hours, but longer period does not seem harmful (3). TH is a promising neuroprotective treatment for SCI and may be reasonably started or continued in case of clinically suspected SCI in neonates.

Conclusion

In conclusion, the diagnosis of neonatal SCI is challenging and could be delayed by coexisting clinical signs of HIE. An accurate neurological examination might suggest the diagnosis. TH is a promising neuroprotective treatment for SCI and may be reasonably started or continued in case of clinically suspected SCI in neonates with HIE. The optimal window for MRI might be right after TH, to allow for a complete treatment and a better sensitivity of lesion detection. Nevertheless, these lesions are often severe and irreversible as shown in our case.

Statement of Ethics

The paper has been sufficiently anonymised not to harm any patient's family and the publication of this case report has been approved by the human research ethics committee of Queen's Fabiola Children's Hospital on the 22nd April 2020.

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Figure 1 : *Non-contrast low-dose head and neck CT-scan (helicoidal CT scanner Somatom Siemens 64) in a) sagittal reconstruct and b) in axial reconstruct, both of them in soft Kernel. (A) High density subdural collection along the tentorium (subdural hematoma) along with a decrease density of the medulla at the C1-C2 level (black arrow). (B) Axial plane MPR showing medullary hypodensity at the C1-C2 level on the left (black arrow) and normal medullary density on the right.*

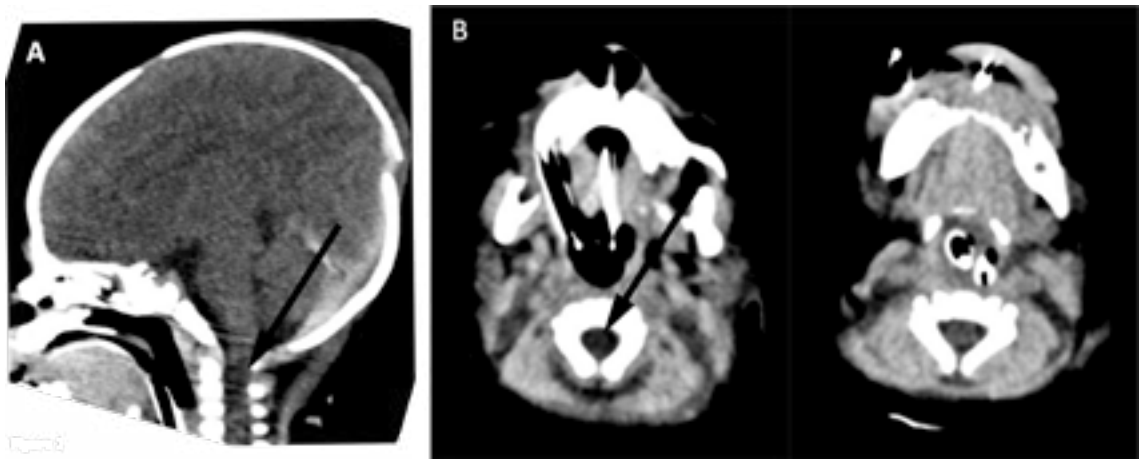
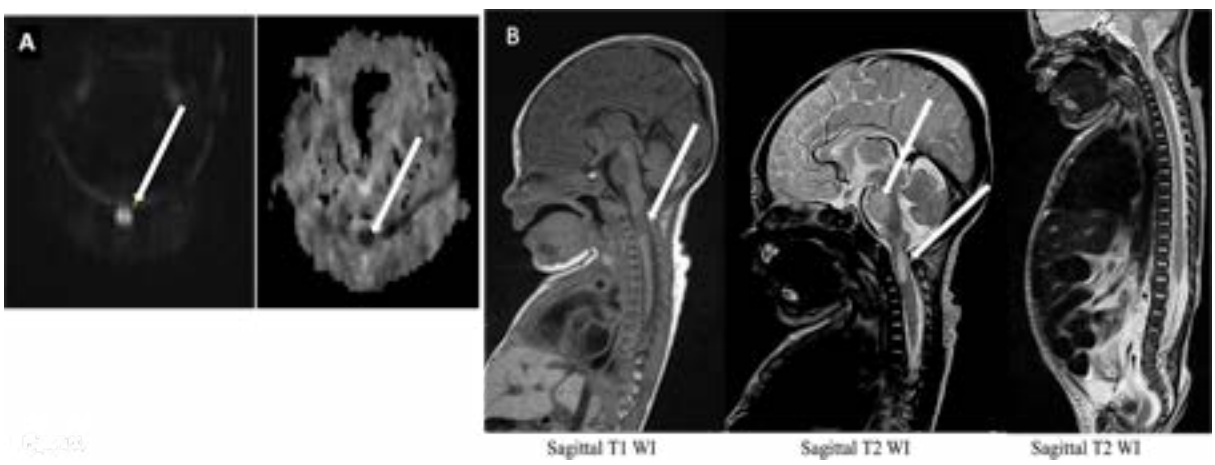


Figure 2 : *1,5 Tesla MRI scanner (Siemens Area) of the brain and spine without contrast in a) diffusion weighted imaging (TRACE) on the left and apparent diffusion coefficient (ADC MAP) on the right and b) T1-weighted sagittal brain and spine on the left, sagittal T2-weighted imaging in the middle and on the right. (A) Signal abnormality in the cervical medulla at the level of C1-C2 showing a high signal in DWI and low signal on ADC MAP illustrating the post anoxic-ischemic lesion of the cervical medulla. (B) Sagittal planes showing the ischemic medullary lesion at the C1-C2 level (lower white arrow) associated with a retrograde Wallerian degeneration of the pons (upper white arrow)*



Desmopressin resistant monosymptomatic nocturnal enuresis: new pathophysiological and pharmacological insights.

PhD thesis presented on 14th of September 2020 at Ghent University, Ghent, Belgium.

Lien Dossche

Department of Paediatric Nephrology, Ghent University Hospital, Belgium.
Department of Internal Medicine and Paediatrics, Faculty of Medicine and Health Sciences, Ghent University, Belgium.

Promotors: Johan Vande Walle (Ghent University, Belgium), Søren Rittig (University of Aarhus, Denmark), Elke Gasthuys,(Ghent University, Belgium)

lien.dossche@ugent.be

Introduction

Nocturnal enuresis (NE) or bedwetting is a frequently encountered problem during childhood, and may adversely affect the psychosocial well-being of both the child and their families (1). Given the significant impact of this condition, treatment is advisable to be initiated from the age of 5-6 years (2). Monosymptomatic nocturnal enuresis (MNE) is a subtype of NE, characterised by micturition during sleep in absence of lower urinary tract symptoms and/or daytime incontinence. Nocturnal polyuria (NP) is recognised as one of the major underlying causes in many children with MNE (3). Since the late eighties, medical researchers were able to explain the phenomenon of NP by a lack of nocturnal increase of arginine-vasopressin (AVP) plasma levels (4). The first-line pharmacological treatment of MNE is therefore orally administered desmopressin (dDAVP), a synthetic AVP analogue. To date, there are two oral formulations available, namely tablet and lyophilisate (where this last one is not reimbursed in Belgium for this indication). However, around 40% of the children with MNE show dDAVP resistance (3). Hypothetically, besides poor adherence to treatment or to administration recommendations, other underlying pathophysiological mechanisms might play a role in dDAVP resistant MNE. Moreover, the prescription of dDAVP in children is only based on sparse paediatric pharmacological data, and therefore deserves further exploration (5). In this PhD-dissertation, we therefore aimed to gain knowledge on underlying mechanisms explaining dDAVP resistance in children with MNE.

