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Short communication

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) – A Polish family with novel SACS mutations

Magdalena Krygier [a,*], *Agnieszka Konkel* [b,c], *Michał Schinwelski* [b,c], *Małgorzata Rydzanicz* [d], *Anna Walczak* [d], *Magdalena Sildatke-Bauer* [e], *Rafał Płoski* [d], *Jarosław Sławek* [b,c]

[a] *Department of Biology and Genetics, Medical University of Gdańsk, Ul. Dębinki 1, 80-211 Gdańsk, Poland*
[b] *Department of Neurology, St. Adalbert Hospital, Copernicus, Al. Jana Pawła II 50, 80-462 Gdańsk, Poland*
[c] *Neurological-Psychiatric Nursing Department, Medical University of Gdańsk, Ul. Dębinki 1, 80-211 Gdańsk, Poland*
[d] *Department of Medical Genetics, Medical University of Warsaw, ul. Pawińskiego 3C, 02-106 Warszawa, Poland*
[e] *Department of Ophthalmology, St. Adalbert Hospital, Copernicus, Al. Jana Pawła II 50, 80-462 Gdańsk, Poland*

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ABSTRACT

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a rare hereditary ataxia, characterized by the triad of early-onset cerebellar ataxia, peripheral sensorimotor neuropathy and lower limb spasticity. Although ARSACS is increasingly reported worldwide, we present the first Polish family with a comprehensive clinical and neuropsychological assessment, harboring two novel mutations in the SACS gene. Our results demonstrate the variability in cognitive and behavioral profiles in ARSACS, which is in line with other heredodegenerative ataxias. One should be aware of ARSACS in cases of autosomally recessive inherited ataxias without common mutations.

1. Introduction

Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is an early-onset hereditary ataxia, caused by mutations in the SACS gene. The disease was initially described in Quebec, but since then there have been subsequent reports on the prevalence of ARSACS worldwide [1,2]. The classic phenotype includes the triad of early-onset cerebellar ataxia, peripheral sensorimotor neuropathy and lower limb spasticity. Atypical cases may present with adult onset ataxia, Charcot-Marie-Tooth-like phenotype or isolated spasticity [3]. The characteristic feature, albeit not obligatory, is an increased demarcation of retinal nerve fibers on Ocular Coherence Tomography, recently described also in ARSACS carriers [4].

The literature regarding neuropsychological status in ARSACS is very limited. Although intellectual impairment and cognitive decline are regarded as occasional features,

* *Corresponding author.*
E-mail address: magdalena.krygier@gumed.edu.pl (M. Krygier).
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several patients with dementia and intellectual disability have been reported [5,6]. Additionally, behavioral and psychiatric manifestations characteristic for the cerebellar cognitive affective syndrome (CCAS) were also recognized, indicating that neuropsychiatric disturbances may be a part of the clinical spectrum of the disease [6–8].

Here we present a description of, to our knowledge, the first Polish family with ARSACS, in which two novel *SACS* mutations were identified.

2. Clinical characteristics

The proband is a 33-year-old woman, born to a non-consanguineous couple from Northern Poland. She has five siblings, of whom two sisters and one brother are also presenting clinical features of early-onset ataxia. Neither their parents nor other relatives were found to have any signs of ataxia. At the time of clinical examination three affected sisters and one affected brother were 47, 45, 33, and 30-years old, respectively. They all manifested first signs of cerebellar ataxia in early childhood. In the teen years the features of gait and limb ataxia were accompanied by dysarthria, spasticity in the lower limbs and peripheral neuropathy. Clinical examination revealed severe peripheral neuropathy in the lower limbs, including distal muscle weakness and atrophy, bilateral pes cavus, loss of Achilles reflexes, and decreased tactile and vibration senses, whereas in the upper limbs moderate atrophy of the interosseous and thenar muscles and slightly decreased tendon reflexes. The patients presented with ataxia, which ranged from 15 to 23.5 scores in the Scale for the Assessment and Rating of Ataxia (SARA) and spasticity in the lower limbs, which ranged from 19 to 30 in the Spastic Paraplegia Rating Scale (SPRS) (Table 1).

Magnetic Resonance Imaging (MRI) revealed severe atrophy of the superior vermis and the cerebellar hemispheres. Additionally, diffuse cortical atrophy, thinning of the corpus callosum, linear T2-hypointensities in the pons, and atrophy of the cervical spinal cord were observed in all affected siblings (Fig. 1). Nerve conductions studies showed mixed pattern of nerve injuries (demyelinating and axonal) with predominant sensory fibers involvement (virtually no responses in both upper and lower extremities). Finally, all of the siblings exhibited a characteristic for ARSACS thickening of nerve fiber layer in the intermaculopapillar region on ocular coherence tomography (Fig. 1).

