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ORIGINAL COMMUNICATION

Determinant of the cerebellar cognitive affective syndrome in Friedreich's ataxia

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Abstract

Background Individuals with Friedreich's ataxia (FRDA) display significantly lower performances in many cognitive domains with a pattern of impairment that falls within the cerebellar cognitive affective syndrome (CCAS).

Objective To assess in a large cohort of individuals with FRDA, the main determinant of the CCAS using multiple variable regression models.

Methods This is a monocentric observational study that included 39 individuals with FRDA. Ataxic motor symptoms were evaluated with the SARA and cognitive functions with the CCAS-Scale (CCAS-S). Age, SARA, GAA1, Age of symptoms onset (ASO), Age and disease duration (DD) were chosen as covariates in a linear regression model to predict CCAS-S failed items and covariates in a logistic regression model to predict definite CCAS.

Results Patients mean age, SARA score, ASO, DD and GAA1 were respectively of 29 ± 14, 22 ± 10, 14 ± 11, 15 ± 9 and 712 ± 238 (4 point-mutations). Mean CCAS-S raw score was of 86 ± 16, mean number of failed items was 2.9 ± 1.6. Twenty-three individuals had definite CCAS. The multiple linear regression model with age, SARA, ASO, DD & GAA1 as covariates was statistically significant to predict CCAS-S failed items. The SARA was the only significant coefficient in regression models for predicting CCAS-S failed items number and the definite CCAS occurrence.

Conclusions CCAS is highly prevalent in adult individuals with FRDA. CCAS is predicted by ataxic motor symptoms severity. This finding supports common core cerebellar pathophysiology in both cognitive and motor symptoms in FRDA and warrants screening for CCAS, especially in patients with SARA > 20.

Keywords Cerebellar cognitive affective syndrome · Friedreich's ataxia · Dentate nuclei · CCAS scale

Introduction

Friedreich's ataxia (FA) is one of the most common causes of inherited cerebellar ataxia. FA pathophysiology relates to reduced levels of frataxin, a mitochondrial protein involved in iron–sulfur cluster synthesis and antioxidant defenses. Lower frataxin levels are due, in 98% of patients, to the homozygous increased expansion of an intronic GAA triplet repeat in the *FXN* gene that represses frataxin expression via an epigenetic mechanism. The 2% remaining cases are compound heterozygotes with either a point mutation or a deletion in the *FXN* gene. In patients with expansions, most residual frataxin expression comes from the shorter GAA repeat expansion (GAA1), whose length explains 30–50% of the variability in age of symptoms onset and is a determinant of disease severity [1]. FA is characterized at the cerebellar level by progressive loss of large neurons in the dentate nucleus (DN) [2, 3], whose axons form the dentato-thalamic pathway that connects the cerebellum with a wide array of neocortical areas. In addition to motor control, the cortico-cerebellar loops play an important role in many perceptual and cognitive processes [4, 5]. Patients with FA due to their prominent DN and efferent tracts involvement are likely to develop cognitive disorders. Yet, on one hand, FA patients display no or slight impairments on the screening tools commonly used to detect cognitive abnormalities, such as the Mini Mental State Evaluation (MMSE) [6, 7] and the Montreal Cognitive Assessment (MOCA) [8]. But, on the other

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hand, FA patients show reduced cognitive processing speed, lower performance in language and visuospatial tasks, impaired executive functioning and poorer ideas generation when complex neuropsychological test batteries are used [9]. This combination of relatively mild but global higher neocortical dysfunction is characteristic of the cerebellar cognitive and affective syndrome (CCAS). The CCAS, first described over two decades ago, is the cognitive pendant of movement dysmetria in cerebellar diseases and comprises a form of thought dysmetria hampering language, emotion regulation, memory, attention, visuospatial and executive functions [10, 11]. A CCAS screening and follow-up scale (CCAS-S) was designed in 2018 based on the neuropsychological tests that could most efficiently single out individuals with cerebellar pathology from healthy individuals and showed a high yield to detect CCAS in patients with both acquired and genetic cerebellar disorders [10]. Interestingly, in the cohorts that validated the CCAS-S, the patients also presented the combination of normal MMSE and MOCA and altered specific neuropsychological tests, similarly to FA patients [10]. Since its validation in 2018, the CCAS-S has been used to screen for CCAS in patients with spinocerebellar ataxia (SCA) 2, SCA3, SCA6 as well as in small cohorts of FA patients and consistently described poorer performances in ataxic patients than in controls [12–14].