New pathophysiological insights in NP and the clinical relevance in dDAVP-resistant enuresis

By studying the circadian regulation of renal function in the pathophysiology of NP, we were able to demonstrate that in a subgroup of children with NE and NP, there was a diminished circadian rhythm of renal functions, such as sodium excretion and glomerular filtration (6).

It is not possible to explain this observation by an AVP disorder alone, since there is not only effect on diuresis but also on osmotic excretion. The latter suggests that alterations in physiologic mechanisms driving circadian rhythms could be involved, such as changes in hemodynamic parameters, body temperature, sleep, sodium, solute-excretion and glomerular filtration (7). Since dDAVP is an AVP-analogue mainly targeting free water excretion, it is plausible that this higher osmotic excretion can be linked with dDAVP resistant NP.

Desmopressin as an illustration of the challenges and the way forward in paediatric drug research

Both the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of dDAVP in children with MNE were studied. As a part of the SAFE-PEDRUG project (safepedrug.eu), a bottom-up approach starting from paediatric specificities was applied to unravel dDAVP resistance. In a first study, we identified that the claimed bioequivalence between the tablet (200 µg) and the lyophilisate (120 µg) in adults cannot be readily extrapolated to children (8). In a second study, we demonstrated that the two available oral formulations of dDAVP are not therapeutically equivalent in children at the currently approved dose levels (9). In a third study, we were able to demonstrate a biphasic absorption of dDAVP lyophilisate in children between the age of 6 months and 8 years, which has never been described before in adults nor in older children (10). To the best of our knowledge, this was the first time that a different absorption profile of dDAVP lyophilisate was demonstrated in children, however the clinical implications of this finding need to be further studied. This confirmed the findings of a previously developed juvenile animal model and PKPD-modelling study from our research group (9,11). In the last study, we showed that current dosing regimens using a flat dose of 120 µg dDAVP lyophilisate is not adequate for children urging the need to further study size-adapted dosing strategies, in order to improve dDAVP response (12).

The main conclusions of this PhD-dissertation regarding the pharmacological aspects of dDAVP are:

1. **Lack of therapeutic equivalence between children and adults**

This finding illustrates that PK/PD trials in children remain necessary to establish efficacy and safety of a drug, and extrapolation of findings in adults need to be done very carefully.

2. **Possible different absorption profile of dDAVP in children**

This observation inquires further research into absorption of oral drugs in children, especially of the lyophilisate formulations. If different absorption of lyophilisate formulations in children in comparison to adults is not only the case in dDAVP, the urge to change the practice of paediatric drug research only increases.

3. **dDAVP is the prototype of an off-patent drug, that is widely prescribed in children**

The existing knowledge gaps, i.e.PK/PD clinical studies, unlikely will be filled by industry-driven studies in the future. We admit that performing PK/PD-studies is ethologically and methodologically challenging in children, but appropriate juvenile animal models and population modelling can optimize the study design and reduce the amount of invasive procedures with even a better quality of the obtained data.

Practical clinical recommendations on dDAVP-resistant enuresis

The main recommendation is to administer dDAVP minimum one hour prior to bedtime, preferably without simultaneous food intake. The therapy should be re-evaluated every three months (treatment withdrawn for at

least one week) to monitor if further treatment is required (2). However, there is no evidence-based guideline, neither expert consensus statement available for a threating physician challenged with the treatment of child with MNE and no or suboptimal response to dDAVP.

The findings obtained in this PhD-dissertation add evidence to some aspects of the pre-existing practical recommendations and provide additional advice on considerations in daily clinical practice:

1. **Be aware of the shortcomings of the current clinical characterization to tackle therapy resistant enuresis**

The current therapeutic approach in clinical management of children with NE recommended by the International Children's Continence Society (ICCS) starts with the clinical characterization of children with NE into MNE and non-monosymptomatic nocturnal enuresis (NMNE)(2). It is well documented that in children with MNE, a significant subgroup exists with NP, who are likely to respond to dDAVP. Although clinical characterization seems a rational first step in the evaluation of children with NE, there is no evidence of its predictive value for treatment selection. Moreover, not all children with MNE have NP, as well as there are children without NP demonstrating a good response to dDAVP. To make it even more complicated, there are children with NMNE with a good response to dDAVP, when used as an add-on therapy or following treatment of lower urinary tract symptoms. Therefore, when dDAVP-resistance occurs, an individualized approach seems the only defendable strategy.

2. **If a child with MNE is treated with dDAVP, consider evaluating not only the anti-enuretic effect (decrease of number of wet nights), but also the antidiuretic effect (reduction of urine production).**

Antidiuretic effect can be screened by measuring the average nightly urine production during one week with and one week without administration of dDAVP, respectivily. The nightly urine production can be evaluated by calculating the sum of the wet diaper weight (minus the weight of a dry diaper) and the volume of the first morning void. Make sure that the amount of fluid intake during the evening is equal during both weeks.

3. **If dDAVP seems to have partial or no antidiuretic effect in a child with NP, consider to perform a renal concentrating capacity test.**

Children with NP and no or partial anti-diuretic effect to dDAVP can be categorised into 2 groups, depending on the presence or the absence of maximal concentrated urine during a renal concentration capacity test.

- If maximal concentrated urine (urinary osmolality > 800 – 850 mosmol/L) can be obtained during the renal concentration capacity test after dDAVP administration, the dDAVP resistance can be related to non-adherence to the dDAVP therapy and/or pathophysiological underlying mechanisms in solute-excretion and circadian rhythms.
- When there is no maximal concentrated urine (urinary osmolality < 800 – 850 mosmol/L) during the renal concentration capacity test, there are arguments that there is an insufficient drug response. This can be related to underlying renal concentrating disorders, e.g. partial diabetes insipidus. If these disorders are ruled out, the lack of response is most likely related to pharmacological aspects.

4. **Consider a diet with reduced osmotic load**, (especially intake of salts and proteins). Theoretically, high salt and protein intake during the evening can negatively influence the antidiuretic response to dDAVP by inducing an osmotic driven NP.
5. **Consider individualizing your prescription of dDAVP**, since dDAVP resistance could be related to unknown specific paediatric pharmacological characteristics of the drug in your specific patient.
   - Be careful with increasing the dose if there is an insufficient response, a higher dose does not necessarily result in a better effect. Moreover, there is always a risk of inducing hyponatremia if fluid is insufficiently restricted after dDAVP administration.
   - Consider to change timing of administration of dDAVP. The general recommendation is to administer dDAVP 1 hour before bedtime, but in a specific patient it is possible that the maximum effect is only reached 2 hours after administration.
   - Avoid concomitant food intake and administer dDAVP at least 1 hour after the evening meal. If it is not feasible for the child and/or parents to avoid concomitant food intake, and a child is using dDAVP tablets, consider a switch to dDAVP lyophilisate.