Extended neuropsychological examination included screening assessment of cognitive functioning and evaluation of specific cognitive domains such as semantic memory, visual confrontation naming, visuomotor coordination, visuospatial skills, attention and concentration, verbal short-term memory, working memory, verbal and non-verbal learning ability, executive functions (verbal fluency, planning and cognitive flexibility) and dynamic praxis. Obtained results revealed that all patients exhibited a significant visuomotor coordination impairment as well as slight deficits in verbal short-term memory and naming. Reduced test scores were also observed in other particular cognitive domains but they varied between subjects. Screening assessment of global cognitive status suggested mild dementia in Patient no. 2, while Patient no. 1 exhibited mild cognitive impairment. Cognitive functions were better preserved in Patients no. 3 and 4. Neither individual reported severe depressive symptoms and there was no history of psychiatric disorders (Table 2).

Table 1 – Clinical characteristics of the four siblings with ARSACS.

Patient no.	Sex	Age	Age at oset	Disease duration (years)	SARA score								
					Gait (0–8)	Stance (0–6)	Sitting (0–4)	Speech disturbance (0–6)	Finger chase (0–4)	Nose-finger test (0–4)	Fast alternating hand movements (0–4)	Heel-shin slide (0–4)	Total (0–40)
1	K	47	1.5	45	7	6	0	2	3	2	1.5	2	23.5
2	K	45	4	41	6	6	0	3	1	1	1	2	20
3	K	33	2	31	3	6	0	2	1	1	1	1	15
4	M	30	5	25	4	4	0	3	1.5	1	1.5	1	16

Patient no.	SPRS (0–52)	MAS (lower limbs)	Nystagmus	Retinal nerve fiber hypertrophy	Tendon reflexes		Babiński sign	Additional symptoms	MRI findings
					Knee	Ankle			
1	30	1.5	+	+	+	–	+	Dysphagia, urinary dysfunction, impaired vibration sense at ankles, pes cavus	Cerebellar atrophy, linear T2-hypointensities in the pons, generalized cortical atrophy, narrowing of the corpus callosum, atrophy of the cervical spinal cord
2	21	1	+	+	++	–	+		
3	19	1	+	+	+	–	+		
4	23	R = 1; L = 1.5	+	+	+++	–	+		

SARA = Scale for the Assessment and Rating of Ataxia; SPRS = Spastic Paraplegia Rating Scale; MAS = Modified Ashworth Scale; MRI = Magnetic Resonance Imaging; R = Right; L = Left.

