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Review

Autosomal recessive spastic ataxia of Charlevoix–Saguenay: An overview

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ABSTRACT

Autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) is a distinct form of hereditary early-onset spastic ataxia related to progressive degeneration of the cerebellum and spinal cord. Following the description of the first patients in 1978, the gene responsible has been mapped and identified. It was also shown that the disease occurred worldwide with more than 70 mutations and diverse phenotypes. Because of the random partition of these mutations in the SACS gene particularly on the largest exon nine, and due to the significant clinical variability between patients described in different countries, it has been difficult to establish a genotype–phenotype correlation for the disease.

This paper reviews the broad clinical features and the various molecular aspects of ARSACS, reported over the last 30 years highlighting the difficulty of finding correlations.

Contents

1. Introduction

Autosomal recessive cerebellar ataxias (ARCA) are a complex group of disorders with more than twenty reported genetic forms. Clinical phenotypes vary from predominantly cerebellar syndromes to sensorimotor neuropathy, ophthalmological disturbances, involuntary movements, seizures, cognitive dysfunction, skeletal anomalies, and cutaneous disorders. The most common form is Friedreich's ataxia with a prevalence ranging from 1 in 30,000 to 1 in 50,000 in most populations and a carrier frequency of approximately 1 in 85 in Caucasians [1]. Ataxia Telangiectasia also occurs worldwide with a variable prevalence, but it seems to affect 1 in 40,000 in the USA [1]. A less frequent ataxia with oculomotor apraxia with two forms AOA1 and AOA2 was first described in Japan, Portugal and Pakistan, and then identified in other parts of the world.

Since it was first described in the 1970s among inhabitants of the Charlevoix–Saguenay region of northeastern Quebec in Canada the autosomal recessive spastic ataxia of Charlevoix–Saguenay (ARSACS) with a carrier prevalence estimated to 1/22 in this small region has been shown to occur elsewhere in the world [2,3]. The disease was initially described as homogeneous syndrome including spasticity, dysarthria, distal muscle wasting, foot deformities, truncal ataxia, absence of sensory evoked potentials in the lower limbs, retinal striation reminiscent of early Leber's atrophy and the frequent presence of mitral valve prolapse. Biochemically, many cases showed impaired pyruvate oxidation, others had hyperbilirubinaemia and some had low serum beta-lipoproteins and HDL lipoproteins [2,4].

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The ARSACS gene is located on chromosome 13q12.12 [5,6] and encodes the large protein sacsin [7]. Initially two founder effect mutations were identified in the Quebec population [7]. Several studies reported that the *SACS* protein product, sacsin, has regions of sequence similarity to several proteins. The strongest similarity identified was between a region near the C-terminus of sacsin and the DnaJ domain of Hsp40 proteins suggesting a chaperone activity involvement for this protein [7–9]. A recent study demonstrated that sacsin may interact with the Hsp70 chaperone machinery, which is an important component of the cellular response towards aggregation prone mutant proteins that are associated with neurodegenerative diseases [9].

Since the identification of several other mutations in many populations, it is now recognized that ARSACS is not only limited to this region but occurs worldwide [7,10–30]. Furthermore, Clinical variations such as mental retardation, later onset, ophthalmoplegia, hyperlipidemia and absence of spasticity and retinal hypermyelination, have been widely reported in non-Quebec patients [7,10–30]. We report here an overview of the clinical and molecular features of ARSACS patients through the world.

2. Clinical manifestations

In common with most ARCA patients, those with ARSACS exhibit early-onset signs of spasticity in the lower limbs. These signs become apparent between the ages of 12 and 24 months when the patients begin to walk and they are specific to only a few forms of ARCA such as Ataxia Telangiectasia and Infantile-onset spinocerebellar ataxia [4,11,12,16,19,20,23,31]. The spasticity observed when the patients are infants is still specific to ARSACS [1]. Although some patients develop these signs later they rarely appear after age twelve. For these patients, progression is slightly slower; they become wheelchair bound later at about age 41 and the mean age of death is 51 [4,6,16,18,24,31]. Dysarthria is reported in all ARSACS patients regardless of origin. Speech is generally slurred in childhood and becomes explosive in adulthood.

Most patients show early and non-progressive signs including: bilateral abnormal plantar responses, saccadic alteration of smooth ocular pursuit and prominent myelinated fibers radiating from the optic disc and embedding the retinal vessels as demonstrated by funduscopy, which indicate an early and abnormal myelination process. Indeed, prominent retinal myelinated fibers were always known as one of the main clinical manifestations of ARSACS; but this was seldom reported in non-Quebec patients [10–12,16,18–20,23]; however, nystagmus was a consistent finding.

