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Juvenile Amyotrophic Lateral Sclerosis: a mini review of literature

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ABSTRACT

Juvenile Amyotrophic Lateral Sclerosis (JALS) is a rare type of motor neuron disease that typically manifests before the age of 25. Research findings indicate that the most prevalent gene mutations linked to JALS are *FUS*, *SETX*, *SIGMAR1*, *SPG11* and *ALS2*. In instances of familial occurrence, the gene mutations are predominantly inherited in an autosomal recessive manner, whereas mutations in SETX follow an autosomal dominant inheritance pattern. The clinical manifestations of JALS encompass a combination of upper and lower motor neuron degeneration, and the disease's prognosis can range from rapidly progressive to a more gradual course. Specific gene mutations may give rise to distinct clinical features in addition to the fundamental motor neuron symptoms. Accurate diagnosis of JALS necessitates thorough clinical evaluation and genetic testing, as understanding the hereditary patterns and accompanying characteristics can offer valuable prognostic insights. Timely identification and proper management of JALS are imperative due to its rarity and significant impact on affected individuals.

Introduction

Juvenile Amyotrophic Lateral Sclerosis (JALS) is a term used to describe patients who develop the disease before the age of 25, with symptoms typically appearing in early childhood [1]. This condition shares common characteristics with the adult form, as it involves progressive degeneration of both upper and lower motor neurons. Patients may exhibit a combination of both UMN and LMN signs, reflecting the dual nature of the disease. The presence of both types of dysfunction can complicate the clinical picture but is essential for understanding the progression and impact of the disease on motor function [2,3].

There are several distinctions between JALS and adult ALS. Firstly, 40% of cases of JALS exhibit a discernible genetic origin, in contrast to merely 10% of cases of Adult-Onset Amyotrophic Lateral Sclerosis (AO-ALS) that are attributed to genetic factors [2,4-8]. Secondly, the prognosis and disease progression in JALS vary depending on the gene mutation, ranging from very aggressive to milder, while adult ALS typically follows a uniformly aggressive course, leading to death within 2-3 years. Thirdly, individuals with JALS may present with a syndromic manifestation, affecting other areas of the central or peripheral nervous system in addition to motor neuron degeneration.

The diagnosis of JALS is significantly dependent on genetic analysis and the development of various methods for discovering genetic mutations. JALS is characterized by multiple genetic subtypes, with the most prevalent mutations occurring in the *FUS, SIGMAR1, SPG11, SETX*, and *ALS2* genes [2,9]. The following are descriptions of the JALS fine main subtypes, as also depicted in the table (Table 1) below.

ALS subtype 2

Genetic Details

The *ALS2* gene encodes the protein alsin and is located on chromosome 2q33 [10]. Mutations in *ALS2* gene are linked to an autosomal recessive form of JALS, initially identified in North African populations [11,12] and Middle Eastern populations [13,14].

Clinical Features

In ALS2-JALS, the degeneration of motor neurons begins early and typically advances slowly [15]. An analysis of 21 cases from various sources revealed an average onset age of 4.9 years, ranging from 1 to 20 years [16]. Clinical manifestations which indicate the degeneration of both upper and lower motor neurons, include early emergence of pathological symptoms like spasticity, dysarthria, dysphagia, bladder dysfunction, and sensory abnormalities [17]. Dysarthria may progress to anarthria within the first ten years of life. Some patients with *ALS2* mutations may present with ataxia and dystonia [18]. While cognitive impairment is not a prominent feature, pseudobulbar affect has been noted in several large familial groups [11,16]. Patients with ALS2-JALS may also develop scoliosis during their second decade of life [19]. Apart from JALS, *ALS2* is linked to a range of conditions such as juvenile primary lateral sclerosis [20], childhood-onset hereditary spastic paraplegia [11], and dystonia [21].

