Case report

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Bilateral striatal necrosis caused by *ADAR* mutations in two siblings with dystonia and freckles-like skin changes that should be differentiated from Leigh syndrome

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Abstract

Pathogenic molecular variants in the ADAR gene are a known cause of rare diseases, autosomal recessive Aicardi-Goutières syndrome type 6, severe infantile encephalopathy with intracranial calcifications and dominant dyschromatosis symmetrica hereditaria, demonstrated mainly in Asian adults. Recently, they have been also found in patients with nonsyndromic bilateral striatal necrosis accompanied by skin changes of the freckles-like type.

Here, we present Polish siblings with acute onset and slowly progressive extrapyramidal syndrome with preserved intellectual abilities and basal ganglia changes found in MRI. A Leigh syndrome was considered for a long time as the most frequent cause of such lesions in children. Finally, two molecular variants in non-mitochondria-related ADAR gene c.3202+1G>A (p.?) and c.577C>G (p.Pro193Ala) were revealed by whole exome sequencing.

We suggest that bilateral striatal necrosis should be always differentiated from LS to prevent the diagnosis delay. The striatal involvement accompanied by the presence of freckles-like skin changes should direct differential diagnosis to the ADAR gene mutations screening.

Key words: *bilateral striatal necrosis, ADAR gene, whole exome sequencing, LS differentiation.*

Introduction

Pathogenic molecular variants in the *ADAR* gene [OMIM*146920] are a known cause of an Aicardi-Goutières syndrome type 6 (ASG6) [OMIM#615010], an autosomal recessive severe infantile encephalopathy with intracranial calcifications [10] and a dyschromatosis symmetrica hereditaria (DSH) [OMIM #127400], a rare dominant disease demonstrated mainly in Asian adults [8]. Recently, they have been also found in patients with nonsyndromic bilateral striatal necrosis (BSN) [6,7] that is a frequent but

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nonspecific MRI feature observed in patients with an extrapyramidal syndrome, some of which had DSH [1]. Bilateral striatal necrosis was the most frequently reported in individuals with mitochondrial pathology presenting Leigh syndrome (LS) and *MTATP6* mutation [3], thiamine metabolism dysfunction syndrome related to *SLC25A19* pathogenic variants [11], and glutaric aciduria I with *GCDH* variants [4], but rarely in Wilson's and Huntington diseases and other of inherited etiology as well as of certain acquired causes [1]. The prognosis for BSN is variable, with patients completely recovered and others developing severe dystonia or a more akinetic-rigid phenotype [7]. The *ADAR* gene (1q21.3) codes for specific deaminase which converses adenosine to inosine in double-stranded RNA, influences glutamate receptor transcripts and acts as a suppressor of type I interferon signaling [10]. It is ubiquitously expressed in all tissues, but until today it has not been known why the signs of its dysfunction are limited to the nervous system and skin.

Case study

Here, we present two Polish siblings, the only children of unrelated parents, born after uneventful pregnancy and delivery. They both demonstrated acute onset with an episode of ataxia that occurred after a nonspecific infantile febrile infection followed by slowly progressive extrapyramidal syndrome (Table I). In infancy their development was mildly delayed, mainly in motor skills as they moved on their fours up to 2 and 3 years (Case 1 and 2, respectively). When they started to walk independently, their movements were disturbed by an increased muscle tone with worsening during emotional stress. Tendency to retropulsion of the head, involuntary movements of facial muscles, athetotic movements of digits as well as dysarthric speech, dysphagia and frequent choking during eating were noticed. They both had small mild freckles-like skin changes on their faces and dorsal surfaces of hands. Both children were small for their age (weight and length < 2.5 SD, OCF < 3SD). Magnetic resonance imaging (MRI) examination (Fig. 1A-C) showed bilateral lesions in putamen on T2-weighted and FLAIR sequences that were suggestive for LS. Magnetic resonance spectroscopy (MRS) did not show any abnormalities. Muscle biopsy investigations did not reveal morphological changes and respiratory chain dysfunction.

During the following years, the clinical course of the disease was slowly progressive with the dominance of dystonic disorder, but intellectual ability was relatively preserved. At present (14 and 12 years), the siblings are wheel-chair bound and need full assistance with dressing and feeding.

Molecular screening for *SURF1*, *SCO2, POLG, MTATP6, MTTL1,* and *MTTK* mutations most frequently detected in Polish LS patients [9] was negative. Whole exome sequencing (WES) did not reveal deleterious mutations in genes responsible for known mitochondrial diseases (MD). Finally, two rare molecular variants (Fig. 1D, E) in non-mitochondria related *ADAR* gene (Ref Seq. NM_001111.4; NP_001102.2) included one novel splicing variant c.3202+1G>A (p.?) and a known recurrent substitution c.577C>G (p.Pro193Ala) were identified by thorough filtration of WES data and confirmed by Sanger sequencing in both siblings.