General conclusion

This doctoral dissertation focused on children with MNE and NP, whereby new insights in possible underlying reasons for dDAVP resistance were gained, as shown in **figure 1.** A bottom-up approach starting from the child with NP and enuresis, was the strategy used to tackle the problem of dDAVP resistance. Regarding the pathophysiological aspects, we confirmed that NP can only partially be explained by blunted circadian rhythm of AVP, and that other alterations in the renal circadian clock might play a role in dDAVP-resistance. Considering the pharmacological aspects of dDAVP, additional insights in the current knowledge gaps when prescribing dDAVP in children with MNE were identified. We could demonstrate for the first time a double peak absorption of the dDAVP lyophilisate in children, which lead to questioning the current flat dosing regimens. Further research is needed to understand the clinical importance of these findings and to develop new therapeutic strategies to tackle dDAVP resistant MNE.

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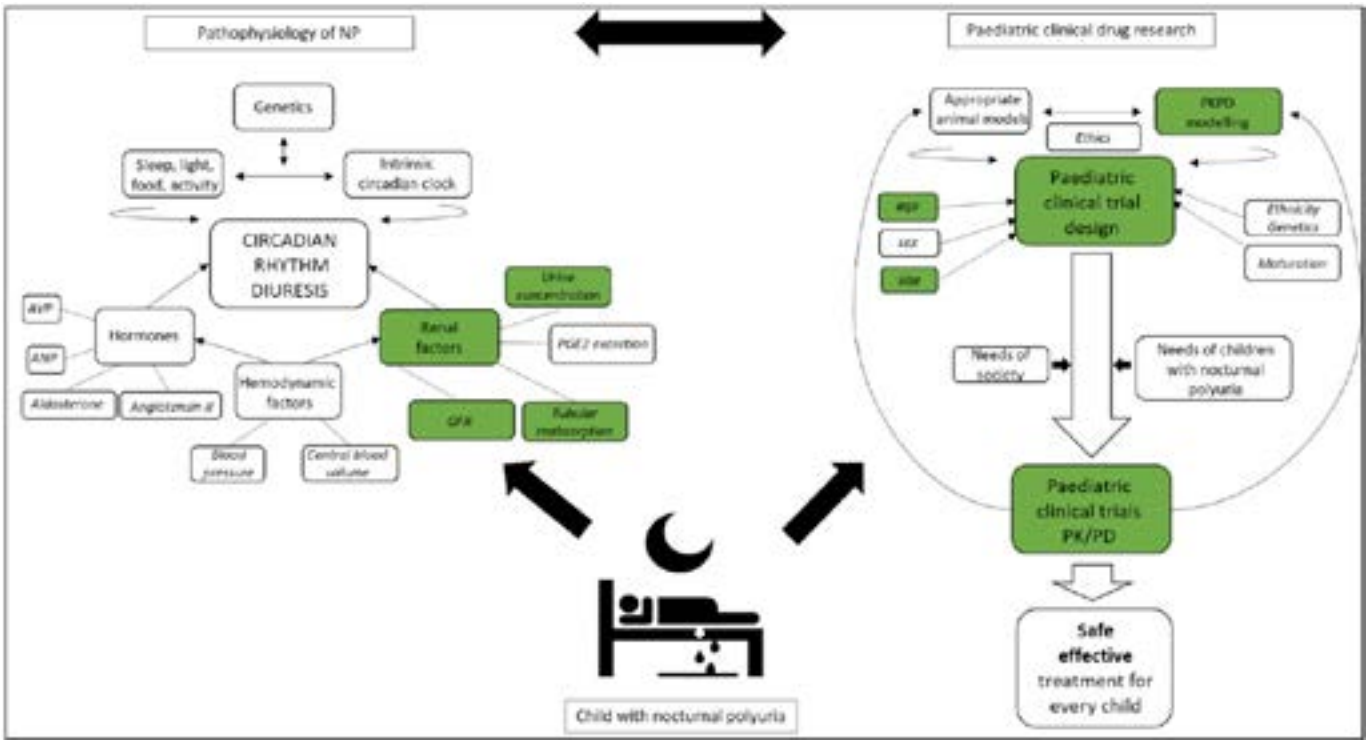
Pediatric Research Laboratory , Aarhus University Hospital , Aarhus , Denmark: J. Hagelskjær Knudsen, S. Rittig

Department of Pediatric Nephrology, Ghent University Hospitals: staff, nurses, trainees

Figure 1: *Approach to a child with nocturnal polyuria (NP = nocturnal polyuria; AVP = arginine-vasopressin; ANP = atrial natriuretic peptide; GFR = glomerular filtration rate; PGE2 = prostaglandin-E2; PK = pharmacokinetics; PD = pharmacodynamics. (*) indicated in green = topics studied in this PhD-dissertation Icon "enuresis" by thenounproject.com*



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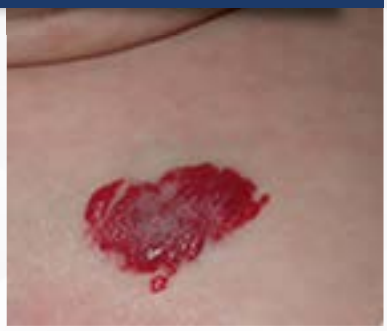
DOIS-JE RÉFÉRER MON PATIENT POUR CET HÉMANGIOME?





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Micturition reeducation in children with cerebral palsy

PhD thesis presented on 23th of September 2019 at Ghent University, Ghent, Belgium

Bieke Samijn

Promotors: Erik Van Laecke, Christine Van den Broeck

Bieke.samijn@ugent.be

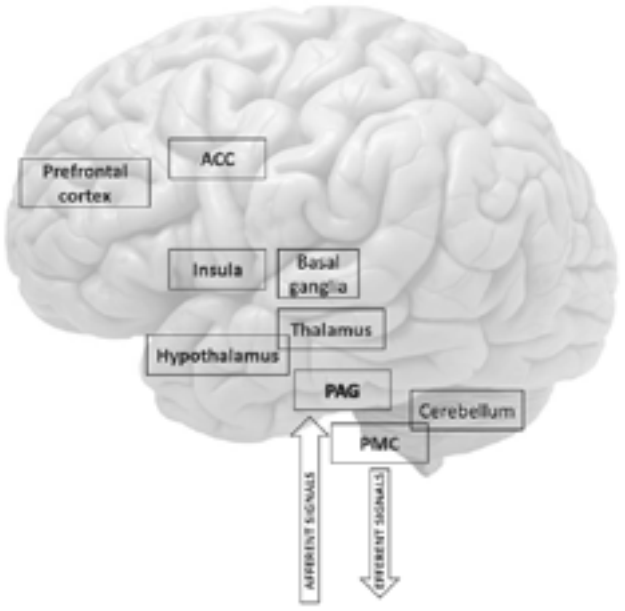
Introduction

Cerebral palsy (CP) is one of the most prevailing syndromes affecting children, with a prevalence of 2.11 per 1000 live-births. CP describes a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (1). The definition of CP was reviewed, as more attention should be given to activity restriction and non-motor problems often accompanying CP (1). Nevertheless, no mention of lower urinary tract dysfunction (LUTD) or incontinence particularly is made in the new CP definition. Although lower urinary tract symptoms (LUTS) are associated with poor quality of life and health status, urinary incontinence in children with CP is often considered a normal, unavoidable or minor problem (2, 3).