ALS subtype 4

Genetic Details

ALS subtype 4 is linked to a mutation in the *SETX* gene. The *SETX* gene, located at genetic position 9q43, encodes senataxin, a DNA/RNA helicase that plays a crucial role in various cellular processes such as DNA repair, replication, recombination, transcription, RNA processing, transcript stability, and translation initiation [22]

Clinical Features

The mutations in the senataxin gene are specifically associated with the autosomal dominant form in JALS and are referred to as ALS4 [23-25]. A study involving 31 patients revealed a gradual progression of the disease, typically starting at the age of 16 [23]. Pathogenic mutations in this gene have also been identified as the cause of Ataxia with Oculomotor Apraxia type 2 (AOA2), a condition characterized by cerebellar ataxia, oculomotor apraxia, neuro-axonal sensorimotor neuropathy, and elevated serum alpha fetal protein levels [26]. The mutations associated with the autosomal dominant form of JALS are typically found within the first 400 amino acids of senataxin, although mutations have been observed throughout the gene, including the helicase domain [27-29].

ALS subtype 5

Genetic Details

ALS subtype 5 is linked to mutations in the *SPG11* gene. This gene encodes the spatacsin protein and is situated in the chromosomal region 15q15-21. Research indicates that both mixed heterozygous and homozygous mutations in the *SPG11* gene are linked not only to the onset of JALS but also to hereditary spastic paraplegia [30,31]. The spatacsin protein is predominantly expressed in neurons of the cerebellar and cerebral cortex. Over 100 pathogenic mutations have been identified, which can result in the absence or dysfunction of the spatacsin protein [32]. Spatacsin plays a role in maintaining cytoskeletal stability and regulating synaptic vesicle transport.

Clinical Features

Mutations in SPG11-JALS usually lead to truncation of the protein. This leads to a functional impairment, which is essential for its involvement in preserving cytoskeletal integrity and modulating the transport of synaptic vesicles [2,31]. The onset of SPG11-JALS typically occurs between 7 to 23 years of age, with the disease lasting around

34.3 years and following an autosomal recessive pattern of inheritance [31]. Bulbar symptoms of SPG11-JALS often manifest early in individuals, while cognitive impairments and mental health issues are less common. Mutations in the spatacsin gene are also associated with hereditary spastic paraplegia (HSP), but the clinical presentation of HSP patients differs from that of SPG11-JALS patients [33]. Magnetic resonance imaging (MRI) of HSP patients typically shows thinning of the corpus callosum, a feature not observed in SPG11-JALS cases [31].

ALS subtype 6

Genetic Details

ALS subtype 6 is caused by genetic mutations in the *FUS* gene. The *FUS* gene, located at position 16p11.2, encodes the fused in sarcoma (FUS) protein which plays a role in RNA processing [34]. This suggests that disruptions in RNA metabolism may be a contributing factor to the development of ALS [35].

Clinical Features

Mutations in the *FUS* gene are predominantly linked to JALS [9,36]. A study analyzing 38 cases of FUS-JALS [1] found that most cases were due to new mutations. Onset of symptoms typically occurs around the age of 21. Patients with FUS-JALS exhibit both upper and lower motor neuron dysfunction, presenting with spasticity and hyperactive tendon reflexes [37]. The disease progression of FUS-JALS is rapid, leading to death from respiratory failure within 1-2 years [38]. Some cases of FUS-ALS have also shown cognitive impairment, and indeed it has been observed frontal lobe atrophy and abnormalities in functional magnetic resonance imaging (fMRI) [39,40].

ALS subtype 16

Genetic Details

ALS subtype 16 is linked to mutations in the *SIGMAR1* gene, which encodes a molecular endoplasmic reticulum (ER) chaperone and is highly expressed in spinal motor neurons. This gene is located on chromosomal region 9q13.3 and is prominently expressed in motor neurons of the brainstem and spinal cord [41]. The *SIGMAR1* gene is involved in various processes such as lipid metabolism, ER stress response, initiation of autophagy, and calcium metabolism, all of which play a role in neurodegeneration. Studies have shown that inactivation of *SIGMAR1* causes mitochondrial dysfunction, dysregulation of calcium hemostasis, and neurodegeneration in cultures of primary motor neurons.

