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SHORT REPORTS

Consolidating the Role of TDP2 Mutations in Recessive Spinocerebellar Ataxia Associated with Pediatric Onset Drug Resistant Epilepsy and Intellectual Disability (SCAR23)

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Abstract
Spinocerebellar Ataxia 23 (SCAR23) is a newly described condition caused by mutations in TDP2 gene. To date, only four patients from two families have been reported, all carrying the same homozygous mutation. We describe a fifth patient, carrying a novel mutation in the same gene, thus confirming the role of TDP2 mutations in determining the disease and defining the main features SCAR23: pediatric onset ataxia and drug-resistant epilepsy and intellectual disability. We further show the clinical presentation which is associated with the neuroradiological evidence of progressive cerebellar atrophy, giving the evidence that SCAR23 can be classified as a degenerative condition.

Keywords Pediatric ataxia · Spinocerebellar ataxia · SCAR23 · TDP2 · Cerebellar atrophy

Introduction

Spinocerebellar Ataxia 23 (SCAR23, OMIM #616949) is a newly described condition mainly characterized by cerebellar ataxia, epilepsy, and intellectual disability [1, 2]. It is caused by biallelic mutations in TDP2 (Tyrosil-DNA Phosphodiesterase 2, OMIM*605764), a gene encoding for a phosphodiesterase of crucial importance for DNA stability, as it is required to repair the accidental double-strand breaks (DSBs) produced by the abortive activity of Topoisomerase II[3]. Recent studies suggest that TDP2 expression is particularly high in human adult brain [3], giving a possible explanation to the neurological phenotype of the patients carrying mutations in this gene. To date, only four patients from two different families have been reported, three Irish brothers and one patient from the USA, all harboring the same homozygous splice site mutation in TDP2. We describe here a fifth patient, from a different ethnic group, who shows an analogous clinical presentation, carrying a novel mutation in the same gene; we further compare our patient with the others so far reported in order to expand and define the phenotypic spectrum of SCAR23.

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Case Report

Our patient is a girl, third child of healthy first cousins Italian parents; family history was referred negative and her two elder brothers have no remarkable medical issue. Pregnancy, birth, and infancy elapsed regularly. Developmental stages were initially normally achieved (independent walking at 11 months, first words at 12 months), but a slowing of language improvement and behavioral problems were later noted. Griffiths scale performed at the age of 5 revealed a GQ score of 37; later developmental evaluations, performed with different scales, confirmed a moderate/severe intellectual disability. At physical examination, she showed long face, mild hypertelorism,

narrow and long nasal ridge with protruding columella, narrow palate, prominent incisors, and micrognathia (Fig. 1). At the age of 12, she experienced the onset of focal frontotemporal epilepsy, with episodes of limbs hypertonia, partial loss of consciousness, and aphasia. In the following years, several antiepileptic drugs (Valproate, Topiramate, Levetiracetam, Clobazam, Oxcarbazepine, Lamotrigine) were tried to control the seizures, in different associations, but always without a full control of the symptom. The neurological examination was characterized by gait ataxia, tremor, dysmetria, and oculomotor and oral apraxia; she later developed severe dizziness, which further compromised her ability to walk. Subsequent brain MRIs were performed, with normal result at 8 and 12 years; at the age of 14, a third exam revealed cerebellar atrophy, associated with milder supratentorial atrophy (Fig. 1); the MRI was unchanged at the age of 17. Metabolic tests (urinary organic acids, plasmatic aminoacids, plasmatic lactate and pyruvate, transferrin isoelectric focusing) and genetic analyses (Array-CGH, NGS panel for epilepsy syndromes) resulted to be negative; muscle biopsy was normal except for a mild Coenzyme Q activity reduction, with normal citrate synthase activity. At the age of 17, the patient, together with her parents, underwent Whole Exome Sequencing (WES) analysis, in order to identify genetic variants that may be responsible for the clinical phenotype, and confirm the adherence to segregation rules for inherited and de novo sequence changes. WES data were analyzed using the VarGenius pipeline [4] and revealed a homozygous nonsense variant in exon 3 of TDP2: c.400C>T (p.Arg134Ter) that was found in both parents in heterozygous state. This is an extremely rare variants (gnomAD allele frequency 0.00000799: 2 heterozygote alleles reported) and it is classified as pathogenic according to ACMG guidelines. The presence of the variant was validated in the patient and her parents using PCR and Sanger capillary bidirectional sequencing.