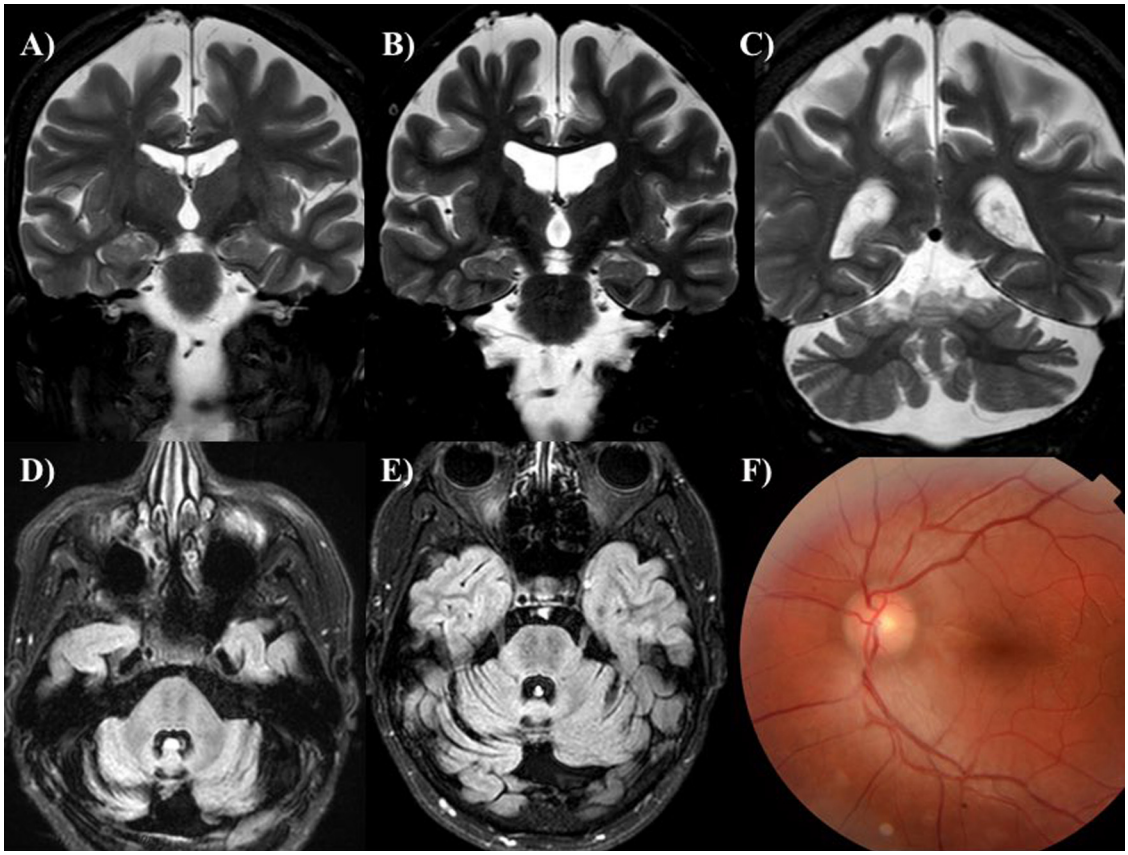

Fig. 1 – Characteristic MRI and ophthalmological findings. Bilateral frontal and parietal atrophy is presented on coronal T2 images for Patient 1 at age 47 years (A) and for Patient 4 at age 30 years (B). Coronal T2 image for Patient 1 demonstrates predominant superior vermis atrophy (C). Axial TIRM cross-sections show linear hipointensities in the pons for Patients 1 (D) and 4 (E). Retinal fundus examination reveals increased demarcation of the nerve fibers close to the optic disk, due to a retinal nerve fiber hypertrophy (Patient 4, F).

3. Molecular methods and results

After obtaining informed consent, next-generation sequencing was performed on the genomic DNA from 30-years old proband, using TruSightOne™ Sequencing Panel Kit (Illumina, San Diego, CA, USA), which targets coding sequence and splice sites of 4813 loci associated with known human clinical phenotypes. Sequencing data were analyzed as previously described [9]. The following two novel variants in the *SACS* gene were detected: p.Ser3268_Ile3269fs/c.9804_9805insC and p.Asp4192Asn/c.12574 G > A (according to the cDNA sequence NM_001278055.1). Both identified *SACS* variants have 0 frequency in all databases uses in this study, including in-house collection of 1343 Polish subjects. Cosegregation analysis by Sanger sequencing confirmed the presence of both alterations in all affected individuals, whereas two healthy siblings and the mother carried one of the two variants. The c.9804_9805insC (p.Ser3268_Ile3269fs) mutation results in a frameshift and premature termination of the predicted protein, which lacks 1140 amino acids. The c.12574 G > A substitution in exon 8 leads to a change of one amino acid (p.Asp4192Asn) and is predicted to be deleterous by SIFT (score: <0.05; http://sift.jcvi.org/) and PolyPhen-2 (score: 1.00; http://genetics.bwh.harvard.edu/pph2/) softwares.

4. Discussion

Presented individuals are compound heterozygotes for the novel frameshift and missense variant in the *SACS* gene. The majority of *SACS* mutations outside of Quebec are private and can be distributed throughout the whole gene. To date no clear genotype-phenotype correlation has been identified [2]. The range of clinical symptoms and the course of the disease in the siblings is consistent with cases described in the literature and there is little intra-familial phenotypic variability. The alterations seen on brain MRI are, however, relatively severe in comparison to other patients. Classic neuroimaging features described in the French-Canadian population were limited to the infratentorial region of the brain. Recent studies on the German and Spanish cohorts revealed, however, a common presence of supratentorial alterations in ARSACS, such as bilateral parietal cerebral atrophy and thinning of the corpus callosum [3,10]. In the presented family these features are also

Table 2 – Neuropsychological assessment.