The International Children's Continence Society (ICCS) subdivides LUTS in children into four groups, i.e. storage symptoms (increased/decreased frequency, incontinence, urgency and nocturia), voiding symptoms (hesitancy, straining, weak stream, intermittency and dysuria), pain-related symptoms and other symptoms (4). LUTS are relevant when present after acquiring bladder control or the age of five years old (4-6).

To assure efficient voiding the bladder and pelvic floor muscles need to act in a coordinated way. During the bladder filling phase the bladder or detrusor has to relax and the pelvic floor muscles have to contract to prevent urine loss. Whereas the pelvic floor muscles have to relax and the bladder contracts during the voiding phase. Underlying conditions for daytime incontinence in typically developing children are often related to dysfunction between bladder and pelvic floor during bladder filling phase or voiding phase. This coordinated activity is directed through the nervous system, with the impact of higher brain centers making voluntary control of voiding possible (fig 1).

Figure 1: *Anatomical representation of higher brain centers related to bladder control*



Legend: ACC Anterior cingulate cortex; PAG Periaqueductal gray; PMC Pontine micturition center

Lesions of the nervous system can result in LUTD, depending on the level of the lesion (7). Lesions above the pons, as expected in children with CP, remove inhibition of bladder contraction during the bladder filling phase.

It is generally accepted that incontinence must be treated. Treatment should be individualized to the child and specific underlying condition (8). Often a combination of treatment modalities is necessary. The ICCS provided an algorithm for the management of children with non-neurogenic daytime incontinence. If no comorbidities are present, all children should start with standard urotherapy.

The ICCS also provided recommendations for therapeutic intervention in the presence of a neurogenic bladder (9). Unfortunately, little attention is given to the use of urotherapy. Standard urotherapy specifically is not mentioned at all.

This PhD project includes several studies conducted with the primary aim to highlight and understand the incidence of LUTS and urinary incontinence in children with CP and contribute to the possible conservative treatment strategies for urinary incontinence in children with CP.

Incidence

Cerebral palsy is a condition beginning in early childhood and persisting through the lifespan (10). As result suffering and costs associated with LUTD can be significant (11). Understanding the incidence of LUTS and incontinence specifically, will indicate the need for evaluation and treatment.

By means of a systematic review the existing scientific literature on the presence of LUTS and pathological urodynamic findings in subjects with CP was investigated. Literature concerning children and adults with cerebral palsy was evaluated.

Twenty-seven studies fulfilled inclusion criteria**.** Studies report that 55.5 % of the children and adults with CP experience one or more lower urinary tract symptom. Excluding hesitancy, no clear differences in LUTS and urodynamic findings were found between children and adults. Urinary incontinence is the most frequently observed symptom in children with CP, with a prevalence rate ranging from 20 to 94 % (12, 13).

Storage symptoms are more common than voiding symptoms due to the high prevalence of neurogenic detrusor overactivity. Patients with voiding symptoms and pelvic floor overactivity are less present but seem to be more prone to progress to upper urinary tract dysfunction in adult life. It is suggested that subjects with storage symptoms more often stay stable and respond to medication, while subjects with voiding symptoms can progress to retention in adult life (14). Recent literature also states that neurogenic detrusor overactivity with reduced bladder capacity in childhood can evolve to neurogenic detrusor underactivity and distention of the bladder with age (15, 16).

Of the children who are dry at adult age, most achieve continence by the age of five years (17, 18). Therefore Reid and Borzyskowski (1993) suggest children with CP can merit early urological evaluation (19). ICCS guidelines recommending urologic evaluation when LUTS are present after the age of five years should also be used in children with CP (4). After the age of five years spontaneous achievement of continence drastically decreases and

parents and physicians should not assume lower urinary tract dysfunction as a normal feature in these children.

Urinary incontinence may be reinforced by the presence of negative prognostic factors. When risk factors for incontinence can be identified in children with CP, attention to these factors may be enhanced and emphasis and direction of treatment can be individualized to the child.

Therefore, a second study identified risk factors for the presence of urinary incontinence in children with CP. A cross-sectional case-control study was conducted including children with CP with or without incontinence. Risk factors were subdivided in three clusters, namely demographic and general medical data, CP classification and bladder and bowel dysfunction. Univariate and multivariate analysis was performed for variables and clusters respectively. A final associative logistic model including all clusters was developed.

Concerning demographic and general medical data, incontinence was associated with intellectual disability (Odds Ratio (OR) 7.69), swallowing problems (OR 15.11), the use of mobility and positioning aids (OR 27.50) and the use of laxatives (OR 13.31).

Within the cluster of CP classification, incontinence was positively associated with dyskinesia (OR 5.67) or combined spasticity and dystonia (OR 4.78), bilateral involvement (OR 4.25), functional impairment with GMFCS (gross motor function classification system) level IV (OR 10.63) and V (OR 34.00) and severe impairment in manual (OR 24.27) or communication skills (OR 14.38). Children with hemiplegia were less likely to be incontinent. Plasticity of the nervous system can enable the unaffected side to assume more control over the bladder during development(15).

Concerning bladder and bowel dysfunction, lower maximum voided volume (OR 0.97) and oral fluid intake (OR 0.96) influenced urinary incontinence negatively. Pathological uroflow curves were not significantly associated with incontinence.

The final associative model defined functional impairment, intellectual disability and oral fluid intake as predictive factors for incontinence. Although children with and without incontinence did not drink enough, oral fluid intake seemed to be an important predictive factor for incontinence. Multivariate analysis demonstrated that an increase of oral fluid intake equal to one percent of recommended fluid intake could have considerable effect on the odds of incontinence.

Diagnosis

The use of non-invasive evaluation of lower urinary tract function by means of uroflow measurement combined with electromyography testing of the pelvic floor (uroflow/EMG) could be informative and explanatory in children with CP to underline influence of pelvic floor hypertonia on micturition.

Current literature demonstrates that many factors, such as age, gender, toilet posture and environmental factors, influence the results of uroflowmetry (20-26). Before the implementation of uroflow/EMG is possible in a population of children with CP, there is the critical raising question of the potential effect of the electrodes on the natural voiding pattern of the subject. Therefore, we investigated if the standard protocol for uroflowmetry, recommended by the ICCS, remains accurate when integrating EMG measurement by means of superficial electrodes (27). This in a population of typically developing children without urinary incontinence.

Based on demonstrated results and time- and cost-efficiency, recommendations are to initiate the procedure with a single uroflowmetry measurement followed by one measurement of uroflow with EMG testing. Literature states that flow rates can be affected by comfort, privacy and anxiety of the patient (28). The possibility to use a uroflow measurement without EMG testing before actual testing could provide a comfortable and private environment for introduction of uroflow measurement to the child. This may lower the sense of anxiety within the child during further testing. The presence of both uroflow measurement and EMG testing during the first void could make habituation more difficult and minimize comfort during the second void, resulting in less evolution to the natural voiding pattern of the child.

Additionally, ICCS guidelines mention voided volumes less than 50 % of expected bladder capacity for age (EBC) are not reliable to interpret. The systematic review in this PhD project reported 73.5 % of the subjects with CP exhibit a reduced bladder capacity compared to EBC. Mean bladder capacity in the review was 58.5 % of the EBC, with a lowest average capacity rate of 47 % of EBC reported by Fernandes Silva et al. (2014) (29). Reduced bladder capacity could therefore influence accurate interpretation of uroflowmetry in children with CP.