However, in FA, the cognitive impairments remains poorly characterized compared to motor symptoms despite increasing evidence for mild but prevalent cognitive dysfunctions [15]. Beyond cerebellar pathology, FA is also associated to neocortical changes with structural atrophy [16], metabolic [17] and functional connectivity impairments [18] that may contribute to alter cognitive performances. Better understanding of the determinants of the cognitive impairments in FA and its relation to cerebellar dysfunction could help clinicians, caregivers and individuals with FA to identify and care for cognitive difficulties.

The aim of this study is, therefore, to assess the burden of the CCAS in a large cohort of individuals with FA and identify what determines CCAS occurrence using regression models.

Subjects and methods

Subjects

This is a Monocentric observational study that included 39 individuals with FA followed at the CUB-Hôpital Erasme, Brussels (Belgium). The subjects' main characteristics are summarized in Table 1. One patient reported occasional cannabis use and one patient was treated by a tri-cyclic antidepressant, no other patients took psychoactive drugs. All participants contributed to the study after written informed consent and prior approval of the study by the CUB Hôpital Erasme Ethics Committee (CCB: B4062021000483).

Table 1 FA patients' characteristics

Age (mean ± SD, years)	29 ± 14
SARA (mean ± SD) /40	22 ± 10
Age of symptoms onset (mean ± SD, years)	14 ± 11
Disease duration (median ± standard deviation; years)	15 ± 9
GAA1 (median, [range])	712 ± 238 (4 point-mutations)

SD standard deviation, *SARA* Scale for the assessment and rating of ataxia, *GAA1* length of GAA expansion on the shortest allele

Clinical evaluations

Ataxic motor symptoms were evaluated with the Scale for the assessment and rating of ataxia (SARA) [19] and cognitive functions with the CCAS-Scale (CCAS-S). The SARA is an eight item scale that assesses gait, stance, sitting, speech, finger chase, nose to finger, upper-limb alternating pronation/supination and heel to chin maneuver rated on 40 (the higher score, the higher the impairment).The CCAS-S is composed of 10 items: a semantic fluency task, a phonemic fluency task, a verbal category switching task, a forward digit span, a backward digit span, a cube drawing task, a verbal registration task, a verbal similarities task, a Go No-Go task, and an affect evaluation [10]. A raw score is obtained for each task, with a minimum passing score. The number of failed tests determines the likelihood that the subject has CCAS: three or more failed tasks make a definite CCAS.

Variable definition and regression models

Age of symptoms onset (ASO), disease duration (DD), GAA1, SARA and age were chosen as variable of interest based on previous studies [20]. These variables were used as covariates in a linear regression model to predict CCAS failed items number and in a logistic regression model to predict definite CCAS occurrence. The relationship between variables/covariates and outcomes was assessed by Nagelkerke correlation coefficient. A value of $p < 0.05$ was considered statistically significant. All statistical analysis was performed using Jasp® 16.0.

Results

Mean CCAS-S raw score was of 96 ± 16 individuals with FA and the mean number of failed items was 3.2 ± 1.8. Twenty-three individuals with FA had a definite CCAS (≥ 3 failed

Table 2 CCAS-S group results

FA patients ($n=39$)	Mean raw score	Number of subjects under passing score, *n* (%)	Passing score/ maximum score
Semantic fluency[a] (mean ± SD)	16.7 ± 5.9	20 (51%)	16/26
Phonemic fluency[a] (mean ± SD)	10.1 ± 3.7	20 (51%)	10/19
Category switching[b] (mean ± SD)	10.8 ± 4.2	16 (41%)	10/15
Digit span forward[c] (mean ± SD)	6 ± 1.2	13 (33%)	6/8
Digit span backward[c] (mean ± SD)	3.9 ± 1.2	16 (38%)	4/6
Cube drawing (mean score ± SD)	12.2 ± 5	6 (15%)	12/15
Verbal recall (number of words, mean ± SD)	13.4 ± 1.8	3 (8%)	11/15
Similarities (correct answers, mean ± SD)	7.5 ± 1	6 (15%)	7/8
Go-No Go (mean score ± SD)	1.8 ± 0.5	2 (5%)	1/2
Affect (number of non-affected items, mean ± SD)	3.2 ± 1.8	23 (58%)	5/6
Total	96 ± 16	3.2 ± 1.8	82/120

SD standard deviation, [a]number of correct words, [b]number of correct alternations, [c]correct numbers of a series