	Patient No.					Patient No.			
	1	2	3	4		1	2	3	4
Screening assessment of global cognitive status					**Verbal learning**				
MMSE (max. 30)	**26**	**21**	29	30	RAVLT – learning curie [intrusions]	5–7–8–9–11 [2]	3–5–8–7–8 [0]	6–12–13–14–14 [0]	7–9–10–11–12 [0]
Semantic memory					RAVLT – corrected recognition* [correct/false positive]	10 [11/1]	10 [10/0]	15 [15/0]	14 [14/0]
Information subtest from WAIS (scaled score)	11	7	8	10	RAVLT – spontaneous recall after 10 min delay [intrusions]	8 [1]	7 [1]	13 [0]	13 [0]
Word retrieval					% Of information recalled after delay	73	88	93	108
BNT (max. 60)	**52**	**34**	**52**	**48**	RAVLT – corrected delayed recognition*	10 [11/1]	11 [14/3]	13 [14/1]	14 [15/1]
Visuomotor coordination					**Nonverbal learning**				
SDMT (scaled score)	**3**	**4**	**4**	**3**	RCFT 3 min immediate recall (max. 36) (T score)	39	28	51	69
Visuospatial function					RCFT 30 min delayed recall (max. 36), (T score)	36	26	47	64
Object perception					**Verbal fluency**				
VOSP Shape Detection (max. 20)	20	20	20	19	Semantic – animals/fruits	17/10	9/12	20/16	16/7
VOSP Incomplete Letters (max. 20)	19	16	19	20	Phonemic – ''K''/''P''/''M''	6/14/9	9/3/7	11/14/14	10/5/6
Space perception					**Cognitive flexibility**				
VOSP Dot counting (max. 10)	9	10	10	10	The Brixton Spatial Anticipation Test (scaled score)	6	6	7	7
VOSP Position Discrimination (max. 20)	20	15	20	20					
VOSP Number Location (max. 10)	9	10	9	8	**Planning**				
VOSP Cube Analysis (max. 10)	9	10	10	10	TOLDX-2 – total move score (standard score)	96	70	106	120
Constructional praxis					TOLDX-2 – total correct score (standard score)	94	88	96	114
RCFT copy (max. 36) (T score)	33	33	36	35	**Dynamic praxis**				
Attention and concentration	**10**	**7**	14	13	*Motor sequence learning task*				
Serial 7 subtraction (max. 14)	**(6 min 14 s)**	**(6 min 42 s)**	(67 s)	(57 s)	1st sequence (max. 5)	**0**	**2**	4	5
Verbal short-term memory					2nd sequence (max. 5)	**0**	**0**	5	5
Digit span – forward	4	3	4	4	*Mood*				
Working memory					BDI	6	7	4	9
Digit span – forward vs. backwards	4/3	3/2	4/3	4/3					
TMT A vs. TMT B (T scores) [errors]	72 [0]/58 [1]	81 [0]/68 [3]	65 [0]/66 [3]	46 [0]/49 [0]					

MMSE = Mini-Mental State Examination; WAIS = The Wechsler Adult Intelligence Scale; BNT = Boston Naming Test; SDMT = Symbol Digit Modalities Test; VOSP = Visual Object and Space Perception Battery; TMT = Trail Making Test; RAVLT = The Rey Auditory Verbal Learning Test, *corrected recognition score = correct recognitions minus false positive recognitions; RCFT = Rey Complex Figure Test and Recognition Trial; TOLDX-2 = Tower of London-Drexel University - 2nd Edition; BDI = Beck Depression Inventory; scores highlighted in bold indicate impairment.

observed and the cerebral atrophy is evident not only in the parietal but also in the frontal lobes.

On neuropsychological examination all individuals presented a significant visuomotor coordination impairment and slight deficits in verbal short-term memory and visual confrontation naming. In other areas we did not observe a common pattern of dysfunction. The presence of mild cognitive impairment in Patient no. 1 and mild dementia in Patient no. 2 may suggest that cognitive functions deteriorate along with the disease duration, which was 45 and 41 years, respectively. Interestingly, the siblings exhibited no significant deficits in object and space perception, as well as constructional praxis. Additionally, there was no history of neuropsychiatric symptoms, commonly reported in patients with lesions involving the limbic cerebellum. However, it should be emphasized that ARSACS is a complex neurodegenerative disorder, thus the presence of such symptoms in previously described cases may result from of the various involvement of supra- and infratentorial structures. To our knowledge in our group the neuropsychological assessment was the most complex when compared to other studies.

Our results indicate that screening for SACS mutations should be considered in patients with autosomally recessive inherited cerebellar ataxia and no common mutations detected. Additionally, neuropsychological profiles of the presented cases demonstrate the diversity in cognitive and behavioral phenotypes in ARSACS, as it is seen in other heredodegenerative ataxias and the profile is not helpful in establishing the diagnosis. On the other hand, Ocular Coherence Tomography might be helpful in differential diagnosis.

Conflict of interest

None declared.

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