Therapy

Despite the high prevalence of urinary incontinence in children with CP, treatment strategies in this population are poorly investigated. The ICCS suggests therapy for urinary incontinence should start with urotherapy (8). Yet no indication of this is made in guidelines for neuropathic bladder dysfunction (9). Some previous studies have tried to implement parts of urotherapy, but none have administered urotherapy as instructed by the ICCS for typically developing children(4, 8, 15, 30, 31)). Treatment generally contains pharmacotherapy or invasive treatment strategies (14, 15, 19, 30). In addition, effectiveness of the chosen treatment is seldom the primary objective of the study.

We applied standard urotherapy as primary starting point in training and investigated if urotherapy could be the basis of an evidence based, effective rehabilitation treatment for incontinence in children with CP. For this purpose a study population of children with cerebral palsy and urinary incontinence and typically developing children with urinary incontinence received treatment for one year. When necessary, standard urotherapy could be strengthened with specific urotherapy interventions or pharmacotherapy. Standard urotherapy, specific urotherapy interventions and pharmacotherapy were individualized to the child based on probable underlying conditions.

Within the group of children with CP, significant overall time-effects were found for daytime incontinence ($p < 0.001$), frequency of daytime incontinence ($p = 0.002$), frequency of enuresis ($p = 0.048$), storage symptoms ($p = 0.011$), good toilet posture ($p = 0.034$) and fecal incontinence ($p = 0.026$).

Results suggested urotherapy can be the basis of an effective long-term treatment for urinary incontinence in children with CP, but effectivity rate of urotherapy is lower and changes occur slower in time in children with CP compared to typically developing children. Increasing fluid intake and bladder capacity and managing constipation were important factors influencing achievement of continence.

Our research, in agreement with previous literature, found that a great amount of subjects with CP had never been put on a toilet before testing as part of the study (32). In accordance with the age where most children with CP experience spontaneous continence achievement and ICCS guidelines, treatment is recommended as early as possible when incontinence past the expected age of bladder control occurs.

Nonetheless, some children with CP can still achieve continence in older age, which indicates the need for continued evaluation and treatment effort throughout the childhood and adolescence of the child (33).

Conclusion

Urinary incontinence in children with cerebral palsy is a frequently present and important problem as a result of neurogenic bladder dysfunction, cerebral palsy characteristics and modifiable environmental factors. Being more or completely dry can positively influence quality of life and health status of the child. This will improve future functioning and adaptation in society and increase the independence level of the child. Despite the obtained information in this doctoral thesis, many factors with possible influence to the presence of incontinence and treatment effectiveness are yet to be investigated.

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*Vanaf nu voor chronische constipatie bij kinderen vanaf 1 jaar

Naam van het geneesmiddel: MOVICOL® Junior Neutral 6,9 g zakje, poeder voor drank. **Kwalitatieve en kwantitatieve samenstelling:** Elk zakje Movicol Junior Neutral bevat de volgende werkzame bestanddelen: Macrogol 3350: 6,563 g, Natriumchloride: 0,1754 g, Natriumwaterstofcarbonaat: 0,0893 g, Kaliumchloride: 0,0251 g. Na oplossen van 1 zakje in 62,5 ml water, bevat deze oplossing de volgende elektrolyten: Natrium: 65 mmol/l, Chloride: 53 mmol/l, Kalium: 5,4 mmol/l, Waterstofcarbonaat: 17 mmol/l **Farmaceutische vorm:** Poeder voor drank. Wit vloeiend poeder. **Therapeutische indicaties:** Voor de behandeling van chronische constipatie bij kinderen vanaf 1 tot 11 jaar. Voor de behandeling van faecale impactie bij kinderen vanaf 5 jaar (gedefinieerd als hardnekkige constipatie met faecale vulling van rectum en/of colon). **Dosering en wijze van toediening:** Dosering: Chronische constipatie: De normale begindosering is 1 zakje per dag voor kinderen van 1 tot 6 jaar en 2 zakjes per dag voor kinderen van 7 tot 11 jaar. Indien nodig moet de dosering verhoogd of verlaagd worden om een regelmatige zachte stoelgang te bekomen. Indien de dosis verhoogd dient te worden, dan gebeurt dit het beste elke tweede dag. Voor kinderen jonger dan 2 jaar dient de maximaal aanbevolen dosis niet hoger te zijn dan 2 zakjes per dag. Voor kinderen van 2 tot 11 jaar, dient de maximaal aanbevolen dosis normaal gesproken niet hoger te zijn dan 4 zakjes per dag. De behandeling van kinderen met chronische constipatie gebeurt doorgaans voor een langere periode (ten minste 6-12 maanden). De veiligheid en doeltreffendheid van Movicol Junior Neutral is slechts bewezen voor een periode tot 3 maanden. De behandeling dient geleidelijk gestopt te worden en hervat te worden als de constipatie terugkomt. Faecale impactie: Een behandeling met Movicol Junior Neutral bij faecale impactie duurt tot 7 dagen en gaat als volgt: Dagelijks doseringsschema: Leeftijd: 5-11 jaar; aantal zakjes Movicol Junior Neutral: Dag 1: 4 , Dag 2: 6, Dag 3: 8, Dag 4: 10, Dag 5: 12, Dag 6: 12, Dag 7: 12. Het dagelijks in te nemen aantal zakjes moet in afzonderlijke dosissen genomen worden binnen een periode van 12 uren. Het bovenvermelde doseringsschema moet gestopt worden zodra desimpactie is opgetreden. Een indicator van desimpactie is de passage van een groot volume stoelgang. Na desimpactie wordt aanbevolen dat het kind een aangepaste stoelgangtraining volgt om reïmpactie te voorkomen (dosering voor preventie van het heroptreden van faecale impactie zou hetzelfde zijn als bij patiënten met chronische constipatie; zie boven). Movicol Junior Neutral worden niet aanbevolen voor kinderen jonger dan 5 jaar voor de behandeling van faecale impactie OF voor kinderen jonger dan 1 jaar voor de behandeling van chronische constipatie. Voor patiënten van 12 jaar en ouder wordt aangeraden om Movicol te gebruiken. *Patiënten met een verminderde cardiovasculaire functie:* Er zijn geen klinische gegevens voor deze patiëntengroep. Daarom wordt Movicol Junior Neutral niet aanbevolen voor de behandeling van faecale impactie bij kinderen met een verminderde cardiovasculaire functie. *Patiënten met nierinsufficiëntie:* Er zijn geen klinische gegevens voor deze patiëntengroep. Daarom wordt Movicol Junior Neutral niet aanbevolen voor de behandeling van faecale impactie bij kinderen met een verminderde nierfunctie. Wijze van toediening: Elk zakje dient opgelost te worden in 62,5 ml (een kwart glas) water. Het juiste aantal zakjes mag op voorhand bereid worden en afgedekt en gekoeld bewaard worden gedurende een periode tot 24 uren. Bijvoorbeeld, ter behandeling van faecale impactie, kunnen 12 zakjes bereid worden in 750 ml water. **Contra-indicaties:** Perforatie of obstructie van de darmen als gevolg van structurele of functionele aandoeningen van de darmwand, ileus, ernstige ontstekingsziekten van de darmen, zoals de ziekte van Crohn, colitis ulcerosa en toxisch megacolon. Overgevoeligheid voor de werkzame stoffen. **Bijwerkingen:** Bijwerkingen gerelateerd aan het gastro-intestinaal systeem komen het vaakst voor. Deze reacties kunnen voorkomen ten gevolge van het uitzetten van de maagdarminhoud, en een toename van de motiliteit die te wijten is aan de farmacologische effecten van Movicol Junior Neutral. Bij de behandeling van chronische constipatie reageren diarree of losse stoelgang gewoonlijk op een verlaging van de dosis. Diarree, abdominale distensie, anorectaal ongemak en mild braken worden vaker waargenomen tijdens behandeling voor faecale impactie. Braken kan vanzelf verdwijnen na verlaging of uitstel van de dosis. De frequentie van onderstaande ongewenste effecten wordt gedefinieerd door de volgende conventie: zeer vaak (≥1/10); vaak (≥1/100, <1/10); soms (≥1/1000, <1/100); zelden (≥1/10.000, <1/1000); zeer zelden (<1/10.000); niet bekend (kan met de beschikbare gegevens niet worden bepaald). Systeem/orgaanklasse – *Frequentie* – Bijwerking: Immuunsysteemaandoeningen: *Zelden:* Allergische reacties, waaronder anafylactische reactie. *Niet bekend:* Dyspnoea en huidreacties (zie hieronder). Huid- en onderhuidaandoeningen: *Niet bekend:* Allergische huidreacties, waaronder angio-oedeem, urticaria, pruritus, huiduitslag, erytheem. Voedings- en stofwisselingsstoornissen: *Niet bekend:* Elektrolytstoornissen, met name hyperkaliëmie en hypokaliëmie. Zenuwstelselaandoeningen: *Niet bekend:* Hoofdpijn. Maagdarmstelselaandoeningen: *Zeer vaak:* Abdominale pijn, borborygmi. *Vaak:* Diarree, braken, misselijkheid en anorectaal ongemak. Soms Abdominale distensie, flatulentie. *Niet bekend:* Dyspepsie en peri-anale ontsteking. Algemene aandoeningen en toedieningsplaatsstoornissen: *Niet bekend:* Perifeer oedeem. Melding van vermoedelijke bijwerkingen: Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via: Federaal agentschap voor geneesmiddelen en gezondheidsproducten, Afdeling Vigilantie, EUROSTATION II, Victor Hortaplein, 40/ 40, B-1060 Brussel of Postbus 97, B-1000 Brussel Madou, Website: www.fagg.be, e-mail: adversedrugreactions@fagg-afmps.be. **Houder van de vergunning voor het in de handel brengen:** Norgine NV, Romeinsestraat 10, B-3001 Heverlee **Nummer van de vergunning voor het in de handel brengen:** BE278643 **Afleveringswijze:** Op medisch voorschrift. **Datum van herziening van de tekst:** 03/2021. De volledige samenvattingen van de productkenmerken zijn op aanvraag verkrijgbaar.

