Cognitive Impairment Is Part of the Phenotype of Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome (CANVAS)

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Cognitive Impairment Is Part of the Phenotype of Cerebellar Ataxia, Neuropathy, Vestibular Areflexia Syndrome (CANVAS)

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ABSTRACT: Background: Little is known about the impact of the cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) on cognition.
Objective: Our objective was to determine the frequency and severity of cognitive impairment in *RFC1*-positive patients and describe the pattern of deficits.
Methods: Participants underwent a comprehensive neuropsychological assessment. Volume of the cerebellum and its lobules was measured in those who underwent a 3 Tesla-magnetic resonance scan.
Results: Twenty-one patients underwent a complete assessment, including 71% scoring lower than the cutoff at the Montreal Cognitive assessment and 71% having a definite cerebellar cognitive affective/Schmahmann syndrome. Three patients had dementia and seven met the criteria of mild cognitive impairment. Severity of cognitive impairment did not correlate with severity of clinical manifestations. Performance at memory and visuospatial functions tests negatively correlated with the severity of cerebellar manifestations.
Conclusion: Cognitive manifestations are frequent in *RFC1*-related disorders. They should be included in the phenotype and screened systematically. © 2024 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: cognitive impairment; cerebellum; *RFC1*-gene; inherited ataxia; neuropathy

Cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS) is a common cause of late-onset ataxia, characterized by sporadic or autosomal recessive inheritance and attributed to biallelic *RFC1* pathogenic variants[1] primarily $(AAGGG)_n$ expansions in intron 2 of the *RFC1* gene. They have been associated with a range of phenotypes, known as *RFC1* CANVAS/spectrum disorders.[2]

CANVAS initially presents as balance disorders associated with sensory neuropathy, cerebellar, and vestibular ataxia. Other common features include chronic cough and dysautonomia.[3] Although cognitive impairment was previously reported,[3-5] limited information is available regarding the impact of CANVAS on cognitive function.[6] Our objective was to describe comprehensively cognitive manifestations in patients with CANVAS/*RFC1*-related disorders.

Methods

Study Population

Thirty individuals with molecularly characterized *RFC1* biallelic $(AAGGG)_n$ expansions were proposed a comprehensive neuropsychological assessment. Five declined, three had moved, and one had recently died. Twenty-one (from 21 unrelated families) participated.

Demographic and Clinical Variables

Sex, age, duration of formal education, and time since the first neurological symptoms were recorded. Neurological evaluation is detailed in Supplementary Data S1.

Molecular Analysis

Genomic DNA was isolated from peripheral blood, and biallelic $(AAGGG)_n$ expansions in *RFC1* gene were identified (Supplementary Data S2).

Cognitive and Behavioral Assessment

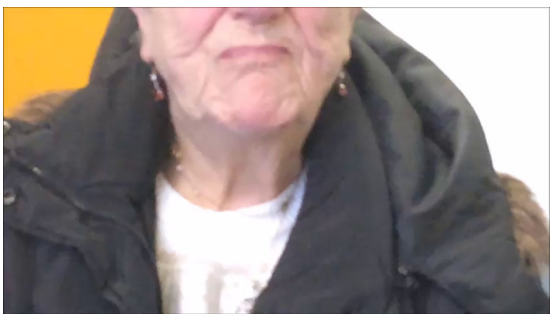
Overall efficiency was assessed by the MoCA-5 minute[7] administered 2 to 4 weeks before the other tests to limit interference. The cerebellar cognitive affective/Schmahmann syndrome (CCAS) was assessed by the dedicated scale.[8] Details of the comprehensive neuropsychological test battery are provided in Supplementary Data S3.

Magnetic Resonance Imaging Acquisition

Seven patients had a 3 Tesla (T) brain magnetic resonance imaging (MRI) scan with a three dimensional T1 sequence.

Ethics Declaration

The study adhered to the Declaration of Helsinki, with written informed consent obtained for genetic testing, publication of the relevant findings, and videos (Video 1).