Discussion

SCAR23 is an ultra-rare condition, described so far in two unrelated families. In Table 1, we summarize the most relevant features of the patients with TDP2 mutations so far reported [1, 2]. Our patient is the first one to be described harboring a different mutation, which, like in the other cases, is identical on both alleles. The clinical presentation of our patient is very similar to the other reported ones, and we can therefore

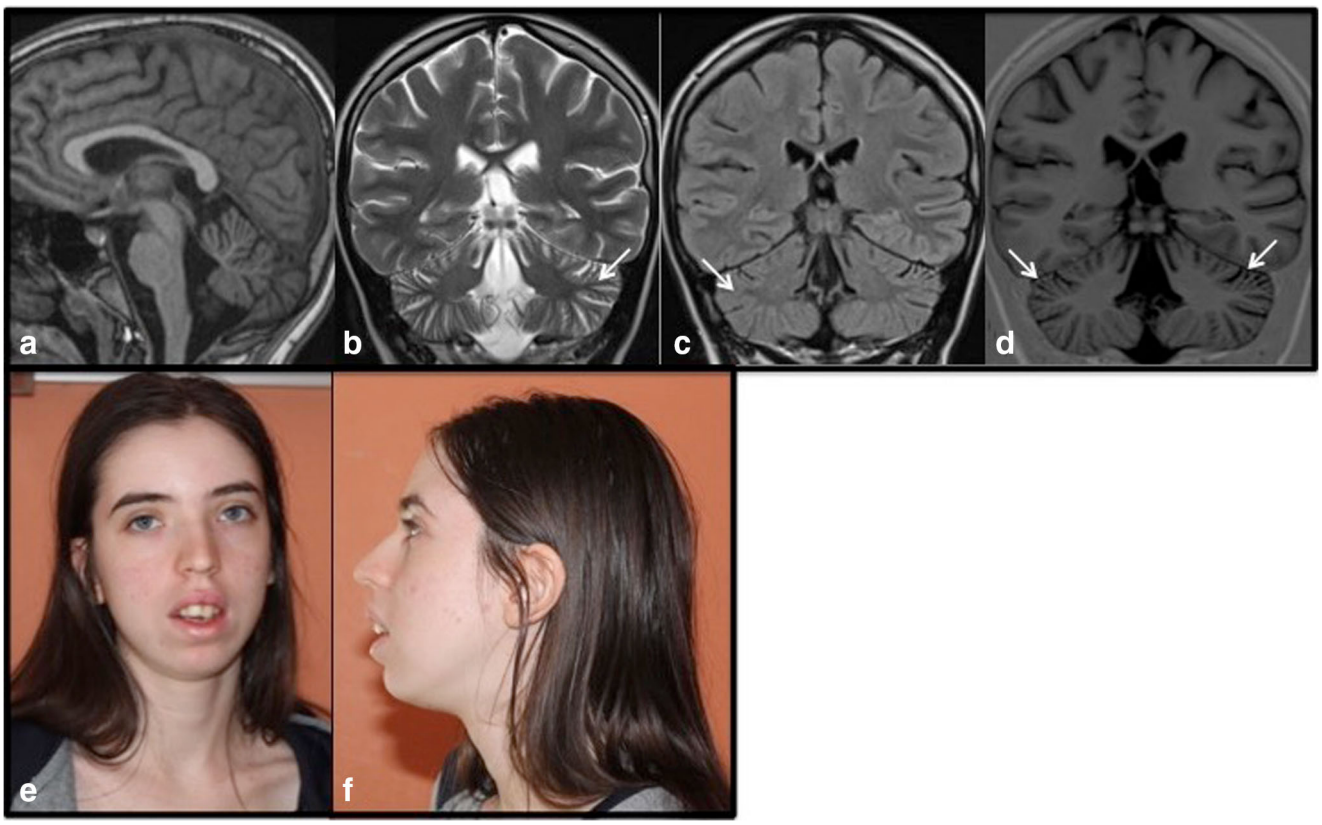

Fig. 1 Brain MRI and facial appearance and of our patient. Brain MRI at 14 years old (A–D): Sagittal T1-w.i.: A, demonstrate mild atrophy of the vermis and mild IV ventricle enlargement. Coronal T2-w, FLAIR and IR images, B–D, show mild enlargement of cerebellar sulci in the region of the horizontal cerebellar sulcus associated with cortical thinning and slight hyperintensity (arrows). Moderate diffuse cerebral atrophy is also visible. Facial appearance at 16 years old (E–F): narrow and long nasal ridge with protruding columella, narrow palate, prominent incisors, and micrognathia

Table 1 Main features of SCAR23 patients

		Patient 1 (present case)	Patient 2[2]	Patient 3[1]	Patient 4[1]	Patient 5[1]
Patients	Age	11 years	6 years	32 years	26 years	23 years
	Sex	F	M	M	M	M
TDP2 mutation	Mutation (HomoZ)	c.400C>T	c.425+1G>A	c.425+1G>A	c.425+1G>A	c.425+1G>A
	Mutation type	STOP p.Arg134Ter	Splicing	Splicing	Splicing	Splicing
Development/cognitive	DD/ID	+	+	+	+	+
	Severity	M/S	NA	M/S	M/S	M/S
	Age walk	11 months	14 months	10–12 months	10–12 months	10–12 months
Auxometry	Microcephaly	+ (< 3°)	+	NA	NA	NA
	Height	25	< 5°	NA	NA	NA
	Weight	< 3°	5°			
Neurologic examination	Ataxia	+	+	+	+	+
	Hypotonia	–	+	+	–	–
	Fatigue	+	+	NA	NA	NA
	Loss of indep. walk	–	NA	+	+	+
Epilepsy	Onset	12 years	5 months	2 months	12 years	6 months
	Type	Focal tonic-DR	Generalized	Generalized tonic-DR	Generalized tonic epilepsy	Generalized tonic-DR
Brain MRI	Cerebellar atrophy	+	–	NA	NA	NA
	Other	Mild supratentorial atrophy	–	NA	NA	NA
Mitochondria studies	Muscle biopsy	Mild CoQ ↓	↓ activity of complex I+III/II+III	NA	NA	NA
	L/P	–	↑ L/P ratio	NA	NA	NA