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Chronic abdominal pain, fatigue and inflammatory bowel disease in children

PhD thesis presented on November 4th, 2020 at University of Groningen

Els Van de Vijver

University of Antwerp, Antwerp University Hospital, department of Paediatrics.

Promotors: Henkjan Verkade, Patrick Ferry van Rheenen

els.vandevijver@uza.be

This dissertation addresses two particular knowledge gaps out of the many that exist in paediatric inflammatory bowel disease (IBD).

In the first part of this thesis, we evaluated diagnostic strategies to assess whether gastrointestinal complaints are due to IBD, for appropriate triage for endoscopic evaluation. In the second part, we quantified and characterised fatigue in IBD.

PART I - Triage for endoscopy

In our effort to develop an appropriate strategy whether or not endoscopy is indicated to evaluate IBD in a child with abdominal complaints, we first evaluated faecal calprotectin (FC) as an isolated triage test. First, we described a cohort of 117 children with chronic diarrhoea and nonspecific abdominal pain. The treating physicians had to base their decision whether or not to perform endoscopy on the standard practice at that time: a combination of signs, symptoms and blood results. Without the knowledge of the FC result, 62% of the patients that were selected for endoscopy were diagnosed with IBD. If they would have based the selection for endoscopy on the combination of raised FC levels (i.e. >50 µg/g) and negative stool cultures, the yield of ileocolonoscopy towards diagnosing IBD would have improved to 78%, without missing any IBD patient. At the same time, FC levels below this cut-off point would have prevented a considerable proportion of patients being subjected to an endoscopic procedure that would not have led to the diagnosis of IBD, and, arguably, could then even have been labelled 'futile'. Even though adding FC results to the decision strategy improved the diagnostic yield compared to the standard diagnostic strategy of that time, still 22% of the patients would have been subjected to an IBD-negative ileocolonoscopy.

Secondly, we evaluated whether another faecal biomarker for mucosal inflammation, calgranulin-C, is better than FC in predicting IBD in children and teenagers. When predefined test thresholds were used (50 µg/g for FC and 0.75 µg/g for calgranulin-C), the diagnostic accuracy of calgranulin-C indeed appeared to be better. However, when receiver-operator characteristic (ROC) curves were used to identify the optimal test threshold for each test separately, what appeared to be 400 µg/g for FC and 0.75 µg/g for calgranulin-C, the superiority of calgranulin-C relative to FC disappeared. We therefore concluded that the diagnostic accuracy of the calgranulin-C test was not superior to the FC test.

The cohort we evaluated included patients with rectal blood loss and perianal disease. These red flag symptoms provide sufficient reasons for immediate endoscopic evaluation to obviate the need for additional diagnostic testing. Inclusion of these patients increases the pre-test probability and causes an overestimation of the discriminating power of FC relative to the practical situation, where a test seems particularly useful to discriminate between those with IBD and those with functional abdominal pain. Children and teenagers presenting with *non-bloody* diarrhoea and abdominal pain, in other words without red flag symptoms, are a spectrum of patients more commonly seen in general paediatric practice. These patients constitute the most challenging group to discriminate IBD from Irritable Bowel Syndrome (IBS) because the pre-test probability for IBD is low. Previously published meta-analyses pooled studies which included patients with red flag symptoms and may have exaggerated the diagnostic accuracy of FC to diagnose IBD.

We therefore set out to determine the optimal test strategy in patients without red flag symptoms. This time we used a FC threshold of 250 µg/g, which was, according to new insights, considered to be the optimal cut-off point to discriminate IBD from functional abdominal disorders (1).

We compared four diagnostic strategies to predict the need of endoscopy based on (A) symptoms alone, (B) symptoms + blood markers, (C) symptoms + faecal calprotectin, and (D) symptoms + blood markers + faecal calprotectin. Triaging with strategy C resulted in 20 of 100 patients undergoing endoscopy, and triaging with strategy D further limited this number to 14 of 100 patients. Eleven out of 14 had IBD and three did not have IBD. No IBD-affected child was missed.