VIDEO 1. Patient had a very atypical presentation, addressed because of a bulbar syndrome associating a severe dysarthria, severe swallowing disorder causing the loss of 26 kg over 18 months and finally a gastrostomy) and gait disorders quickly requiring the use of a walker. Amyotrophic lateral sclerosis was first suspected, but the electroneuromyography showed a pure sensitive neuronopathy. The patient had a normal vital capacity and no motor (nor central nor peripheral) impairment. [Color figure can be viewed at wileyonlinelibrary.com]
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mds.29750

Statistical Analysis

Quantitative variables were described as means (standard deviations) in case of normal distribution or median (interquartile range) otherwise. Normality of distributions was assessed using histograms and the Shapiro–Wilk test. Categorical variables were described as frequencies and percentages.

Spearman's correlation coefficients were computed between the cognitive variables and (1) the Newcastle Mitochondrial Disease Scale for Adults (NMDAS) score (global clinical alteration); (2) the Scale for the Assessment and Rating of Ataxia (SARA) score (cerebellar dysfunction), (3) time since the first neurological symptoms; (4) the basal ganglia volume; and (5) the volume of the cerebellum and its lobules. For all analyses, the statistical significance threshold was set at *P*-value <0.05 after false discovery rate (FDR) correction.

Results

Demographic and Clinical Characteristics

Twelve men and nine women (mean age, 64.5 (±8.4) years) were included. The median duration of formal education was 11.5[3] years, and the median duration of neurological symptoms 12[11] years.

The mean NMDAS and SARA scores were 6.19 (±3.52) and 8.00 (±6.07), respectively.

All patients had neuropathy, 17 cerebellar ataxia, 15 chronic cough, 10 pyramidal signs, four myopathy, four claw toes, two extrapyramidal signs, two hypoacusis, one ptosis, and one dysphonia. Twelve received treatment for neuropathic pain. Only one patient had a parkinsonian syndrome confirmed by the dopamine transporter single-photon emission computed tomography. None of the participants was an excessive alcohol user. CANVAS grading details are in Supplementary S4. A very atypical patient is presented in Supplementary Data S5.

Cognition and Behavior

Detailed cognitive performance is provided in Supplementary Data S6. As shown in Figure 1A, 15 (71%) of the participants had a score lower than the cutoff value at the Montreal Cognitive Assessment (MoCA)-5 minute. Fifteen (71%) had a definite CCAS (failure at three or more subtests of the CCAS scale). Four additional patients had a probable CCAS (failure at two subtests). Figure 1B illustrates the patterns of failures at