Table 3 Linear regression coefficients

	Coefficient	95% CI	*p*
SARA	0.100	0.017–0.182	**0.019**
GAA1	0.001	− 0.002–0.004	0.377
DD	0.035	− 1.975–2.045	0.972
Age	− 0.025	− 2.023–1.973	0.979
AOO	0.011	− 2.015–2.036	0.992

SARA Scale for the assessment and rating of ataxia, *GAA1* length of GAA expansion on the shortest allele, *DD* disease duration, *AOO* age of symptoms onset, *CI* confidence interval

Bold value indicates the Statistically significant *p*

Table 4 Logistic regression coefficients

	Coefficient	95% CI	*z*	*p*
SARA	0.227	0.04–0.41	2.384	**0.017**
GAA1	− 0.001	− 0.007–0.004	− 0.434	0.664
A00	6.760	− 2344–2358	0.006	0.996
Age	6.732	− 2344–2358	− 0.006	0.995
DD	− 6.814	− 2358–2344	0.006	0.996

SARA Scale for the assessment and rating of ataxia, *GAA1* length of GAA expansion on the shortest allele, *DD* disease duration, *AOO* age of symptoms onset, *CI* confidence interval

Bold value indicates the Statistically significant *p*

items) and all participants failed at least one item. Table 2 summarizes the results of the CCAS-S.

The multiple linear regression model with Age, SARA, ASO, DD & GAA1 as covariates was statistically significant to predict CCAS-S failed item number ($R^2=0.54$, $t=10.34$, $p<0.001$) with only SARA as significant coefficient (Table 3).

The multiple logistic regression model was statistically significant to predict definite CCAS ($R^2=0.56$, $\chi 2$/dof:16/25, $p=0.007$) with SARA as only significant coefficient in the model. (Table 4, Fig. 1.) The SARA score Odd Ratios for definite CCAS are: 1.255 [1.041–1.513].

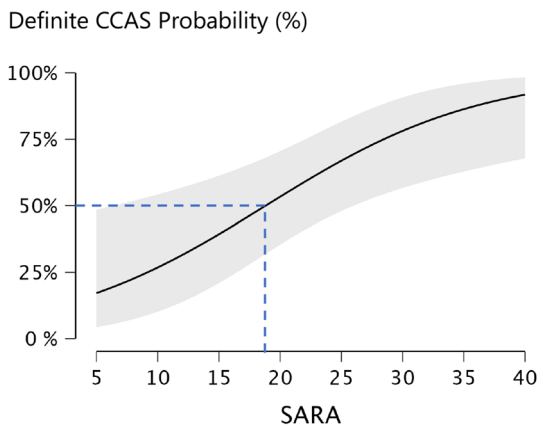

Fig. 1 Probability of definite CCAS according to SARA severity. Individuals with SARA of 20 and upwards have increasingly high probability of displaying definite CCAS. CCAS stands for cerebellar cognitive affective syndrome and SARA for Scale for the assessment and rating of ataxia

Discussion

The main findings of this study are that CCAS is highly prevalent in individuals with FA and that its occurrence can be predicted from ataxic motor symptoms severity.

Despite our relatively small sample of individuals with FA, these results are likely to be generally valid in other populations of individuals with FA. Indeed, our cohort shares the same characteristics in terms of age, age of onset, disease duration, SARA score and size of GAA1 than the average characteristics of the larger published cohorts of FA patients [20–22].

