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Single Case – General Neurology

Thirty-Year Follow-Up of Early Onset Amyotrophic Lateral Sclerosis with a Pathogenic Variant in SPTLC1

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Abstract
Dominant mutations in *serine palmitoyltransferase long chain base subunit 1* (*SPTLC1*), a known cause of hereditary sensory autonomic neuropathy type 1 (HSAN1), are a recently identified cause of juvenile amyotrophic lateral sclerosis (JALS) with slow progression. We present a case of *SPTLC1*-associated JALS followed for 30 years. She was initially evaluated at age 22 years for upper extremity weakness. She experienced gradual decline in muscle strength with development of weakness and hyperreflexia in lower extremities and diffuse fasciculations in the upper extremities at 26 years. She lost independent ambulation at age 45 years. Pulmonary function declined from a forced vital capacity of 94% predicted at 27 years to 49% predicted at 47 years, and she was hospitalized twice for respiratory failure. To our knowledge, this is the longest documented follow-up period of JALS caused by a de novo pathogenic variant in *SPTLC1*.

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder of upper and lower motor neurons in the central nervous system resulting in decreased motor function [1]. Most cases of ALS are sporadic with onset of symptoms around age 60 years. Familial ALS accounts for approximately 10% of cases; they have a slightly younger mean age at onset of symptoms (40–60 years) [1, 2].

Juvenile ALS (JALS) is a rare form of ALS defined by age at onset of less than 25 years, with a genetic cause identified in at least 40% of cases [3, 4]. The most common genes associated with JALS include *Fused in Sarcoma* (*FUS*), *Senataxin* (*SETX*), and *ALS2/Alsin* [4]. There are at least twelve additional JALS genes, including *serine palmitoyltransferase long chain base subunit 1* (*SPTLC1*) [3, 4]. *SPTLC1* and *SPTLC2* encode subunits of serine palmitoyl transferase (SPT) [5], which catalyzes the rate-limiting step in sphingolipid biosynthesis [5, 6].

SPTLC1 is the known genetic cause of hereditary sensory autonomic neuropathy type 1 (HSAN1) [7]. Surprisingly, several mutations in exon 2 of *SPTLC1* were recognized as a cause of JALS in 2021 [5, 8]. In reported cases, the age of onset was 3–16 years of age [3, 5, 8] and most cases had a follow-up period from 5 to 24 years. Patients typically present with spasticity or weakness of the lower extremities [5, 8] followed by progressive weakness that can include respiratory or bulbar muscles [5, 8].

We describe a case of JALS due to a de novo pathogenic *SPTLC1* variant who was followed for 30 years at a single academic center, adding to our understanding of the clinical course and phenotypic spectrum of this rare disease. The CARE checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000530974).

Case Report

A 22-year-old female presented to the neuromuscular clinic with upper extremity weakness resulting in difficulty lifting objects overhead. In retrospect, she and her parents felt she had normal strength through at least 18 years of age, with subsequent insidious development of arm weakness. She was otherwise healthy, and she had no family history of weakness. Her physical exam at age 22 showed marked wasting of arms, significant proximal > distal muscle weakness in her upper extremities, and near-normal strength in the legs. Deep tendon reflexes were absent in her arms and 3+ in the legs. Sensory examination was normal. Nerve conduction studies were normal in both upper and lower limbs. Electromyography showed diffuse fibrillation potentials and p waves in the upper and lower extremities, indicative of a chronic motor neuron disease. Deltoid muscle biopsy showed marked type 1 fiber predominance and large groups of angular atrophic fibers interspersed with normal-sized muscle fibers (Fig. 1). The fiber type predominance was interpreted as reinnervation fiber type grouping that is skewed toward type I fibers, and rare myonecrosis was considered a secondary myopathic feature. A C-spine MRI showed a segmentation anomaly at T1–T2, but the spinal cord was normal. Based on these findings, she was given the presumptive diagnosis of late onset spinal muscular atrophy (SMA).