The study was approved by the Bioethical Commission of the CMHI.

Discussion

In the reported family the extended metabolic and mitochondrial investigations have been inconclusive for approximately 14 years. Our patients developed signs of the disease as a sequel of the infection, the finding pointed also by Livingston *et al*. [7]. Freckles-like skin changes on the face and the dorsal surface of hands were noticed in their medical documentation but were neglected in the differential diagnostics. Bilateral putaminal lesions found in MRI were not specific enough to establish a final diagnosis but together with the secondary abnormalities in lactate and alanine concentrations led us to consider for a long time a mitochondrial disease as the most frequent cause of such features in children. Our patients similar to those described in a cohort of children with nonsyndromic BSN [7] did not have any signs of calcification in the striatum or other localizations that were reported by Kumar *et al*. [5] in AGS brains.

It is worth noting that the c.577C>G (p.Pro193Ala) substitution was detected earlier in at least eleven AGS6 families [7,10] and it was identified in the general population. The minor allele frequency (MAF) already recorded in ExAC database of 65000 exomes was 0.002142 (http://exac.broadinstitute.org), in 1000 Genomes was 0.0013 (http://browser.1000genomes.org), and in our in-house-made 400 exomes database it was evaluated as 0.0014. It is located in

Table I. Clinical and biochemical characteristics of the siblings with *ADAR* mutations

Factor	Case 1	Case 2
Gender	Male	Female
Birth data (weight/length/OCF/Apgar points)	3050 g/53 cm/36 cm/9	3400 g/56 cm/33 cm/10
Motility:		
Sitting	6 mo	7 mo
Start to walk	10 mo	14 mo
Stop to walk independently	4 yrs	> 4 yrs
First symptoms	12 mo	8 mo
Extrapyramidal signs	3 yrs: dystonia, elevated tendon reflexes, striatal great toe	4 yrs: axial and limbs hypotonia, dystonic hypertonia, elevated and polyclonal reflexes
Neurologic examination:		
EEG	Normal	Normal
EMG	Normal	Normal
Fundoscopy	Normal	Normal
Nerve conduction	Sensory-motor neuropathy of axonal type	Sensory-motor neuropathy of axonal type
MRI	Symmetrical changes in putamen	Symmetrical changes in putamen
MRS	Normal	Normal
Leiter International Performance Scale*	100	112
CSF examination:		
Pleocytosis	1/ml	
Protein content (ref. 200-450 mg/dl)	239 mg/dl	
Glucose (ref. 45-80 mg/dl)	50 mg/dl	
Lactate (ref. < 2.2 mmol/l)	1.1 mmol/l	1.57
Alanine (ref. 65 µmol/l)	98.8 µmol/l	51.9
Threonine	67.4 µmol/l	
Laboratory tests for IEM:		
Plasma lactate (ref. < 2 mmol/l)	3.08, 2.42	3.01
Plasma alanine (ref. < 450 µmol/l)	706.8 µmol/l	
Threonine	170.9 µmol/l	
Urine biopterin concentration (based on creatinine (C) conc.)	4594 nmol/l (2.7 nmol B/µmol/C)	
Urine neopterin concentration (based on creatinine (C) conc.)	2027 nmol/l (1.2 nmol//µmol/C)	
Muscle biopsy investigations:		NA
Morphology	No changes	
OXPHOS function	Normal	
Amount of E1-alfa subunit of PDHC	79.5% of ref.	
Molecular screening for *SURF1*, *SCO2*, *MTATP6*, *POLG*, *MTTL1*, *MTTK* common mutations**	Negative	NA

*Leiter RG. Instruction Manual for the Leiter International Performance Scale. Stoelting Co., Wood Dale 1979
c.845_846delCT, c.312_321delinsAT (*SURF1***), c.418G>A (***SCO2***), m.8993T>G, m.8993T>C (***MTATP6***); c.1399G>A, c.2243G>C, c.2542G>A (***POLG***); m.3243A>G (***MTTL1***), m.8344A>G (***MTTK***)

mo – months, yrs – years, EEG – electroencephalography, EMG – electromyography, MRI – magnetic resonance imaging, MRS – magnetic resonance spectrometry, IEM – inborn errors of metabolism, OXPHOS – oxidative phosphorylation system, PDHC – pyruvate dehydrogenase complex, NA – not analyzed, ref. – control values

