Case Report

Alsin Related Disorders: Literature Review and Case Study with Novel Mutations

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Mutations in the ALS2 gene cause three distinct disorders: infantile ascending hereditary spastic paraplegia, juvenile primary lateral sclerosis, and autosomal recessive juvenile amyotrophic lateral sclerosis. We present a review of the literature and the case of a 16-year-old boy who is, to the best of our knowledge, the first Portuguese case with infantile ascending hereditary spastic paraplegia. Clinical investigations included sequencing analysis of the ALS2 gene, which revealed a heterozygous mutation in exon 5 (c.1425_1428del p.G477Afs*19) and a heterozygous and previously unreported variant in exon 3 (c.145G>A p.G49R). We also examined 42 reported cases on the clinical characteristics and neurophysiological and imaging studies of patients with known ALS2 gene mutations sourced from PubMed. This showed that an overlap of phenotypic manifestations can exist in patients with infantile ascending hereditary spastic paraplegia, juvenile primary lateral sclerosis, and juvenile amyotrophic lateral sclerosis.

1. Introduction

Three apparently distinct disorders involving retrograde degeneration of the upper motor neurons of the pyramidal tracts seem to be caused by mutations in the ALS2 gene, which provides instructions for making a protein called Alsin. They comprise a clinical continuum from infantile ascending hereditary spastic paraplegia (IAHSP) (OMIM number 607225), to juvenile forms without lower motor neuron involvement, namely, juvenile primary lateral sclerosis (JPLS) (OMIM number 606353), and to forms with lower motor neuron involvement, namely, autosomal recessive juvenile amyotrophic lateral sclerosis (JALS) (OMIM number 205100) [1, 2]. There is no available data on the prevalence of ALS2 related disorders. However, they are probably currently underdiagnosed, even if they have been described in individuals from a variety of ethnic backgrounds, mainly from the Mediterranean [1].

All the patients are homozygous or heterozygous compounds for ALS2 mutations [1]. To date, a total of 45 patients with known mutations in the ALS2 gene have been described, but the phenotype-genotype correlation remains unclear [2]. In the present study, we describe the clinical and genetic features of a 16-year-old boy with IAHSP from Northern Portugal (Table 1).

2. Case Report

The patient was born after a twin pregnancy from nonconsanguineous parents and the pregnancy included maternal hemorrhage in the second trimester. Delivery was at the
Table 1: Mutations in ALS2 related disorders.

| Patient | Exon/intron | Mutation | Predicted protein | Phenotypic classification | References |
|---------|-------------|----------|-------------------|---------------------------|------------|
| 1       | Intron 24   | c.3836+1G>T | p.k1234fs*3       | IAHSP                     | Racis et al., 2014 [5] |
| 2       | Intron 9    | c.2000-2A>T | p.E724fs*3        | IAHSP                     | Herzfeld et al., 2009 [6] |
| 3       | Exon 9      | c.1825_1826ins5 | p.E609fs*9    | IAHSP                     | Sztiriha et al., 2008 [7] |
| 4       | Exon 13     | c.2529G>T | p.G1777*          | IAHSP                     | IAHSP      |
| 5, 6    | Exon 10     | c.2134C>T  | p.Q715*           | IAHSP                     | Verschuuren-Bemelmans et al., 2008 [8] |
| 7, 8    | Exon 4      | c.467G>A   | p.C156Y           | IAHSP                     | Eymard-Pierre et al., 2006 [9] |
| 9, 10   | Exon 18     | c.2992C>T  | p.R998*           | IAHSP                     | Devon et al., 2003 [10] |
| 11      | Exon 32     | c.4844delT | p.I331fs335       | IAHSP                     | Gros-Louis et al., 2003 [11] |
| 12–17   | Exon 4      | c.1130delAT | p.I331fs335       | IAHSP                     | IAHSP      |
|         | Exon 13     | c.2660delAT | p.N845fs858       | IAHSP                     | IAHSP      |
|         | Exon 6      | c.1471_1480del10 | p.V491Gfs*3 | IAHSP                     | IAHSP      |
|         | Exon 22     | c.3742delA | p.M1206*          | IAHSP                     | IAHSP      |
| 18–20   | Exon 5      | c.1548delAG | p.T475fs*70       | IAHSP                     | Hadano et al., 2001 [4] |
| 21      | Exon 5      | c.1427_1428del | p.G477fs*19 | IAHSP                     | Our study  |
|         | Exon 3      | c.145G>A   | p.G49R           | IAHSP                     | IAHSP      |
| 22–23   | Exon 4      | c.299G>T   | p.S100I          | JALS                      | Luigetti et al., 2013 [13] |
|         | Exon 14     | c.2580-2A>G | p.V1189WfsX19   | JALS                      | Shirakawa et al., 2009 [2] |
| 24–25   | Exon 22     | c.3565delG | p.T185fsX5       | JALS                      | Kress et al., 2005 [14] |
| 26      | Exon 4      | c.553delA  | p.A46AfsX5       | JALS                      | Kress et al., 2005 [14] |
| 27–38   | Exon 3      | c.138delA  | p.A46AfsX5       | JALS                      | Hadano et al., 2001 [4] |
| 39–41   | Intron 17   | c.2980-A>G | p.T999fs*7       | JPLS                      | Mintchev et al., 2009 [15] |
| 42      | Exon 6      | c.1619G   | p.G540E          | JPLS                      | Panzeri et al., 2006 [16] |