Clinical Features

In terms of clinical presentation, mutations in the transmembrane region [42] and frame-shift mutations upstream at position 95 (p. L95fs)

Table 1. Main subtypes of juvenile ALS and their genotype–phenotype correlations.

Type	Gene	Locus	Protein	Inheritance	Phenotype
ALS2	*ALS2*	2q33.1	alsin	AR	AAO: juvenile; Onset: LL, UL; PLS, IAHSP; Progression: gradual; UMN dominant > UMN + LMN
ALS4	*SETX*	15q15.1	senataxin	AD	AAO: juvenile > adult; Onset: LL > UL; AOA2, cerebellar ataxia, motor neuropathy; Progression: gradual; UMN + LMN > LMN dominant
ALS5	*SPG11*	15q15.1	spataxin	AR	AAO: juvenile > adult; Onset: bulbar, limb; HSP, autonomic dysfunction, intellectual disability; Progression: gradual; UMN dominant > UMN + LMN
ALS6	*FUS*	16p11.2	fused in sarcoma (FUS)	AD, AR, De Novo	AAO: adult > juvenile; Onset: UL, bulbar > LL; PMA, Parkinsonism, essential tremor, intellectual disability; Progression: swift > gradual; UMN + LMN > LMN dominant
ALS16	*SIGMAR1*	9q13.3	chaperone	AR	AAO: juvenile; Onset: LL > UL; motor neuropathy; Progression: N/A; UMN + LMN

Abbreviations: AAO; age at onset, AD; autosomal dominant, ALS; amyotrophic lateral sclerosis, AOA2; ataxia and oculomotor apraxia type 2, AR; autosomal recessive, HSP; hereditary spastic paraplegia, IAHSP; infantile onset ascending hereditary spastic paralysis, LL; lower limb, LMN; lower motor neuron, N/A; not available, PLS; primary lateral sclerosis, PMA; progressive muscular atrophy, UL; upper limb, UMN; upper motor neuron

have been described [43]. Individuals with SIGMAR1-JALS typically experience onset at 1-2 years of age with muscle weakness and spasticity. Especially, the distal muscle weakness initially affects the hands and forearms, eventually progressing to involve the proximal muscles, leading to complete atrophy of the forearm extensors and triceps [42]. However, no bulbar involvement has been reported and cognition is preserved. It is worth noting that SIGMAR1-ALS in adults may be associated with frontotemporal dementia (FTD), although cognitive impairment is not observed in SIGMAR1-JALS [43,44]. Furthermore, *SIGMAR1* mutations have been linked to distant hereditary motor neuropathy (dHMN) [45] and reduced levels of *SIGMAR1* have been found in the spinal cord of ALS patients [46].

Discussion

Diagnosing JALS poses a challenge due to its rarity and similarities with other motor neuron diseases [2]. The clinical presentation of JALS can vary depending on the specific gene mutation involved, with common symptoms including progressive muscle weakness and atrophy, spasticity, hyperreflexia, bulbar symptoms, and cognitive and behavioral changes [2,8].

Electrodiagnostic studies, such as electromyography (EMG) and nerve conduction studies, play a crucial role in confirming the presence of denervation and reinnervation in multiple myotomes, supporting the involvement of lower motor neurons. Findings may include fibrillation potentials, positive sharp waves, increased amplitude and duration of motor unit potentials, or reduced recruitment of motor units [2].

MRI of the brain and spinal cord can reveal non-specific changes or features related to the underlying genetic mutation. Findings may include cortical and spinal cord atrophy, corticospinal tract signal changes, frontal cortical atrophy, thin corpus callosum, and leukoencephalopathy in some cases [8].