The disease progression is more obvious in the teens and twenties with a progressive increase in muscle tone and in deep tendon reflexes. Discrete to marked distal amyotrophy is usually seen later. Tendon reflexes disappear around age 25 after being brisk before in the majority of cases. This seems to be the result of the progressive distal neuropathy; however, ankle reflexes remain present to brisk in other patients [10,16,18,23]. This pattern is considered distinctive for ARSACS, since nearly all the other ARCAs are characterized by reduced or absent tendon reflexes [1]. Babinski sign was positive in nearly all ARSACS patients, revealing pyramidal tract involvement. Some patients present with skeletal deformities such as pes cavus and hammer toes [2,4,5,10,13,21].

Although spasticity is considered a core clinical feature of ARSACS, some patients without leg spasticity have been reported [14,17].

Electromyography generally shows signs of severe denervation in the distal muscles by the time the patients are in their late twenties, which indicates with the other progressive signs, an axonal degeneration in the peripheral nervous systems. It may also show signs of chronic neurogenic atrophy in some patients [21].

Nerve conduction studies in patients with ARSACS demonstrate signs of severe to moderate axonal neuropathy associated with some demyelinating features generally confirmed by nerve biopsy [10,13,16,32]. Motor nerve conduction velocities are usually moderately reduced which indicate the association of axonal involvement and primary peripheral myelinopathy. Sensory action potentials are absent in all four limbs in the Quebec patients, while they are reduced to normal in other patients [10]. Sensory evoked potentials are frequently and markedly altered revealing severe involvement of the lemniscal pathway [10]. This pattern is different from other ARCA forms such as Friedreich's ataxia and Ataxia with vitamin E deficiency that are usually characterized by a severe to moderate axonal sensory neuropathy [1,33], but it remains similar to Ataxia telangiectasia and Ataxia with Oculomotor apraxia [1].

Sural nerve biopsy reveals severe axonal degeneration with loss of large myelinated fibers, associated with regenerating axonal clusters and rare demyelinating aspects. This pattern is consistent

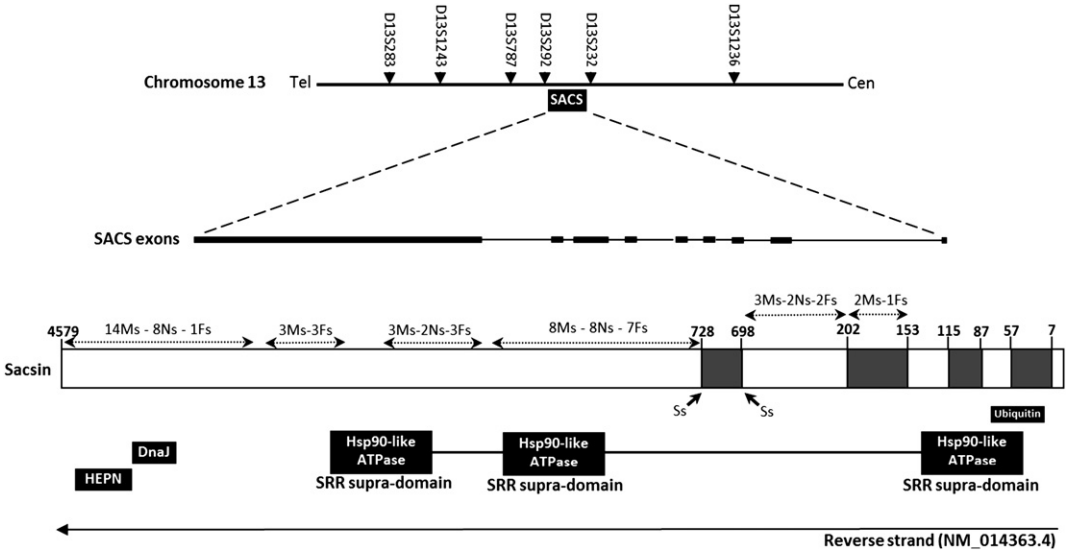

Fig. 1. Overview of the SACS gene, the Sacsin protein with the predicted domains and an approximate location of most the reported mutations. Numbers from 7 to 4579 represent the number of residues. Ms: Missense mutation, Ns: Nonsense mutation, Fs: Frameshift mutation, Ss: Splice Site mutation.