Autosomal recessive spastic ataxia of Charlevoix-Saguenay in a Portuguese child caused by a novel SACS mutation

Joana Pimenta1*, Carmen Costa1, Isabel Alonso2,3, Ana Filipa Brandão2, Jorge Sequeiros2,3, Luis Negrão4 and Isabel Fineza1

1Neuropediatrics - Centro de Desenvolvimento da Criança, Hospital Pediátrico de Coimbra, CHUC, Portugal
2CGPP, IBMC – Instituto de Biologia Molecular e Celular, i3S – Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal
3ICBAS, Universidade do Porto, Portugal
4Unidade de Doenças Neuromusculares - Serviço de Neurologia, CHUC, Portugal

Abstract

Introduction: Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) is a rare neurodegenerative disease characterized by cerebellar ataxia, peripheral neuropathy and pyramidal tract signs. Since its first report from Québec, more than 100 disease-causing variants have been reported in ARSACS, with variable clinical presentation. MRI imaging may help establishing the clinical diagnosis, especially if typical changes are present.

Clinical case: A 7-year-old boy presented an early-onset, progressive ataxia, with sensory-motor neuropathy, nystagmus, feet deformities and cognitive impairment. MRI findings showed cerebellar and cervical spine atrophy and linear areas of hypointensity in the pons. The finding of a novel homozygous mutation – c.3066del(p.Asn1025Metfs*10) - in the SACS gene, resulting in a frameshift and a premature stop codon, allowed the genetic confirmation of the clinical diagnosis.

Keywords: ataxia of Charlevoix-Saguenay, SACS, early-onset ataxia, spastic paraparesis, polyneuropathy

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especially in the upper vermis. T2-weighted and FLAIR axial section images showed linear pontine hypointensities (Figure 1). Optical coherence tomography showed no abnormalities.

The molecular study of the FXN gene GAA expansion and normal vitamin E values excluded Friedreich ataxia and AVED as possible diagnoses. A novel variant was found, in homozygosity, in exon 10 of the SACS gene, c.3066del(p.Asn1025Metfs*10), corresponding to a thymine deletion at position 3066, and leading to a frameshift resulting in a truncated protein (thus proving to be the cause of the disease). The parents, clinically normal, were heterozygous for that mutation.

The disease progressed with severe gait-erected horizontal nystagmus, with poor ocular pursuit, hyporeflexia of brachioradialis and ankle myotatic reflexes, extensor plantar reflexes, reduced pallesthesia and proprioception, and feet deformities (claw fingers and ulcer lesions) (Figure 2a). Treatment with a combination of baclofen (30mg daily) and botulinum toxin was established at age 15 years. In 19 years, he presented with gait with steppage, needing orthotics support, and bladder dysfunction (Figure 2b). Cardiovascular and ophthalmological exam remained normal at that stage.

Discussion

ARSACS is a complex recessive and progressive ataxia. Age of onset and clinical presentation in this case were similar to the initial reports, except for cognitive disability, described only occasionally in reports outside Québec [22,23], IQ score, when normal, tend to be in the lower range. Most affected individuals are able to manage daily tasks [5].

Retinal changes were absent in this case. Recent descriptions of ARSACS outside Québec also reported normal retinal fibres [7,10]. Neuropathy usually presents after the 2nd decade of life and progresses to spastic paraparesis; [9] in that case, the authors highlight the early onset of neuropathy, with rapidly progressive distal weakness, resulting in loss autonomous gait.

Typical MRI changes helped establishing the diagnosis in this case [15,24]. Electrophysiological findings, such as the demyelinating component of the sensorimotor peripheral neuropathy, may help distinguishing ARSACS from common recessive ataxias like Friedreich ataxia.

Predicting the clinical implications of novel variants can be challenging and variants of uncertain clinical significance (VUS) are frequent in SACS [10]. This c.3066del(p.Asn1025Metfs*10) genetic variant is not present in population databases and is predicted to produce a truncated protein; it is, thus, most probably disease-causing and likely to be associated with this more aggressive early-onset phenotype, with loss of autonomous gait by the 2nd decade. Follow-up of this patient will contribute to elucidate this.

ARSACS should be evoked in the differential diagnosis of children presenting with early onset ataxia and spastic paraparesis. Supportive treatment is available for ARSACS patients. Genetic counselling and carrier testing must be proposed to adult relatives of these patients.

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