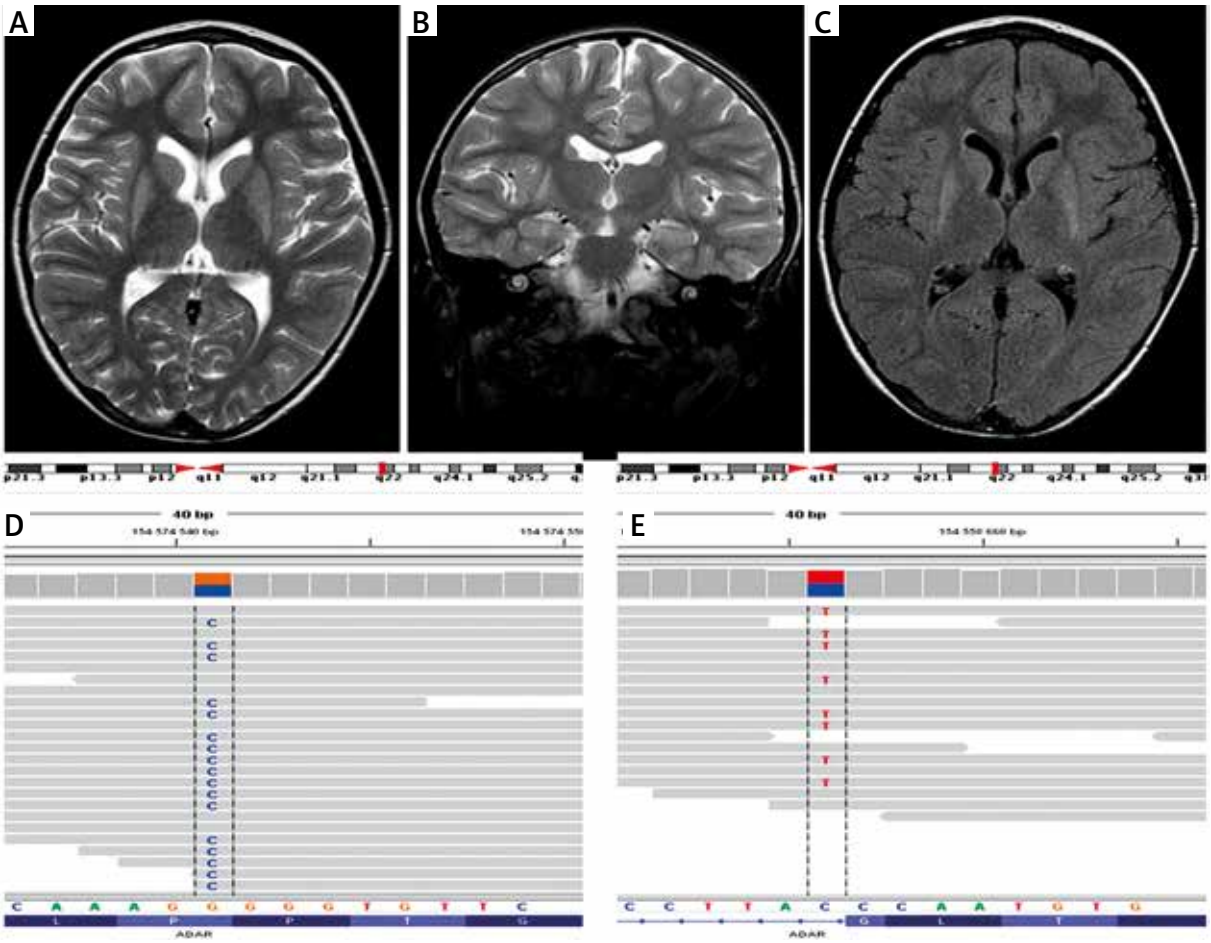

Fig. 1. Magnetic resonance imaging and molecular findings revealed in Case 1. **A-C)** Bilateral involvement of the putamen with hyperintense signal on T2-weighted images: axial plane, coronal plane, and on FLAIR sequence, respectively. **D, E)** Integrative Genomics Viewer picture of identified *ADAR* causative variants c.577C>G and c.3202+1G>A. The depth of coverage across the variants was 8/16 and 18/37, respectively

the highly evolutionary conserved z-alpha adenosine deaminase domain and results in removing important atomic interactions between protein and DNA/RNA [2].

Conclusions

In conclusion, we suggest that the disease should be always differentiated from LS to prevent diagnosis delay. We would like to underline that presence of specific MRI features of bilateral striatal necrosis and freckles-like skin changes should direct differential diagnosis to the *ADAR* mutations screening.

Acknowledgements

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Disclosure

Authors report no conflict of interest.

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