Markedly, all patients failed at least one item of the CCAS-S and over 50% of individuals showed a definite CCAS illustrating the prevalence of cognitive difficulties in FA and the yield of the CCAS-S to detect them. The fact that most patients failed one or more CCAS-S items is in line with a recent meta-analysis that found that, when sought for, most individuals with FA have difficulties in some cognitive tasks [15]. Yet, compared to population with cerebellar ataxia of other origin, individuals with FA seems to perform better on CCAS-S raw scores. In studies that assessed CCAS in cerebellar disorders, the cerebellar type of Multiple System Atrophy and cerebellar strokes display the lowest CCAS-S raw score, around 60, while SCA2 and SCA3 patients score better, around 80, even if slightly lower than our individuals with FA [10, 13, 23]. This suggests that the CCAS may be partly delayed by compensatory mechanisms in more progressive disorders. On a clinical standpoint, the items that FA patients mostly failed, in the CCAS-S were the affect, the verbal fluency tasks and the digital span tasks items. This pattern of impairment is, however, not specific of FA: the same items are also the most frequently impaired in patients with SCA3 and SCA6 [12] as well as the most sensitive to detect CCAS in SCA2 individuals [13]. This pattern highlights the difficulties that individuals with cerebellar disorders have with executive tasks and probably explains why five out of the ten items that discriminated patients with cerebellar diseases from healthy individuals and, therefore, selected to build the CCAS-S, are tasks that depend on executive functions [10]. Indeed, verbal fluency tasks and digit span tasks are considered to rely strongly on executive function [24–26], beyond testing respectively language and working memory skills [10, 27]. The executive and verbal fluency impairments in FA also stress out the potential confounding bias of mood disorders. Mood disorders and especially depression affect performances on executive tasks such as verbal fluency tasks [28–30]. In the CCAS-S, the mood item from the CCAS-S was pathologic in 58% of our FA patients, a finding that parallels the rate of positive neuropsychiatric symptoms reporting in patients with cerebellar disorders using the Neuropsychiatric Inventory-Questionnaire [31]. However, the mood item of the CCAS-S is only a basic screening for mood disorders and depression and does not allow to identify links between potential mood disorders and CCAS-S performances. Only severe depression impacts significatively verbal fluencies[30] and while depression affects around 14% of FA patients [32] the majority of FA patients with depression scores in the "minimal" range of the Beck depression inventory [33]. This suggests that CCAS-S performances probably reflect more cerebellar dysfunction than mood disorders in FA patients.

The close relation between the SARA et CCAS-S pleads for DN pathology as the main determinant of CCAS in individuals with FA and makes DN pathology more likely to explain the lower cognitive performances in FA than FA related neocortical alterations. DN pathology could also explain part of the cortical structural and functional disorders that are observed in FA. Indeed, the cerebellum efferent tracts are involved in inhibiting the cortical activity. The loss of that cerebellar brain inhibition is thought to be responsible for the motor and thought dysmetria observed in cerebellar disease. Thus, the disconnection from the cerebellum due to efferent tracts progressive atrophy in FA could explain the higher cortical glucose metabolic rate and the higher resting state functional connectivity described in individuals with FA [17, 18]. Cortical disconnection from cerebellar inputs also leads to cortical hypoperfusion, hypometabolism and atrophy [34], this may also potentially explain the cortical atrophy found in individuals with FA. This hypothesis could be further explored in dedicated studies that would, for instance, assess the correlations between CCAS-S performances and functional connectivity between the cerebellum and cortical executive networks.

Meanwhile, the CCAS-S has become a tool to evaluate cognition as well as a cognitive outcome measure in studies that include patients with both acquired and genetic cerebellar disorders [35, 36]. Our study suggests that cognitive disorders in FA relate to cerebellar pathophysiology and can be captured by the CCAS-S. The CCAS-S could thus serve as both a screening tool and an outcome measure in FA future natural history and interventional studies. However, our study has limitations. First, the study is cross-sectional and the correlation between CCAS-S and SARA score should be confirmed by longitudinal studies to validate that motor and cognitive symptoms follow a parallel path of progressive impairment. One way to evaluate that would be to add the CCAS-S, a scale that can be done in less than 10 min, as a variable in the Friedreich's Ataxia Consortium for Translational Studies registries. Second, this study was designed to identify within a cohort of FA patients the determinant of CCAS and did not include controls. While FA patients were showed to perform poorer than controls in small scale studies [12], the CCAS-S still lacks normative data along life-span. Larger control cohorts would help compare FA patients' and healthy subjects' cognition more accurately. Finally, our study, due to the lack of evaluation of depression and other psychiatric symptoms, fails to explore the relationship between FA mood disorders and cognitive impairments.

This caveat warrants further investigations to weight the different role of chronic disease associated mood disorders and cerebellar pathology in FA cognitive symptoms.

In summary, cognitive dysfunction is a dynamic process in individuals with FA that correlates with ataxic motor symptoms. While relatively mild, cognitive impairments should be sought for in individuals with FA, especially when the SARA score is over 20. A better identification of cognitive difficulties in individuals with FA may help individuals with FA and caregivers to better manage affective, social and professional issues that could arise due to the apparition of a CCAS.

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Data availability The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

Declarations

Conflict of interest None of the authors disclose financial or non-financial interests that are directly or indirectly related to the work.

Ethical approval The studies involving human participants were reviewed and approved by CUB-Hopital Erasme Ethics Committee.

Informed consent Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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