36th week of gestation by Cesarean section. The twins were dizygotic twins and the patient’s twin sibling is healthy. His 42-year-old mother is healthy and his father died at the age of 35 after a car accident, without any signs of a neurological disorder. The boy acquired cephalic control at three months and started to sit unaided at six months, crawl at nine months, and walk with support at 10 to 11 months. Stiffness of the lower limbs and tiptoeing with hyperactive deep tendon reflexes were noticed at the age of three and scissoring gait started during his fourth year. He was never able to walk without support and underwent Achilles tenotomy at the age of seven and he was wheelchair bound at the age of eight. An ascending progression of motor difficulties was observed, with spasticity becoming evident in the upper extremities after the age of six. Muscle atrophy in the lower limbs was evident after the age of seven and he was anarthric at the age of 13. At the age of 14, there was clinical worsening and since then he has had bilateral limitation of horizontal eye movements, dysphagia when drinking liquids, chewing difficulties, severe drooling, and paroxysms of laughter. Cognitive function is still normal at the age of 16.

3. Material and Methods

DNA was extracted from a peripheral blood sample from the patient, his mother, and twin brother. All 34 exons of the ALS2 gene were analysed by PCR and sequencing of both DNA strands of the entire coding region was carried out, including the highly conserved exon-intron splice junctions.

We also reviewed all cases of ALS2 related disorders with known ALS2 gene mutations and detailed clinical, neurophysiological, and imaging data that have so far been reported in PubMed. Continuous variables with asymmetric distribution are described by medians (minimum to maximum) and categorical variables are described by absolute and relative frequencies. To compare the three phenotypes (IAHSP, JALS, and JPLS) we used the Kruskal-Wallis test if the variables were continuous and the Monte Carlo test if they were categorical. The statistical analysis was performed using SPSS v.20 (IBM, USA) and P values of less than 0.05 were considered significantly different.

4. Results and Discussion

Our patient displays a clinical picture that is highly suggestive of ALS2 related disorder. This case study presents evidence of previously unreported heterozygous variants in
Table 2: Summary of the characteristics of 42 patients with known ALS2 gene mutations.

