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ORIGINAL PAPER

Cognitive and Psychiatric Evaluation in *SYNE1* Ataxia

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Abstract

SYNE1 gene mutations were identified as a cause of late-onset pure cerebellar syndrome. Non-cerebellar symptoms, including cognitive impairment, were already described in this condition. The aim of this study was to perform a detailed cognitive and psychiatric description of patients with *SYNE1* gene mutations. We performed neuropsychological and psychiatric evaluations of six patients with *SYNE1* ataxia and compared their performance with 18 normal controls paired for age and education level. *SYNE1* ataxia patients present cognitive dysfunction, characterized by impairment in attention and processing speed domains. Otherwise, the psychiatric assessment reported low levels of overall behavioral symptoms with only some minor anxiety-related complaints. Although this is a small sample of patients, these results suggest that *SYNE1* ataxia patients may represent a model to investigate effects of cerebellar degeneration in higher hierarchical cognitive functions. For further studies, abstract thinking impairment in schizophrenia may be related to dysfunction in cerebellum pathways.

Keywords Hereditary ataxias · *SYNE1* mutations · Cognitive impairment · Cerebellar cognitive affective syndrome

Introduction

Hereditary ataxias are a clinically and genetically heterogeneous group of neurological diseases characterized by a degenerative process in the cerebellum and their pathways. The most common hereditary ataxias include the autosomal dominant spinocerebellar ataxias (SCA) and Friedreich ataxia (FRDA), which is autosomal recessive [1, 2]. With the advance of genetic diagnostic techniques, such as whole-exome sequencing, several new genes have been identified as the cause of previously undetermined ataxias [3].

SYNE1 gene mutations were identified in 2006 as a cause of late-onset pure cerebellar syndrome (autosomal recessive cerebellar ataxia) in French–Canadian population. These patients presented with cerebellar ataxia, retained deep tendon reflexes, and cerebellar atrophy [4]. Conversely, recent studies have demonstrated that *SYNE1* ataxia may present with a more complex phenotype, with variable degrees of non-motor and extracerebellar symptoms, such as motor neuron disease, brainstem dysfunction, cognitive impairment, and focal dystonia. Musculoskeletal abnormalities, including kyphosis, scoliosis, *pes cavus*, and contractures, have also been described [5, 6]. In spite of that, clinically, patients with *SYNE1*

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ataxia usually present with a pure cerebellar syndrome and a pure cerebellar atrophy.

Considering cognitive function, several studies have described cognitive impairment in different forms of acquired and hereditary ataxias. In 1998, Schmahmann and Sherman described a condition called cerebellar cognitive affective syndrome (CCAS), changing the concepts that the cerebellum has a pure motor function. This syndrome is characterized by executive dysfunction, disruption of visuospatial cognition, personality changes and linguistic impairment [7]. CCAS is attributed to a damage in cerebellar posterior lobe, also named cognitive cerebellum, which modulates neural circuits that links prefrontal, posterior parietal, superior temporal, and limbic cortices with the cerebellum [8]. Since then, other studies have described cognitive impairment not only in different SCA subtypes and other hereditary ataxias [9–11] including *SYNE1* ataxia [12] but also in different underlying cerebellar disorders (cerebellar agenesis, ischemic/hemorrhagic strokes, tumor resections) [8]. However, there are also negative studies and doubts about the involvement of the cerebellum in cognition [13, 14].

Considering that there is a widespread degeneration besides the cerebellum in patients with *SYNE1* ataxia, we postulated that CCAS might be found in those patients. In a preliminary study with *SYNE1* patients from Canada, cognitive symptoms were observed, but not affective symptoms, and CCAS was not completely characterized [12].

In order to evaluate if patients with *SYNE1* ataxia may have the clinical features of CCAS, we studied through a detailed protocol, the cognitive and psychiatric function in these patients and compared to a healthy control group.