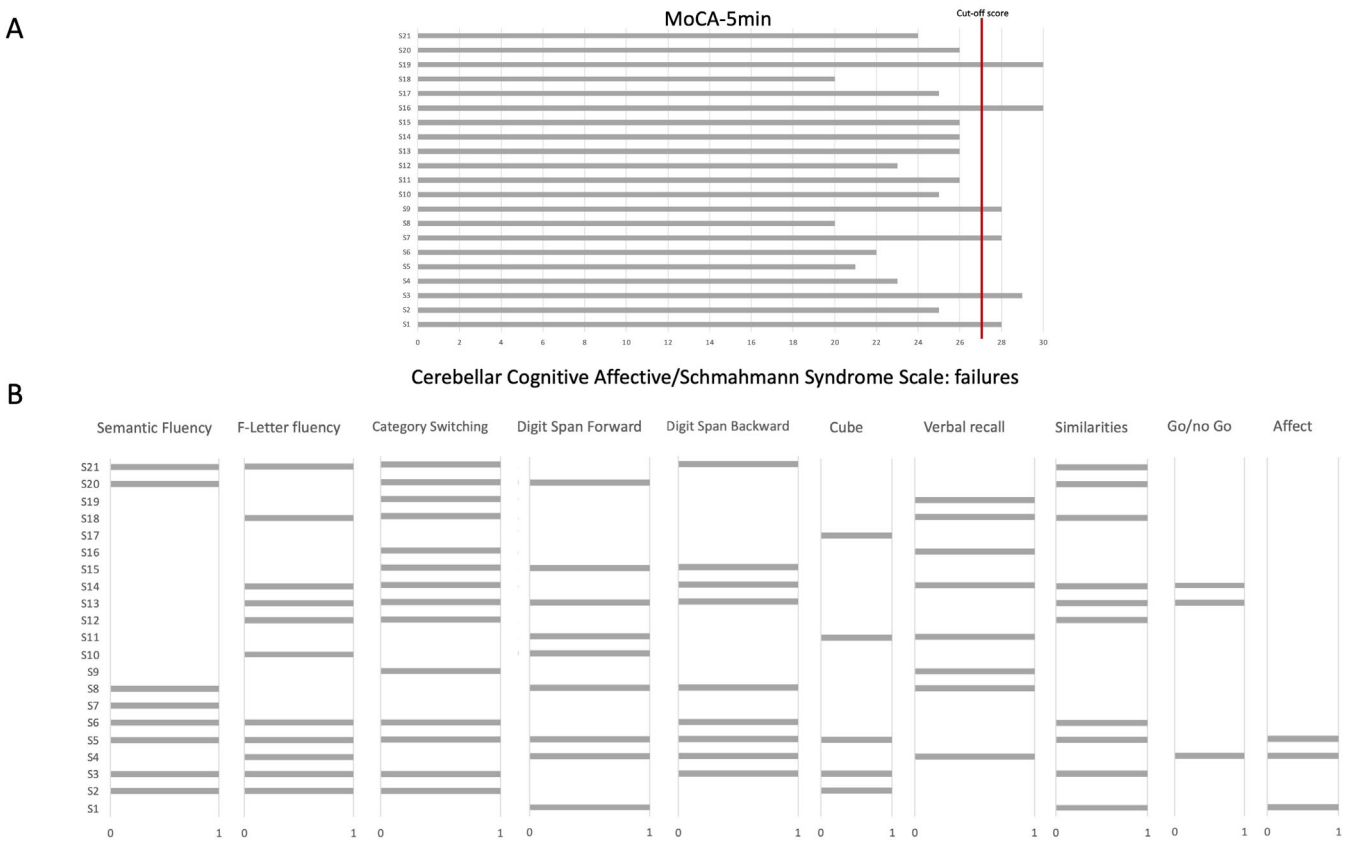


FIG. 1. (**A**) Individual performance at the phone-administered version of the Montreal Cognitive Assessment (MoCA-5 minute). A score lower than the cutoff value indicates a deficit. (**B**) Failures at the subtests of the cerebellar cognitive affective/Schmahmann syndrome scale. Each gray line indicates that the individual failed at this subtest. [Color figure can be viewed at wileyonlinelibrary.com]

