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Case study

Infantile-onset ascending hereditary spastic paralysis: A case report and brief literature review

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ABSTRACT

Background: Infantile-onset ascending hereditary spastic paralysis (IAHSP) is a rare, early-onset autosomal recessive motor neuron disease associated with mutations in *ALS2*.
Aim: We studied a 17-year-old boy who had features of IAHSP. We also reviewed the current literature on *ALS2*-related syndromes.
Methods: Clinical and neuroimaging studies were performed. Blood DNA analyses were combined with mRNA studies in cultured skin fibroblasts.
Results: Like previously described cases, the patient presented with severe spastic paraparesis and showed rapid progression of paresis to the upper limbs. He also developed bulbar involvement and severe scoliosis during childhood. In blood DNA we identified a novel splice-site homozygous mutation in *ALS2* (c.3836+1G > T), producing exon skipping in fibroblast mRNA and predicting premature protein truncation.
Conclusions: This case adds to the allelic heterogeneity of IAHSP. Review of the pertinent literature indicates a fairly homogeneous clinical picture in IAHSP that should facilitate molecular confirmation and prevention of long-term complications.

1. Introduction

The hereditary spastic paraplegias (HSPs) are a group of clinically and genetically heterogeneous neurodegenerative disorders of the motor system characterized by insidiously progressive weakness and spasticity in the lower limbs (pure forms), which may be combined with additional neurological or non-neurological manifestations (complicated phenotypes). The HSPs are associated with a plethora of loci (about 60) and related genes (more than 30)[1,2] and it is therefore hardly surprising that genotype–phenotype correlations are weak.

Mutations in *ALS2*, located on chromosome 2q33 and encoding alsin, are responsible for a spectrum of rare autosomal recessive disorders ranging from infantile ascending hereditary spastic paralysis (IAHSP, MIM 607225) to juvenile primary lateral sclerosis (JPLS, MIM 606353) with retrograde degeneration of the upper motor neurons, and juvenile amyotrophic lateral sclerosis (MIM 205100), in which there is both upper and lower motor neuron involvement.[3–5]

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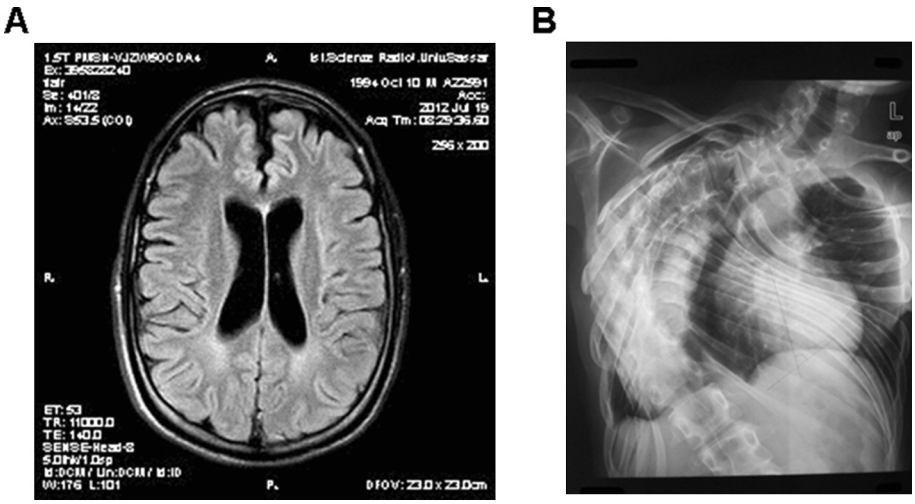

Fig. 1 – Imaging studies in a patient harboring a novel mutation in *ALS2*. A Brain MRI at age 17 years, FLAIR image: hyperintensities in posterior periventricular areas. B Spine X-ray of the dorsal tract: severe deformity due to right convex rotoscoliosis.

Although these syndromes were initially confined to few kindred in the Mediterranean area, 14 *ALS2* families have now been identified worldwide.

We here present clinical and molecular findings in an additional patient from Sardinia, Italy, and review the literature dealing with alsin phenotypes.

2. Case study

This 17-year-old boy was born after an uneventful pregnancy to healthy, apparently unrelated parents. His six-year-old sister is healthy. The patient sat up unsupported at the age of six months, and uttered his first words at the age of nine months. At 12 months, he manifested leg stiffness and bilateral clubfoot. At the age of two years he needed bilateral assistance while walking on tiptoes, and he has never been able to walk independently. At two years, neurological examination revealed lower extremity spastic hypertonia with enhanced deep tendon reflexes, bilateral ankle clonus, and Babinski sign. He could control his head and maintain the sitting position and he also showed good coordination and hand manipulation. His language skills were adequate and he interacted well both with people and with the environment. The disease progressed and, at the age of eight years, the patient showed weakness and spasticity in the upper limbs, mild dysphagia and dysarthria, and was wheelchair-bound. Within the following year he lost the ability to sit unsupported. He also began to develop scoliosis. Towards the age of 11 years the patient showed anarthria and difficulty chewing. By this time, handwriting was impossible. However, he continued to be mentally unimpaired and was able to attend both primary and secondary school profitably using special aids for communication.

We first saw him at the age of 17 years when, on neurological examination, he was found to be collaborative and responsive to stimuli. He was able to achieve a full range of eye movements with no nystagmus, while the reduced mobility of his facial muscles resulted in a "forced smile".[8] He had decreased tongue mobility in all directions, but no fasciculations or amyotrophy. A videofluoroscopy confirmed inhalation of liquids. His upper limbs showed hypertonia with residual gross and fine motor functions, whereas his lower limbs were plegic. We did not observe lower limb fasciculations, muscle atrophy, or gross sensory deficits, and did not record sphincter dysfunction. The patient displayed retractions at the knee and ankle joints. EMG showed a marked reduction of voluntary recruitment, in particular in the lower limbs, without signs of denervation. Motor and sensory nerve conduction velocity studies were normal. Somatosensory evoked potentials (SEPs) showed, only in the legs, increased latency of a cortical component (P37) bilaterally. Brain MRI showed hyperintensities in posterior periventricular areas (T_2-weighted images and FLAIR) (Fig. 1A). These abnormalities had been reported since the patient was aged 10 years, but we did not have access to earlier scans and were therefore unable to assess any progression. The patient also presented severe scoliosis. His spine X-ray and MRI images showed severe dorsal and lumbar rotoscoliosis, right convex in the dorsal tract (Fig. 1B), but without spinal cord thinning or compression.

Direct sequencing of the coding exons of *ALS2* (NM_020919.3) in blood DNA revealed a homozygous c.3836+1G > T mutation at the consensus splice-donor site of intron 24 (Supplementary Fig. 1). The mutation was novel, found to be heterozygous in the healthy parents, and not detected in 500 healthy, ethnically-matched control chromosomes. The new c.3836+1G > T predicts *in silico* exon skipping (www.fruitfly.org/seq_tools/splice.html). To test this, we purified and reversely transcribed polyA + RNA from cultured skin fibroblasts, amplified alsin cDNA with primers located in exons 20 and 27, and directly sequenced PCR-amplified fragments with the corresponding primers. In cultured cells, we detected two equally abundant *ALS2* transcripts, one missing