Material and Methods

Subjects

Six clinically and genetically confirmed patients with *SYNE1* ataxia were evaluated in the Ataxia Unit from December 2016 to February 2017. They were compared with 18 age- and education-matched healthy control subjects (Table 1). Causes of autosomal dominant, recessive, and sporadic ataxias were ruled out in these six patients with *SYNE1* ataxia (negative tests for SCA panel—SCA1, 2, 3, and 6; negative test for FRDA; normal biomarkers: vitamin E, albumin, and alpha-fetoprotein). All patients and controls signed a written informed consent to be enrolled in this study.

SYNE1 Mutation Screening

To identify SYNE1 variants, we performed a 48.48 Access Array IFC (Fluidigm) to capture their 144 coding exons (NM_182961). A total of 77 variants in SYNE1 were observed across all cases, and four of these were both homozygous and truncating. Three are stop codon mutations (p.W4260*, p.W5556*, and p.K7297*) and one 2-bp frame shift deletion (p.T4341fs). The stop codon mutation p.W4260* was observed in three patients, who were members of the same family.

Clinical Evaluation

All *SYNE1* ataxia patients were evaluated for the following demographic and clinical features: age, age of symptoms onset, and neuroimaging findings. Ataxia severity was evaluated using an international cooperative ataxia rating scale (ICARS) and the Brazilian-validated scale for the assessment and rating of ataxia (SARA) (Table 1).

Comprehensive Neuropsychological Evaluation

Neuropsychological evaluation consisted of a 2-h battery of tests measuring memory (verbal and visual), visuoconstructive abilities, attention, processing speed, executive functions, and language. All tests were scored according to standard procedures as outlined in test manuals. Subjects were allowed to take breaks when needed.

Memory was tested using the Rey Auditory–Verbal Learning Test (RAVLT) to measure verbal memory (learning, immediate, and delay recall) [15] and Rey Complex Figure (RCF) for visual memory (immediate recall) which also assesses constructional praxis through the copy of the complex figure [16]. Attention was tested using the Color Trails Test (CTT) 2 for complex attention [17], digit span (DS), and picture completion (PC) subtests of the Wechsler Adult Intelligence Scale III (WAIS III) [18]. Processing speed was assessed using the digit symbol-coding test (DSC) of the WAIS III [18]. Executive functions were evaluated using the matrix reasoning (MR) subtest of the WAIS III, semantic verbal fluency (animals) (SVF), and Stroop test (board 3) [18–21]. Language was measured using the Boston Naming Test adapted [22]. The raw scores were compared between control and patient groups.

Psychiatric Evaluation

For diagnostic definition, the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [23] was administered to patients and healthy controls. Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) [24, 25], the Community Assessment of Psychic Experience (CAPE) [26], the Hamilton Depression Rating Scale (HAM-D) [27], the Hamilton Anxiety Rating Scale (HAM-A) [28], and the Young Mania Rating Scale (YMRS) [29]. Only for the patient group, global severity was measured using the Clinical Global Impression Scale (CGI-S) [30], and functioning was

Table 1 Clinical characteristics of patients and control subjects

Clinical variables	*SYNE1* patients ($n = 6$)	Controls ($n = 18$)	p value
Age (years)	43.3 (11)	45.7 (10.8)	0.463 (NS)
Gender (% female)	3 (50%)	17 (94.4%)	0.011
Education level (years)	7.5 (4.6)	8.1 (4.4)	0.564 (NS)
Psychiatric history	4/6 (66.7%)	7/18 (38.9%)	0.237 (NS)
Mean age of onset disease (years)	29.6		
Mean duration of disease (years)	12.6		
SARA scale (max = 40)	12.91 (9.69)		
ICARS scale (max = 100)	30.83 (16.1)		
Neuroimaging findings	Cerebellar atrophy 6 (100%)		

Data expressed as means ± SD. The p value represents significance after non-parametric Mann–Whitney U

NS not significant

assessed by the Global Assessment of Functioning Scale (GAF) [31]. All raters were trained in periodic group meetings.