Other		Dysmorphisms Dizziness	Failure to thrive, neutropenia	Dysmorphisms	Dysmorphisms	Dysmorphisms

HomoZ HomoZygous, *NA* not available, *M/S* moderate/severe, *indep. walk.* independent walking, *DR* drug resistant

confirm that the core phenotype of SCAR23 is characterized by cerebellar ataxia, drug-resistant epilepsy, and moderate/severe intellectual disability. The three elder patients reported completely lost the ability to walk, which in our patient is still possible although severely compromised by ataxia, dizziness, and fatigue. Unfortunately, we are not able to compare the neuroradiological data of our patient with those of the other cases, as a brain MRI is missing for the first three cases and it resulted to be normal in the other one; this latter case is a 6-year-old boy and at that age, our patient also showed a normal brain MRI. Given the progressive worsening of the clinical issues in the cases so far reported, the development of cerebellar atrophy in our patient, and the poor pharmacological control of the epilepsy, we can infer that SCAR23 can be considered a degenerative disorder. This would strengthen the hypothesis of Zagnoli-Vieira and colleagues [2], who suggested that SCAR23 could be considered as a DSB repair defect disease. On the other hand, some of the features of the patients recall mitochondrial diseases and the patient reported by the same group showed, like our patient, minor alterations of muscle biopsy and laboratory tests consistent with mitochondrial dysfunction and also had mild symptoms improvement with the intake of ubiquinol, carnitine, and leucovorin. Further confirmations and case descriptions are needed to better define either the phenotype of these patients and the metabolic pathways implicated in the disorder, as well as to pave the way for a possible treatment.

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Compliance with Ethical Standards

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

Informed Consent An informed consent was obtained from the patient's parents for data and pictures publication.

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