| Patient | Age | Origin | Motor onset | Walking onset | Upper limb involvement | Bulbar involvement | Wheelchair bound | Speech impairment | Ocular movements | EMG Evoked potentials | Brain imaging | Phenotypic classification | References |
|---------|-----|--------|-------------|--------------|------------------------|--------------------|------------------|------------------|-----------------|------------------------|--------------|-------------------------|------------|
| 1       | 7 y | Italy  | Ab          | 12 mo        | NA                     | 8 y                | 8 y              | Daystheria at 6 y | NE              | Ab                      | SSPE-Ab      | Ab                      | IAHSP       |
| 2       | 7 y | Germany| Ab          | 8 mo         | NA                     | <2 y               | 2 y              | Anarthria at 1 y | No              | Ab                      | IAHSP        | Ab                      | IAHSP       |
| 3       | 11 y| Hungary| Ab          | 12 mo        | NA                     | 2 y                | 5 y              | No               | No              | Motor ab                | IAHSP        | Ab                      | IAHSP       |
| 4       | 6 y | Hungary| Ab          | <1 y         | NA                     | 3 y                | 5 y              | No               | No              | Unobtainable           | IAHSP        | Ab                      | IAHSP       |
| 5       | 13 y| Hungary| Ab          | 8 mo         | NA                     | Yes                | 13 y             | N                | N               | Unobtainable           | IAHSP        | N                       | IAHSP       |
| 6       | 12 y| Turkey | Ab          | 1 y          | 12 y                   | 12 y               | 12 y             | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 7       | 12 y| Turkey | Ab          | 1 y          | 10 y                   | 13 y               | 13 y             | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 8       | 12 y| Turkey | Ab          | 1 y          | 11 y                   | 13 y               | 13 y             | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 9       | 14 y| Turkey | Ab          | 18 mo        | 12 y                   | Dysarthria at 1 y  | N                | N               | N               | Ab                      | IAHSP        | Ab                      | IAHSP       |
| 10      | 14 y| Turkey | Ab          | 1 y          | 4 y                    | 6 y                | Dysarthria at 6 y | N                | No              | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 11      | 14 y| Turkey | Ab          | 1 y          | 6 y                    | 6 y                | Dysarthria at 6 y | N                | No              | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 12      | 30 y| Algeria| Ab          | 1 y          | NA                     | <7 y               | Dysarthria at 1 y | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 13      | 31 y| Algeria| Ab          | 1 y          | NA                     | <7 y               | Dysarthria at 1 y | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 14      | 24 y| Algeria| Ab          | 1 y          | NA                     | <7 y               | Dysarthria at 1 y | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 15      | 18 y| France | Ab          | 15 y         | 4 y                    | 6 y                | Dysarthria at 6 y | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 16      | 23 y| Italy  | Ab          | 14 y         | 5 y                    | 10 y               | Dysarthria at 6 y | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 17      | 20 y| Italy  | Ab          | 15 y         | 4 y                    | 9 y                | Dysarthria at 6 y | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 18      | 14 y| Kuwait | Ab          | 14 mo        | 2 y                    | 9 y                | Dysarthria at 6 y | N                | N               | MEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 19      | 6 y | Kuwait | Ab          | 6 mo         | NA                     | 5 y                | Dysarthria at 6 y | N                | No              | MSEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 20      | 21 y| Kuwait | Ab          | 9 mo         | NA                     | 5 y                | Dysarthria at 6 y | N                | No              | MSEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
| 21      | 16 y| Portugal| Ab          | 3 y          | NA                     | 6 y                | Dysarthria at 6 y | N                | No              | MSEP and SSEP abnormal   | Ab           | Ab                      | IAHSP       |
Table 2: Continued.

