A DIFFERENT VIEW

The ADHD Tetragrammaton taken in vain in neurogenetic disorders?

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School teachers and parents often refer children to medical attention for ‘ADHD’ (for attention-deficit/hyperactivity disorder) rather than for qualified complaints or symptoms. In our experience, this trend also seems to increasingly affect parents of children with diagnosed severe neurogenetic disorders (e.g. Angelman syndrome), who are tempted to single out their children’s cognitive and behavioural features as being consistent with ADHD. It is as if a diagnosis of ADHD renders the symptoms less outlandish and more acceptable to parents. More consequentially, it often calls for prescription of ‘ADHD drugs’. It may also bring about a fair amount of confusion, including for research. We offer the view that a diagnosis of ADHD in people with neurogenetic disorders is currently not helpful.

ADHD IS A MEDICAL CONSTRUCT
ADHD is essentially a medical diagnosis (1). Like many disorders, it is a reformulation of problems set within the framework of current physiological knowledge. The core symptoms of ADHD appear to be continuously distributed in the general population of children, challenging the notion of a categorical disorder. Nothing about the disorder is unambiguously distinctive. Rather, the diagnosis is based on a set of clinical criteria that have been validated in typical school-age populations.

ADHD AND INTELLECTUAL DISABILITY
In recent years, the ADHD label has been tentatively applied in atypical populations. One interesting example concerns children with intellectual disability. As a group, children with ADHD tend to have a slightly lower IQ than the general population (2). This may be due to several factors, including impairments in behavioural inhibition and executive functions that can hamper some IQ subscale results (3). The validity of previous DSM classification systems for individuals with intellectual disability has been questioned (4). ADHD symptoms and associated patterns in children with low IQ are similar to those observed in average IQ children (5).

ADHD IN NEUROGENETIC DISORDERS
DSM-IV-TR diagnostic criteria for ADHD exclude patients in whom symptoms can be attributed to pervasive developmental disorder (1). Nevertheless, in recent years, the ADHD label has been applied to children with neurogenetic disorders in which the latter is highly prevalent. More generally, symptoms of ADHD are particularly prevalent in a number of neurogenetic syndromes as part of the behavioural phenotype, such as fragile X syndrome, Williams syndrome, Down syndrome, velocardiofacial syndrome (alias 22q11.2 deletion syndrome or CATCH 22), Prader–Willi syndrome, Wolf–Hirschhorn (4p-) syndrome or Angelman syndrome to name but a few. As a result, the diagnosis of ADHD is commonly reported in those patients, implying that the cluster of manifestations corresponds to ADHD as observed in otherwise typical children. This approach may be misleading in many respects.

From the diagnostic point of view, inaccurate description of the patients’ cognitive and behavioural traits might blur the distinctiveness of the behavioural phenotype that characterizes each of these conditions. Many authors tend to include ADHD in the description of the phenotype. Often, this is not based explicitly on the DSM criteria. Using some items broadly related to these criteria, one group challenged the notion that ‘ADHD-type’ behaviours were characteristic of Angelman syndrome (6). The impact and severity of these features are often much higher than in the common ADHD context. Evaluation of the features must judiciously take the developmental complexity into...
account. Moreover, restrictive symptom interpretation might overlook factors such as anxiety, depression or differently qualified behavioural problems, which may be difficult to recognize in those children, but might be amenable to effective management.

More importantly, the main justification of the ADHD diagnosis is management. As regards the current accent on pharmacological treatment, there has been limited indication of effectiveness of psychostimulant drugs in various neurogenetic disorders (7–9). However, particular caution is needed considering the very small number of studies, which have involved relatively small numbers of patients, have not covered the range of drugs prescribed in ADHD and have given little, if any, attention to safety (10).

Finally, misuse of the ADHD label may seriously hinder research on physiological determinants and processes that result in the symptoms. One of the main difficulties encountered in genetic and neurobiological studies of ADHD is heterogeneity. Pooling phenotypes of characterized neurogenetic disorders with those of more typically developing children would only enhance this problem. The temptation to link the known chromosomal or gene defects with the emerging biological findings in ADHD would probably lead to hazardous deception. Although there is strong evidence for genetic factors in ADHD, abnormalities in currently identified candidate genes are not known to give rise to well-characterized neurogenetic conditions. Including ‘ADHD’ in the phenotype of probably inherited conditions, for example, FG syndrome (alias X-linked multiple congenital anomalies/mental retardation), has no effect on the search for causal genes. On the other hand, some of the neurotransmitter systems putatively incriminated in ADHD may be marginally implicated in several neurogenetic disorders, including fragile X syndrome, Down syndrome and velocardiofacial syndrome. However, more specific abnormalities have been described, for example, in glutamatergic transmission in fragile X syndrome (11) and in GABAergic transmission in Angelman syndrome (12), whereas the physiological link with the cognitive and behavioural phenotype remains to be established. Despite speculations on similarly involved neural pathways in neurogenetic syndromes and ADHD (e.g. a model of fronto-motor cortex uncoupling leading to cortical hyperexcitability due to a ‘lazy frontal lobe’ in both Rett syndrome and ADHD; 13), it seems unlikely that shared causal pathways account for the manifestations seen in patients with these varied neurogenetic conditions and typically developing children with ADHD. On the contrary, segregating differences is likely to prove important in order to make new advances in this domain.

Rather than keeping a somewhat artificial focus on DSM-IV-TR-defined ADHD, we suggest that the traits observed in neurogenetic conditions with a complex behavioural phenotype be subjected to objective assessment. This should be based on measurable criteria in multiple domains, such as intellectual functioning, attention deficits, speech and communication, motor control, social impairment, and other behavioural disturbances (e.g. self-injury).

Finding the appropriate tools for testing may often be difficult, for example, in conditions where patients cannot use verbal language. This approach is also required for management, as correct identification of certain communication strategies or certain behavioural problems should direct the therapeutic approach while avoiding inappropriate treatment.

CONCLUSION

ADHD currently appears as a pragmatic concept that can be applied to the benefit of patients with otherwise typical development and provide a framework for neurodevelopmental research. Its use in neurogenetic conditions with a complex behavioural phenotype may be misleading for counselling, management and research issues. Therefore, we advise that children with a neurogenetic condition should not be given a diagnosis of ‘comorbid ADHD’ or ‘syndromic ADHD’.

Well-designed studies are urgently needed to evaluate the effect of drugs commonly prescribed to improve ‘ADHD symptoms’ in selected neurogenetic syndromes. It would seem particularly important to study medication with expected action on mood, anxiety and attention.

References