Statistical Analyses

Statistical analyses were conducted using SPSS V20 and Minitab 16. The Mann–Whitney tests for independent samples were performed to compare between-group differences on demographic and clinical variables. Data from the neuropsychological assessment was assessed for normal distribution using Kolmogorov–Smirnov test. All neuropsychological measures followed a non-normal distribution and therefore were analyzed with non-parametric Mann–Whitney test. Correlational analyses were performed to cognitive variables with severity of motor symptoms on SARA and ICARs scale using Spearman's correlation coefficient. Results were presented as 95% confidence interval (95% CI) and were statistically significant when $p < 0.05$.

Results

Patients with *SYNE1* did not differ significantly from control subjects with regard to age and level of education (Table 1). Among patients with *SYNE1*, the mean age of disease onset was 29.6 years and mean disease duration 12.6 years. Considering the psychiatric evaluation, one patient fulfilled criteria for general anxiety disorder, two patients for past adjustment disorder, one patient for past alcohol abuse disorder, and two patients had no diagnosis. In the control group, three subjects fulfilled criteria for depression, one subject fulfilled criteria for general anxiety disorder, two fulfilled criteria for panic disorders, and one had past history of depression. Noteworthy, five patients scored moderate to severe in the PANSS item no. 5 (difficulty in abstract thinking) regardless of psychiatric diagnosis. The scores of the standardized rating scales are displayed in Table 2. The average total score on the SARA Scale (max = 40) was 12.91 (9.69), and the average total score on the ICARS Scale (max = 100) was 30.83 (16.13). All six patients showed diffuse severe cerebellar atrophy on MRI.

Neuropsychological Assessment

Neuropsychological assessment revealed significant impairment on CTT 2 test for complex attention and in digital symbol coding test (processing speed) in patients with *SYNE1* when compared with matched controls. In semantic verbal fluency test (executive function), there was a tendency to a statistical significance finding (p 0.065). There were no clinically significant deficits in language, memory functions (verbal or visual immediate and delayed recall), and visuoconstructive abilities (Table 3). Spearman's rank correlation coefficient showed no correlation between SARA and cognitive deficit and also no correlational between ICARS and cognitive tests (Table 4).

Discussion

This study demonstrated that patients with *SYNE1* ataxia may present impairment in attention, processing speed domains, and maybe in executive function. In this study, we have a very small sample and choose a p value 0.05 instead of a p value 0.10 to have a methodological strictness analyses and some results may have lost meaning, as in the case of the executive function, where we find a difference close to p 0.05. Correlational analyses suggested that cognitive deficits could not be explained by the severity of motor deficits. Although this is a small sample, these findings reinforce that *SYNE1* ataxia may fulfill some features of the CCAS [32].

According to CCAS description, the psychiatric symptoms consists in emotional lability, flattening of affect, disinhibition, impulsivity, paranoid ideation, bizarre illogical, and

Table 2 Psychopathological features of the patient with *SYNE1* ataxia ($n = 6$)

Scale	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Mean ± SD
SCIDI-I	No diagnosis	No diagnosis	Past alcohol abuse	Past adjustment disorder	Past adjustment disorder	General anxiety disorder	–
PANSS	39	48	51	64	60	66	54.6 ± 10.4
PANSS-N5	1	4	5	4	5	5	4 ± 1.5
CGI-S	1	1	1	2	1	3	1.3 ± 0.8
GAF	80	90	90	90	90	70	85.6 ± 8.3
YMRS	3	3	3	1	2	3	2.5 ± 0.8
HAM-D	5	1	5	4	1	6	3.6 ± 2.1
HAM-A	1	1	5	5	0	11	3.8 ± 4.1

PANSS Positive and Negative Syndrome Scale, *CGI-S* Clinical Global Impression Scale, *GAF* Global Assessment of Functioning Scale, *YMRS* Young Mania Rating Scale, *HAM-D* Hamilton Depression Rating Scale, *HAM-A* Hamilton Anxiety Rating Scale

psychotic thinking [33]. Our patients in the psychiatric assessment reported surprisingly low levels of overall behavioral symptoms, with only some minor anxiety-related complaints, which is not entirely in accordance with CCAS psychiatric manifestations. The contemporary evidence shows that cerebellum vermis and fastigial nucleus have connections with limbic and paralimbic cortical and subcortical regions [34], and these behavioral changes have a predilection for lesions