Genetic testing is essential for diagnosing JALS and identifying the specific gene mutation responsible. Understanding the genetic cause can provide valuable information for prognosis and management [2,8]. There are further recorded instances of JALS resulting from mutations in genes commonly associated with adult ALS, such as *SOD1* (Copper/zinc superoxide dismutase-1), *UBQLN2* (Ubiquitin-like protein, specifically ubiquilin 2), and *TARDB* (TAR DNA binding protein), which have been thoroughly examined in existing literature. Alternatively, mutations in other genes like *SPTLC1* (Serine palmitoyltransferase, long-chain base subunit 1) [47], *ERLIN1* (Endoplasmic reticulum lipid raft-associated protein 1) [48], *GNE* (glucosamine (UDP-N-acetyl)-2-epimerase/N-acetylmannosamine kinase) [49], *VRK1* (vaccinia-related kinase 1) [50], *BICD2* (BICD cargo adaptor 2) [51], *SYNE1* (spectrin repeat containing the nuclear envelope protein 1) [52], *DDHD1* (DDHD domain containing 1) [53], and *CLEC4C* (C-type lectin domain family 4 member C) [51,52,54] have also been identified as leading to clinical manifestations resembling JALS, especially if symptoms manifest before the age of 25.

Other clinical conditions that may present similar symptoms to JALS include Juvenile Primary Lateral Sclerosis (JPLS) and HSP, both of which primarily exhibit upper motor neuron lesion signs like spasticity and dysarthria. HSP may have an earlier and more rapid onset of symptoms, while JPLS may be characterized by abnormal oculomotor findings [55]. Mutations in genes such as *alsin*, *SPG11*, and *ERLIN1* have been associated with HSP. Additionally, Spinal Muscular Atrophy (SMA) and distal hereditary motor neuropathy (dHMN), which predominantly affect the lower motor neuron, can also present symptoms similar to JALS. A case study reported a 10-year-old girl with a mitochondrial neurodegenerative disease showing clinical features resembling JALS, but further investigation revealed abnormal iron accumulation in the basal ganglia due to a compound heterozygous mutation in the C19orf12 gene [56]. Mutations can either be passed down from one parent or arise spontaneously in an individual with the disease. The mode of inheritance, whether autosomal recessive or autosomal dominant, depends on the specific gene involved. Nevertheless, the majority of cases of JALS are of the familial form.

The treatment modalities available for JALS are not specifically defined, with patient management primarily aimed at alleviating symptoms and enhancing mobility. Pharmacological interventions are frequently employed to combat fatigue and diminish muscle cramps. The for-

mulation of personalized treatment plans necessitates collaborative efforts among multidisciplinary healthcare teams [57-61]. Significant advancements have been made in the exploration of potential therapeutic strategies. A prominent area of research focuses on the influence of genetic factors in JALS. Investigations have revealed various genetic mutations, including those in the *SOD1* gene, which may play a role in the disease's onset [62]. By elucidating the genetic underpinnings of juvenile ALS, researchers aspire to create targeted therapies that address the specific molecular pathways implicated [62]. Furthermore, there is ongoing research into innovative neuroprotective strategies, such as the modulation of oxidative stress, the reduction of protein aggregation, and the alleviation of inflammatory responses [63]. These approaches aim to decelerate or potentially halt the disease's progression by targeting the fundamental pathogenic mechanisms responsible for motor neuron degeneration. Another promising research direction involves the exploration of stem cell-based therapies for juvenile ALS. These therapies seek to replace or support damaged motor neurons, thereby aiming to restore functionality and enhance the quality of life for affected individuals. As research progresses, the scientific community remains optimistic that the advancement of more effective treatments for juvenile ALS will yield improved outcomes and enhance the prognosis for those impacted by this debilitating condition [62-65].

Conclusion

In conclusion, the diagnosis of JALS necessitates a high level of suspicion, a thorough clinical assessment, electrodiagnostic studies, genetic testing, and neuroimaging. It is important to distinguish JALS from other motor neuron diseases, spinal muscular atrophies, and hereditary spastic paraplegias [8]. A comprehensive clinical evaluation, along with electrodiagnostic studies and genetic testing, is essential for establishing the diagnosis of JALS and ruling out other conditions. Early recognition is crucial for guiding management and providing appropriate genetic counseling to the patient and their family.

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Conflict of interest statement
The authors declare no conflict of interest.

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