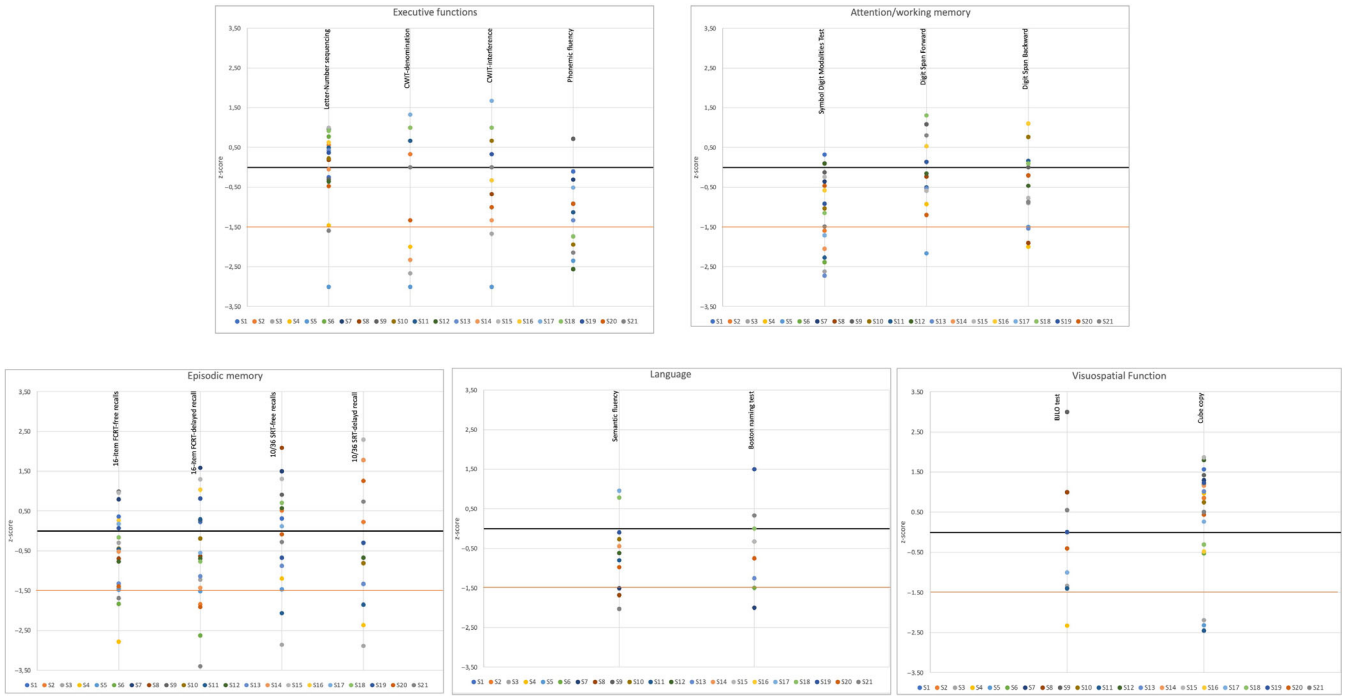


FIG. 2. Individual performance at each test of the comprehensive neuropsychological test battery expressed in z-scores. Tests are grouped by cognitive domains. The red line indicated the cutoff value. BJLO, Benton judgment of line orientation; CWIT, color word interference test; FCRT, Free and Cued recall test; SRT, spatial recall test. [Color figure can be viewed at wileyonlinelibrary.com]

the CCAS scale. Thirteen (62%) participants had deficits at both scales. Two had a definite CCAS, but normal overall efficiency. Two were impaired at the MoCA-5 minute, but had no definite CCAS.

Individual z-scores on tests of the neuropsychological test battery are mapped out in Figure 2. The proportion of subjects with a z-score ≤−1.5 was higher in the executive function and attention/working memory domains than in the others. Considering these deficits along with the history of cognitive changes over time and/or the individual's functional status, the cognitive status of each participant was defined. Three (14%) had dementia.[9] Seven (33%) had mild cognitive impairment (MCI),[10] including four with an amnesic and three with a non-amnesic subtype.

Severity of overall cognitive impairment and of the CCAS did not correlated with clinical severity (NMDAS score, $r_s = -0.234$, $P = 0.306$ and $r_s = -0.133$, $P = 0.566$, respectively) nor with the severity of the cerebellar syndrome (SARA score, $r_s = -0.292$, $P = 0.199$ and $r_s = -0.193$, $P = 0.401$, respectively) nor with time since the first neurological symptoms ($r_s = 0.141$, $P = 0.542$ and $r_s = 0.243$, $P = 0.289$, respectively).

Regarding the other cognitive tests, we found a significant correlation between performance at symbol digit modalities test ($r_s = -0.677$, $P_{FDR} = 0.016$) and at the Benton judgment of line orientation test ($r_s = -0.619$, $P_{FDR} = 0.031$) and severity of the cerebellar syndrome. No other correlation was significant.

Depression was clinically significant in two (10%) participants. Two (10%) had clinically significant anxiety and six (29%) clinically significant apathy. MRI results are provided in Supplementary Data S7.

Discussion

Our study aimed to describe cognitive function in patients with *RFC1*-related disorders. We found that 71% of the participants had cognitive impairment, as detected by overall cognitive efficiency scales. A total of 33% met the criteria for MCI and 14% had dementia. Therefore, cognition is frequently altered in *RFC1*-related disorders. Although it was previously reported,[3-5] the frequency was notably higher than in Traschütz et al.[3] Moreover, we did not observe any significant correlation between overall cognitive efficiency and severity of clinical symptoms nor disease duration nor cerebellar atrophy. This underlines the diversity of the *RFC1*-related disorders, with patients experiencing varying degrees of cognitive impairment independent of other neurological manifestations.