Table 3 Results of the neuropsychological tests in *SYNE1* patients and controls

Group		Average	Median	Standard deviation	Q1	Q3	N	IC	*p* value
RAVLT sum	Control	41.2	40.0	9.2	36.0	46.5	19	4.1	0.285
	Patient	34.2	39.5	11.1	28.3	41.8	7	8.2	
RAVLT 6	Control	7.3	7.0	2.9	5.3	10.0	19	1.3	0.523
	Patient	6.5	6.5	1.9	5.3	7.8	7	1.4	
RAVLT 7	Control	7.8	8.5	2.7	6.3	9.8	19	1.2	0.214
	Patient	6.5	7.0	2.2	5.5	7.8	7	1.6	
RCF Mem	Control	11.1	10.5	5.9	7.3	15.1	19	2.6	0.350
	Patient	12.5	12.5	2.0	11.0	13.0	7	1.5	
RCF Copy	Control	25.6	28.8	8.8	19.6	32.4	19	4.0	0.391
	Patient	23.9	24.0	7.7	23.5	29.0	7	5.7	
CTT2	Control	143.5	123.5	65.9	105.3	163.3	19	29.6	0.009
	Patient	248.2	220.0	77.3	195.0	321.0	7	57.3	
DS	Control	10.5	10.0	3.0	8.3	11.8	19	1.3	0.814
	Patient	10.2	11.0	4.3	8.5	12.8	7	3.2	
PC	Control	9.2	7.0	6.4	4.0	13.8	19	2.9	0.461
	Patient	10.3	11.5	3.8	8.5	13.0	7	2.8	
Stroop 3	Control	33.4	29.5	11.4	27.3	41.3	19	5.1	0.095
	Patient	40.8	41.5	7.7	34.0	47.5	7	5.7	
MR	Control	8.1	8.0	4.7	4.5	9.8	19	2.1	0.421
	Patient	6.3	5.5	3.0	4.3	6.8	7	2.2	
SVF	Control	15.4	14.5	4.3	13.0	17.0	19	1.9	0.065
	Patient	11.8	11.5	3.1	10.3	12.8	7	2.3	
DSC	Control	43.3	39.5	19.2	31.0	52.3	19	8.7	0.004
	Patient	18.6	18.0	5.8	15.0	21.0	7	4.3	
Boston	Control	45.9	47.0	6.9	41.5	50.8	19	3.1	0.385
	Patient	48.5	49.5	4.6	45.3	52.3	7	3.4	

p significance after non-parametric Mann–Whitney *U*

RALVT Rey Auditory–Verbal Learning Test, *RFC mem* Rey Figure Complex for visual memory, *CTT* Color Trails Test, *DS* digit span, *PC* picture completion, *MR* matrix reasoning, *SVF* semantic verbal fluency, *DSC* digit symbol-coding test

Table 4 Correlation of SARA and ICARS with neuropsychological performance in patients with *SYNE1* ataxia

		SARA		ICARS	
		Corr (*r*) (%)	*p* value	Corr (*r*) (%)	*p* value
Verbal memory	RAVLT sum	− 23.2	0.658	− 37.1	0.468
	RAVLT 6	2.9	0.957	− 8.6	0.872
	RAVLT 7	− 29.4	0.572	− 55.1	0.257
Visual memory	RCF Mem	− 56.4	0.322	− 60.0	0.285
Constructional praxis	RCF Copy	10.3	0.870	− 30.0	0.624
Attention	CTT2	− 5.1	0.935	− 30.0	0.624
	DS	− 26.1	0.618	− 54.3	0.266
	PC	39.7	0.436	23.2	0.658
Executive function	Stroop 3	55.1	0.257	48.6	0.329
	MR	26.5	0.612	14.5	0.784
	SVF	− 5.8	0.913	8.6	0.872
Processing speed	DSC	82.1	0.089	40.0	0.505
Language	Boston	− 52.9	0.280	− 46.4	0.354

p value < 0.05 (statistical significance); Spearman's rank correlation coefficient