Clinical Implications

Our search for the optimal diagnostic approach to triage paediatric patients with gastrointestinal complaints and absence of red flags for endoscopy culminated in a combination of meticulous history taking with measuring C-reactive protein in blood and calprotectin in stool. This strategy provides an easy and effective way to correctly selecting those who appeared to have IBD. Clinical practitioners can be reassured that in patients with a low CRP (≤10 mg/L), normal haemoglobin and low FC (<250 µg/g), endoscopy can safely be avoided without missing a case of IBD. Effective therapeutic interventions in children with a negligible risk for IBD, e.g. gut-directed hypnotherapy, can be initiated without losing time on further diagnostics. Simultaneously, children with increased FC in combination with increased CRP, low haemoglobin, or both, who have a high risk for IBD, can have an endoscopic confirmation of this diagnosis sooner and consequently have an earlier start of appropriate treatment.

Omitting the diagnostic strategy that comprises the combination of CRP, haemoglobin and calprotectin in children with *non-bloody* diarrhoea and abdominal pain may cause considerable harm, such as linear growth impairment and progressive bowel damage requiring surgery early after diagnosis (2, 3-5).

Tips for reliable faecal calprotectin results

The reliability of the diagnostic strategy strongly depends on biological, pre–analytical and analytical factors influencing the FC test. Stool samples are relatively easy to obtain, but there are several obstacles in the trajectory from stool collection to analysis that can affect the test result. First, it is advisable to use the first bowel movement of the day to catch the highest possible concentration of calprotectin (6). The faeces sample must not come into contact with toilet water as it may contain bleaches and disinfectants that may degrade calprotectin. Secondly, medication that is commonly prescribed in patients with abdominal pain, including non-steroidal anti-inflammatory drugs (e.g. aspirin or

ibuprofen) and proton pump inhibitors, can increase FC (7, 8). Ideally, these medications should be discontinued a week before stool collection. Thirdly, recent publications have shown that the protein calprotectin may be less stable at room temperature than previously thought (6, 9, 10). Protein degradation can be delayed when the filled stool container is refrigerated until delivery at the laboratory. Unrefrigerated stool samples of children with vague gastrointestinal complaints that arrive with a delay exceeding 48 hours and with a FC result between 50 and 250 *µg*/g, may falsely reassure doctors and patients because of degradation of initially increased FC levels and therefore require analysis of another fresh faecal sample.

Comparison of FC test accuracy per manufacturer

At present, most clinical practitioners have access to one or more faecal calprotectin tests, but these tests are neither standardized nor harmonized. We nevertheless feel that our findings can be extrapolated to settings with calprotectin tests from different manufacturers, as they fairly agree in the lower range (below 250 µg/g) (11). Above this cut-off point however, inter-assay variability is considerable. On the other hand, tests with a limited measuring range (say 50 to 300 µg/g) are considered unsuitable for triaging for endoscopy. In the absence of assay standardisation, more assay-specific cut-offs are needed.

Applicability in the primary care setting

Our test-strategy was evaluated in second- and third-line care settings, but not in primary care. In primary care, where IBD prevalence is low, an isolated positive FC result is rarely indicative of IBD, but an FC result below 50 µg/g on the other hand, does rule out IBD (13). The decision to refer children for endoscopy should therefore not be made at the general practitioner's level, but at the level of the paediatrician.

For this part of the thesis we conclude that the inclusion of the FC test in the triage for endoscopy allows to accurately select individuals with a high risk for IBD from a cohort of children with non-specific chronic intestinal complaints. Even in settings with high pre-test probability for IBD (i.e. prevalence > 70%), the optimal decision strategy based on symptoms, blood markers and faecal calprotectin continues to be beneficial. Paediatricians working at either secondary or tertiary care level can be reassured that this is a highly accurate and non-invasive approach to determine the likelihood of IBD.

PART II - Quality of life beyond clinical remission: fatigue in paediatric IBD

Children with IBD often experience fatigue and consider it one of the most burdensome symptoms. Fatigue is common at times of active inflammation, but a considerable proportion of the children also experiences fatigue when their IBD is in remission. The rates of fatigue in paediatric IBD are comparable to rates observed in paediatric oncology patients (50-75%) (14). IBD-related fatigue negatively impacts the quality-of-life and daily activities, including school attendance and sports participation. Despite its frequent occurrence, fatigue has been addressed in paediatric IBD literature only scarcely and not in considerable detail.

We systematically reviewed existing literature to identify factors contributing to fatigue. In the absence of randomised controlled trials, we selected cross-sectional or case-control studies reporting on fatigue in paediatric patients with IBD. The selected studies varied in the methodology to quantify or measure fatigue. Several studies used self-reporting surveys or a combination of parent-proxy reports and self-reports; only one tried to measure decline in activity with a portable pedometer. While working on the literature review it became clear that fatigue should be regarded as a multidimensional phenomenon, characterised by biological, psychobehavioural and functional factors (**table 1**).

Consequently, we assessed the relationship between biological and functional factors and IBD-associated fatigue. We evaluated haemoglobin, iron status, calprotectin (as marker of intestinal inflammation), disease-specific quality-of-life (with the IMPACT-III questionnaire) and physical fitness (by 6 minute walking distance, 6MWD) in children with quiescent, mild or moderate IBD. Using the PedsQL™ multidimensional fatigue scale, participating children with IBD were classified as fatigued or non-fatigued. We found no differences between the fatigued or non-fatigued groups in terms of haemoglobin concentration, faecal calprotectin, and ferritin concentration. The mean 6MWD in the cohort of paediatric IBD patients was 1 standard deviation below age-related healthy controls, but the mean 6MWD in the fatigued and non-fatigued IBD patients was not significantly different. The quality-of-life score was inversely related to fatigue: the more fatigued, the lower the quality-of-life score.

Table 1: *Identification of factors contributing to IBD-associated fatigue. Adult studies printed in grey*

Predictors of fatigue	Effect on fatigue	
	Aggravation	**Alleviation**
Biological factors		
Disease activity	Compared to patients with quiescent disease, adolescents with active disease have impaired physical wellbeing and more trouble sleeping (15) IBD adolescents are more tired in case of active disease (16)	Effective induction and maintenance therapy
Medication	Use of corticosteroids, thiopurines, and anti-TNF agents are associated with more fatigue (17-19)	Anti-inflammatory management. (20, 21)
Haematological factors	Iron deficiency anaemia(22)	iron supplements or intravenous iron therapy
Psychobehavioural factors		
Family support	Family dysfunction (23)	Maternal positive affect (23)
Psychological factors	Depression and anxiety (24)	Mindfulness and relaxation (25) Cognitive behavioural therapy (25, 26)
Functional factors		
Physical activity	Impairment in motor functioning(27) Decreased physical exercise (28)	Physical training reduces fatigue in postoperative IBD patients (29)

Future perspectives

Despite the high impact of fatigue in paediatric IBD there has been very limited evidence on successful pharmacological or non-pharmacological interventions, neither in paediatric nor in adults studies (25). Future research needs to make use of validated measures of fatigue, and interventions should have a measurable effect on these fatigue scores.

Non-pharmacological treatments also warrant further investigation in the paediatric IBD population. Physical activity, mindfulness, cognitive and behavioural therapy are some of the treatments to be investigated, particularly in children and adolescents with cancer. Despite the scarce data in children, Robinson et al. underline the beneficial effect of physical activity interventions and relaxation or mindfulness exercise in the management of fatigue in children and adolescents with cancer (14). Future research can show whether these beneficial effects can also be obtained in children with IBD.