| Patient | Age | Origin | Motor development by 1 year | Age at onset | Loss of walking | Upper limb involvement | Bulbar involvement | Speech impairment | Ocular movements | Wheelchair bound | EMG | Evoked potentials | Brain imaging | Phenotypic classification | References |
|---------|-----|--------|----------------------------|--------------|-----------------|------------------------|-------------------|------------------|-----------------|-----------------|-----|-----------------|-------------|--------------------------|------------|
| 22      | 27y | Italy  | N                          | 3y           | 1y              | Dysarthria at 7 y; anarthria at 14 y | Ab                | SSEP N           | N               | JALS            |     |                 |             |                          | [13]       |
| 23      | 21y | Italy  | N                          | 6y           |                 | Ab                      | Ab                | SSEP N           | N               | JALS            |     |                 |             |                          | [13]       |
| 24      | 32y | Japan  | N                          | 13 mo        | No              | Dysarthria at 11 y; anarthria at 14 y | No                | Ab               | N               | JALS            |     |                 |             |                          | [2]        |
| 25      | 23y | Japan  | N                          | 3y           | No              | Dysarthria              | No                | Ab               | N               | JALS            |     |                 |             |                          | [2]        |
| 26      | 32y | Turkey | Ab                         | 22 mo        | 16 y            | 12 y                    | 15 y              | 18 y             | 16 y            | Ab             | Motor ab, SSEP N | N           | JALS                    | Kress et al., 2005 [14] |
| 27      | 60y | Tunisia| N                          | 10 y         | 10 y            | Ab                      | N                 | Motor N          | JALS            |                 |     |                 |             |                          |            |
| 28      | 36y | Tunisia| N                          | 6.5 y        | 6.5 y           | N                       | Motor N, SSEP ab   | SSEP ab          | JALS            |                 |     |                 |             |                          |            |
| 29      | 27y | Tunisia| N                          | 3.5 y        | Yes             | N                       | Motor N           | JALS            |                 |                 |     |                 |             |                          |            |
| 30      | 22y | Tunisia| N                          | 6.5 y        | 6.5 y           | Motor N                 | JALS             |                 |                 |                 |     |                 |             |                          |            |
| 31      | 14y | Tunisia| N                          | 9 y          | 9 y             | Motor N                 | JALS             |                 |                 |                 |     |                 |             |                          |            |
| 32      | 41y | Tunisia| N                          | 10 y         | 3.5 y           | Yes                     | N                 | Motor N          | JALS            |                 |     |                 |             |                          |            |
| 33      | 23y | Tunisia| N                          | 6.5 y        | 6.5 y           | Motor N                 | JALS             |                 |                 |                 |     |                 |             |                          |            |
| 34      | 28y | Tunisia| N                          | 6.5 y        | 6.5 y           | N                       | Motor N           | JALS            |                 |                 |     |                 |             |                          |            |
| 35      | 32y | Tunisia| N                          | 7.5 y        | 7.5 y           | Motor N                 | JALS             |                 |                 |                 |     |                 |             |                          |            |
| 36      | 22y | Tunisia| N                          | 6.5 y        | 6.5 y           | Motor N                 | JALS             |                 |                 |                 |     |                 |             |                          |            |
| 37      | 21y | Tunisia| N                          | 10 y         | Yes             | Motor N, SSEP ab         | SSEP ab           |                 |                 |                 |     |                 |             |                          |            |
| 38      | 7y  | Tunisia| N                          | 6 y          | Yes             | Motor N                 | JALS             |                 |                 |                 |     |                 |             |                          |            |
| 39      | 55y | Cyprus | N                          | 2y           | 50 y            | Yes                     | Ab                | 50 y            | SSEP N          | JPLS           |     |                 |             |                          |            |
| 40      | 42y | Cyprus | N                          | 2y           | 2y              | Yes                     | Ab                | 2y              | SSEP N          | JPLS           |     |                 |             |                          |            |
| 41      | 20y | Cyprus | N                          | 2y           | Yes             | Ab                      | Ab                | No              | N               | JPLS           |     |                 |             |                          |            |
| 42      | 34y | Italy  | N                          | 2y           | 19 y            | 2 y                     | 6y                | Dysarthria at 6 y; anarthria at 20 y | Ab              | 34 y           | Ab             | Motor ab       | N           | JPLS                    | Panzeri et al., 2006 [16] |

EMG: electromyography; N: normal; Ab: abnormal; NA: not achieved; y: years; mo: months; MEP: motor evoked potentials; SSEP: somatosensory evoked potentials.
exon 5 (c.1425_1428del p.G477Afs*19) and exon 3 (c.145G>A p.G49R).

To date, case studies of 45 patients with ALS mutations have been reported. Four patients with JALS were excluded because a detailed clinical description was not available [3]. The clinical characteristics and neuropathological and imaging studies of the remaining 41 cases, plus our case study, are summarized in Table 2. Of these, 21 (50%) of the patients were classified as having an IAHSP phenotype, 17 (40.5%) had a JALS phenotype, and four (9.5%) had a JPLS phenotype. Median age at onset of walking loss, upper limb involvement, speech impairment, and becoming wheelchair bound was similar between the three groups.

The heterozygous variant in exon 5 (c.1425_1428del p.G477Afs*19) creates a shift in the reading frame, starting at codon 477. The new reading frame ends in a stop codon in this region (c.1427_1428delAG), which also causes a frameshift, has previously been described as disease causing for ALS2 [4]. The other unreported heterozygous variant was found in exon 3 (c.145G>A p.G49R), which is located in a moderately conserved amino acid, with moderate physicochemical differences between the amino acids glycine and arginine. Polyphen-2, SIFT, and MutationTaster predict that this variant is probably damaging. This variant in exon 3 was also found in our patient’s twin brother and their mother, who were both healthy. It was impossible to test his father because he was dead.

Despite the limited number of patients reported in the literature with known ALS2 mutations and considering the bias related to the age, the majority of clinical characteristics were similar between both groups. Because all the families reported to date have had different ALS2 mutations, it is impossible to draw any genotype-phenotype correlation.

5. Conclusions

Despite the limited information about clinical characteristics, patients with IAHSP, JALS, and JPLS may present with different phenotypes that overlap.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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