A significant portion of our study population exhibited a CCAS, a syndrome initially described by Schmahmann and Sherman.[11] It is characterized by deficits in executive function, linguistic processing, spatial cognition, and affect regulation, leading to a general decline in intellectual functioning. CCAS is commonly associated with damage or degeneration in the posterior regions of the cerebellum.[11,12] In our study, executive function subtests were the most affected. In contrast, few participants showed impairment in visuospatial

function (5/21) and affect regulation (3/21). The CCAS we observed was, therefore, more limited in scope than the initial description.[11] Both the CCAS scale and the MoCA seem to be suitable tools for detecting cognitive impairment in *RFC1*-related disorders.

Results from the comprehensive neuropsychological test battery confirm that attention/working memory and executive function were the most affected domains. Speed of processing was negatively correlated to cerebellar manifestations' severity, which is consistent with the role of the cerebellum in this ability.[13] Approximately one third of the patients exhibited episodic memory deficits, mainly resulting from impaired executive control of memory, which is consistent with the initial description of the CCAS[11] and usually observed in frontostriatal dysfunction.[14] However, three patients exhibited a different pattern with significant storage deficits, suggesting damage or dysfunction of the hippocampus or temporal cortex. Two of these patients had an amnestic subtype of MCI, whereas the other had dementia.

Visuospatial function was generally preserved (only four participants showing significant deficits, two had dementia and the two others non-amnestic MCI). Nevertheless, correlation analysis revealed that more severe cerebellar manifestations were associated with lower performance on visuospatial functions test. The cerebellum's role in visuospatial function has been demonstrated in the initial description of the CCAS[11] and in neuroimaging studies of healthy individuals.[15-17] In spinocerebellar ataxias, visuospatial deficits are observed in some types,[18-20] but not in others,[21,22] suggesting that this disorder may depend on the localization and severity of cerebellar damage. Further studies incorporating systematic neuroimaging and cognitive assessment are necessary to clarify the alteration of visuospatial functions in patients with CANVAS and its relationship with cerebellar or other brain structures damage.

Over 50% of participants displayed significant deficits in the F-letter fluency test, and 38% in semantic fluency. Moreover, performance in phonemic fluency correlated with the volume of the cerebellum. The cerebellum was shown to be an essential part of the language networks[23] and verbal fluency deficits have been associated with loss of volume or lesions of the posterior lobe of the cerebellum.[12,24] The cerebellum damage may, therefore, play a role in the cognitive impairment experienced by patients with *RFC1*-related disorders.

In our study, only few patients displayed clinically significant depression or anxiety, and their frequency was lower than the reported rates in the general population.[25,26] This was also in contrast with a study reporting behavioral-psychiatric symptoms as the first manifestation of CANVAS.[27] This might reflect some anosognosia or difficulties in recognizing emotions, which is one aspect of alexithymia.[28] However, further investigation using specific scales is required to elucidate this issue. Moreover, the frequency of apathy was relatively high (29%) in our study population. It could result from the basal ganglia circuits dysfunction associated with CANVAS,[29] affecting the motivation brain network.[30]

Our study has several limitations. First, it was conducted at a single center, with a limited number of participants. Nevertheless, it was the first comprehensive exploration of cognition in *RFC1*-related disorders. It confirms the existence of cognitive symptoms in patients whose initial reason for seeking medical attention is neuropathy or ataxia. Our findings underscore the presence of central alterations in these patients and emphasize the necessity of more extensive clinical assessments. Second, neuroimaging data were available for only a small subset of patients, which restricts interpretation of the anatomo-clinical links. This aspect should be systematically explored in future prospective studies. Third, we lacked a control group, making it impossible to determine whether the deficits we observed are specific to *RFC1*-related disorders. However, we accounted for the effects of age and education by transforming individual performance into z-scores. Therefore, it is highly unlikely that the deficits we reported solely result from the influence of these primary risk factors for cognitive impairment.

Conclusion

Cognitive impairment is an integral component of *RFC1*-related disorders' phenotype, regardless of other neurological manifestations. Routine cognitive screening is recommended in *RFC1* patients.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

Rare Missense Variants in *KCNJ10* Are Associated with Paroxysmal Kinesigenic Dyskinesia

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