In conclusion, this dissertation addressed the diagnostic strategy that best selects, out of a group of children with gastrointestinal complaints, those that are most likely to have IBD. Secondly, it provides an attempt to quantify and characterise fatigue in children with IBD.

With regard to the former point, we are confident in the quality of the optimal diagnostic strategy (with CRP, haemoglobin and faecal calprotectin). In the field of IBD-associated fatigue, however, it has become apparent that there is a lack of good quality studies. Measuring the efficacy of both pharmacological and non-pharmacological interventions for fatigue should be a research priority to improve the quality-of-life of children with IBD.

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Treating acute infectious diarrhoea: use of probiotics no longer supported by the evidence?

Anne-Catherine Vanhove[a,b], Koen Huysentruyt[c], Trudy Bekkering[a], Filip Cools[a]

[a] Cochrane Belgium, Belgian Centre for Evidence-Based Medicine (Cebam)
[b] Centre for Evidence-Based Practice (CEBaP) of the Belgian Red Cross-Flanders
[c] Vrije Universiteit Brussel (VUB), Universitair Ziekenhuis Brussel (UZ Brussel), Department of paediatric gastroenterology, Laarbeeklaan 101, 1090 Brussels, Belgium.

info@cochrane.be

Question

Are probiotics effective in shortening the time until symptom resolution in proven or presumed cases of acute infectious diarrhoea?

Context

Infections of the gut by viruses, bacteria and parasites can cause acute diarrhoea. While acute diarrhoea usually spontaneously resolves within a few days, it can cause severe dehydration and even death. Rehydration is the key treatment. Certain probiotics, which are “friendly” bacteria and yeasts, are thought to be able to restore the natural balance in the gut after disruption due to illness and possibly reduce the duration and intensity of symptoms. It has been proposed that certain “core” mechanisms (e.g. competitive exclusion of pathogens) might be present in many probiotics, with other mechanisms possibly being species or strain specific. Nonetheless, their effectiveness in the treatment of acute infectious diarrhoea remains in doubt.

An update of an existing Cochrane systematic review on probiotics for acute infectious diarrhoea was performed (Collinson 2020). The earlier version of this review, published 10 years ago, was based on many small studies (Allen 2010). It indicated that probiotics shortened the mean duration of diarrhoea and reduced the number of children with diarrhoea lasting four days or longer.

Criteria for study selection

This updated review included studies comparing a specified probiotic compared to placebo or no probiotic in people with acute diarrhoea which was proven or presumed to be infectious in nature. The main outcomes were diarrhoea lasting 48 hours or more and the duration of diarrhoea.

Summary of the results

In total, 82 studies with 12.127 participants were included in the review. This included 11.526 children (younger than 18 years) and 412 adults as well as 189 adults and children whose age group was not specified. Most of the studies (53 studies) were performed in countries where both child and adult mortality were low or very low, and 26 studies in countries where child or adult mortality was high with three studies recruiting from populations crossing the mortality data.

The risk of bias was high or unclear in many studies. Moreover, when the studies were statistically combined in a meta-analysis, there was large diversity in effect sizes. This heterogeneity could not be explained by type of probiotic, type of participant (age, high vs low mortality risk, region of the world), diarrhoea in children caused by rotavirus, exposure to antibiotics or treatment with zinc. However, statistical tests and funnel plots showed that results of small studies differed from those of large studies for the main outcomes of this review. This tendency for effect estimates to differ between small and large studies is called small-study effects. This can be due to several reasons including poor methodological quality leading to spurious inflated effects in smaller studies and publication bias for example. The review authors think it is likely that publication bias occurred in this case. Publication bias results from the failure to publish certain studies based on the direction or the strength of their results. Failure of inclusion of unpublished studies can, thus, lead to skewed effect estimates. In this review the many small studies showed positive effects of probiotics, while larger, more recent and well-conducted studies showed null effects. This suggests that the small studies which showed no effect (or even harmful effects) of probiotics were never published or published in small, non-English journals which are often difficult to search.

For the above-mentioned reasons, the review authors decided to only include studies with low risk of bias (i.e. scoring "low" on all 6 items of the Cochrane Risk of bias assessment tool) in their main analyses. This considerably reduced the number of studies from 82 studies to 7 studies (and thus the number of different probiotic strains) which could be included in the analyses. The use of probiotics probably results in little or no difference in the number of people with diarrhoea for 48 hours or longer (placebo: 536 per 1000 vs probiotics: 536 per 1000 (95% CI*: 488-584); 2 studies, 1770 participants, moderate-certainty evidence). Both North American studies were published in 2018, were similar in design and assessed the effects of *L. rhamnosus* GG (LGG) or a different strain of *L. rhamnosus* in combination with *L. helveticus*. We are uncertain of the effect of probiotics on the mean duration of diarrhoea (MD^: 8.64 hours lower (95% CI: 29.38 hours lower to 12.1 hours higher); 6 studies, 3058 participants, very low-certainty evidence). These studies were done either in India (3/6) or North-America (3/6) and investigated LGG (4/6), *L sporogenes* (1/6) or a combination of *L. rhamnosus* Rosell-11 and *L. helveticus* (1/6).

For the secondary outcomes of this review, the meta-analyses were not restricted to low risk of bias studies alone and the certainty of the evidence was not assessed. Results suggest that there is no evidence that probiotics reduced risk of hospitalization or risk of diarrhoea lasting 14 days or longer, but they may reduce duration of hospitalisation. No serious adverse events were reported among people who took probiotics.

Conclusion

The conclusions of this updated review differ from that of the previous version, which may be due to publication bias in the previous version. Small studies had mostly positive results and probably skewed the analyses in the previous version of this review. Current analyses based on two large trials

with low risk of bias show that probiotics (more specifically strains of *L. rhamnosus* with or without *L. helveticus*) probably make little or no difference in the number of people with diarrhoea lasting 48 hours or longer. We remain uncertain of their effect on the duration of diarrhoea. The review authors state that the heterogeneity in this review and other reviews on the topic argues against the presence of "core" properties shared by different probiotics that are active against diarrhoea due to several infectious agents. Future research should focus on probiotics with properties that address specific pathogenic mechanisms, probably limiting them to certain infectious agents or populations.

Implications for practice

While the ESPGHAN guidelines of 2014 recommend the use of LGG and *Saccharomyces boulardii* (strong recommendations, low-quality evidence), as well as *L. reuteri* and *L. acidophilus* (weak recommendation, very low-quality evidence), the results of this review show that one needs to be careful when formulating recommendations based on evidence from mostly small low-quality studies. The findings of this review suggest that at least the guideline for LGG needs to be reviewed as the current evidence does not support its use for the treatment of acute infectious diarrhoea.

REFERENCE:

Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, Dans LF, Allen SJ. Probiotics for treating acute infectious diarrhoea. Cochrane Database of Systematic Reviews 2020, Issue 12. Art. No.: CD003048. DOI: 10.1002/14651858.CD003048.pub4.

Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H; European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; European Society for Pediatric Infectious Diseases. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases evidence-based guidelines for the management of acute gastroenteritis in children in Europe: update 2014. J Pediatr Gastroenterol Nutr. 2014 Jul;59(1):132-52. doi: 10.1097/MPG.0000000000000375.

Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD003048. DOI: 10.1002/14651858.CD003048.pub3.

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