SARA Scale for the Assessment and Rating of Ataxia, *ICARS* International Cooperative Ataxia Rating Scale, *RALVT* Rey Auditory–Verbal Learning Test, *RFC mem* Rey Figure Complex for visual memory, *CTT* Color Trails Test, *DS* digit span, *PC* picture completion, *MR* matrix reasoning, *SVF* semantic verbal fluency, *DSC* digit symbol-coding test, *Corr* correlation

involving the vermis and paravermian regions [35–37]. In our sample, all the patients had diffuse cerebellar atrophy and not restricted to a specific area. Moreover, in the psychiatric evaluation, most of the patients presented moderate to severe levels in the PANSS item N5 (difficulty in abstract thinking), the strongest cognitive predictor among PANSS items. This item is scored after questioning the subjects about similarities and the meaning of well-known proverbs. Higher scores indicate worse ability to define abstract aspects, which is compatible to the levels expected for patients with executive dysfunction. Nevertheless, a meta-analysis conducted by Van Overwalle et al. [38] covered more than 350 fMRI studies to provide insight into the role of the cerebellum in social cognition. The authors found that the cerebellum is strongly involved during abstract mentalizing, suggesting that the cerebellum may be a modulator of cognitive processes in abstract thinking.

Although previously reported as a pure cerebellar ataxia syndrome, recent studies have demonstrated that *SYNE1* ataxia patients may present a wide heterogeneity of clinical features, including motor neuron disease, pyramidal signs, and cognitive decline [5, 22, 39, 40].

As aforementioned in introduction section, the previous study by Laforce et al. failed to proof CCAS in patients with *SYNE1* ataxia, but they showed significant difference in cognitive domains when compared to healthy controls. Besides attention and processing speed domains, verbal working memory and visuospatial/visuoconstruction abilities were also impaired. Moreover, five patients with *SYNE1* ataxia had a diffuse cerebellar hypometabolism associated with a small area of right parietal metabolism, which is consistent with disruption of visuospatial and visuoconstructive skills [12]. No affective changes were observed in the study of Laforce et al., in opposite to the affective and psychiatric changes observed in some of our patients with *SYNE1* ataxia [12].

According to the main studies on CCAS, cognitive impairment may occur in posterior cerebellar lobe lesions, disrupting cerebellar modulation of cognitive loops with cerebral association cortices. As a result, the parietal lobe hypometabolism seen in the previous reports may also represent disruption of the posterior cerebellum connection with cerebral association cortices [41]. Our group also evaluated patients with hereditary ataxias using functional brain imaging. Twenty-nine patients with spinocerebellar ataxias type 3 (SCA3) and 25 controls performed photon emission computed tomography (SPECT) imaging. SCA3 patients showed lower brain perfusion in the cerebellum, left and right temporal lobes, right and left limbic lobes, and right and left occipital lobes compared to control subject [42]. As in *SYNE1* patients, our results pointed to a more restricted cortical involvement including visuospatial processing areas.

This study has some limitations. Firstly, the small sample size of patients ($n = 6$). Also, a functional imaging study could better differentiate the cortical and cerebellar areas involved in patients with cognitive and affective symptoms. In spite of this, the cognitive profile of our sample together with the psychiatric findings is a possible link to the CCAS.

This study contributes to better understand the role of the cerebellum in cognition and affective symptoms. Furthermore, our data reinforces that *SYNE1* ataxia may

present with cognitive changes and, to a lesser extent, with psychiatric symptoms. Therefore, we postulate that the cerebellum may modulate some cognitive domains. Future studies with a large number of patients, together with neuroimaging techniques, may be helpful to better elucidate the hypothesis of CCAS in *SYNE1* ataxia.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Statement Patients signed an informed consent and allowed publication of this data.

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