Over the next 4 years, weakness progressed to involve both upper and lower extremities, and she developed fasciculations in bilateral arms and tongue, a subtle waddling gait and persistent hyperreflexia (3–4+) in her lower extremities. Diagnostic and carrier testing for SMA were normal. Forced vital capacity (FVC) was normal (serial testing is summarized in Fig. 2). She began to use a manual wheelchair for long distances at age 34 years, and at 36 years she was having difficulty with activities of daily living, such as bathing herself and driving. New findings on examination

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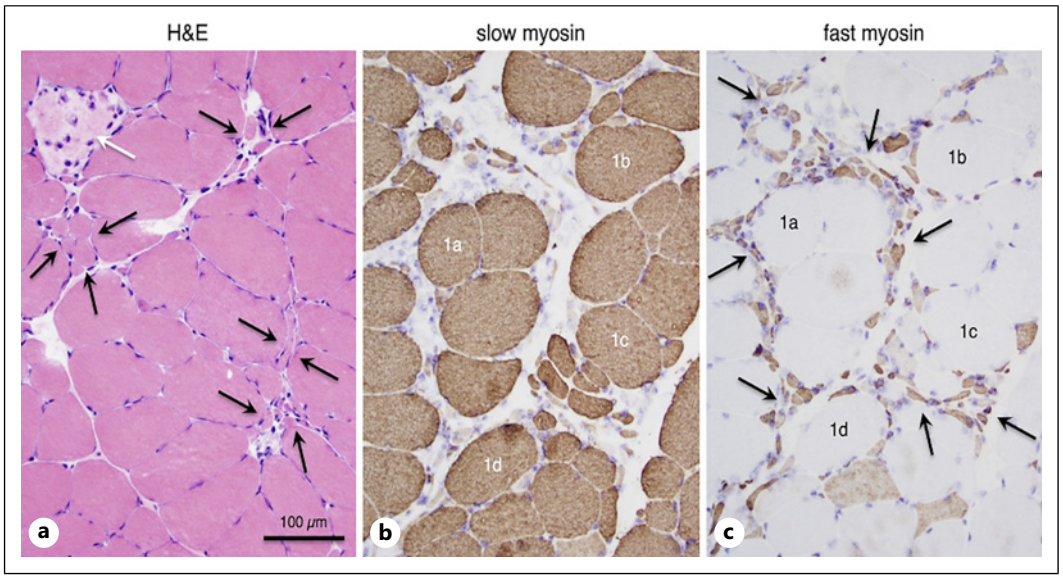

Fig. 1. Pathological findings from left deltoid muscle biopsy at age 22 years. Groups of angular atrophic fibers (black arrows in panels **a** and **c**) are interspersed with normally sized to mildly hypertrophic muscle fibers. The slow myosin immunostaining (panel **b**) is roughly equivalent to ATPase at pH 4.3 and stains positive for type 1 muscle fibers (slow twitch). Type 1 muscle fibers are negative on fast myosin immunostaining (see, for example, muscle fibers 1a, 1b, 1c, and 1d in panel **c**). The fast myosin immunostaining (panel **c**) is roughly equivalent to ATPase at pH 9.4 and it stains positive for type 2 muscle fibers (fast twitch). Type 2 muscle fibers are negative on slow myosin immunostaining (see, for example, most of the angulated atrophic fibers in panel **b**). Widely scattered fibers are undergoing myonecrosis/myophagocytosis (white arrow in panel **a**).

included mild facial weakness and dysarthria. EMG/NCV studies were unchanged and remained consistent with a motor neuron disease. She developed increased work of breathing with use of accessory respiratory muscles and a weak cough when evaluated at age 39 years. Following referral to a pulmonologist, the use of cough assist was started.

She was hospitalized locally for hypercapnia due to respiratory insufficiency at age 44 years. She was initially placed on nocturnal continuous positive air pressure and later switched to bi-level positive airway pressure and daily use of cough assist. One year later, she was hospitalized for 9 days for hypoxemic hypercapnic respiratory failure. She was placed on an average volume assured pressure support system at night and later that year daytime mouthpiece ventilation was added.

She started to experience short-term anterograde memory loss following her first hospitalization. Neuropsychiatric testing at age 44 years showed moderate focal impairment felt secondary to recurrent hypercapnia episodes and a progressive syndrome was not suspected. C9orf72 genetic testing was normal.

She lost independent ambulation at age 45 years and required increased daytime use of the mouthpiece ventilation. At her most recent follow-up at age 51 years, she was no longer able to lift her hand to her mouth to feed herself but she could take steps in the house with use of a walker. She continued to use noninvasive ventilation at night and frequently during the day. Muscle strength testing was mostly unchanged; she lacked antigravity strength in nearly all upper extremity muscle groups, while in lower extremities she had at least antigravity strength, and quadriceps and hamstrings had normal strength on manual muscle testing. Tongue atrophy was not observed, and all other physical exam findings were unchanged compared to prior visits.

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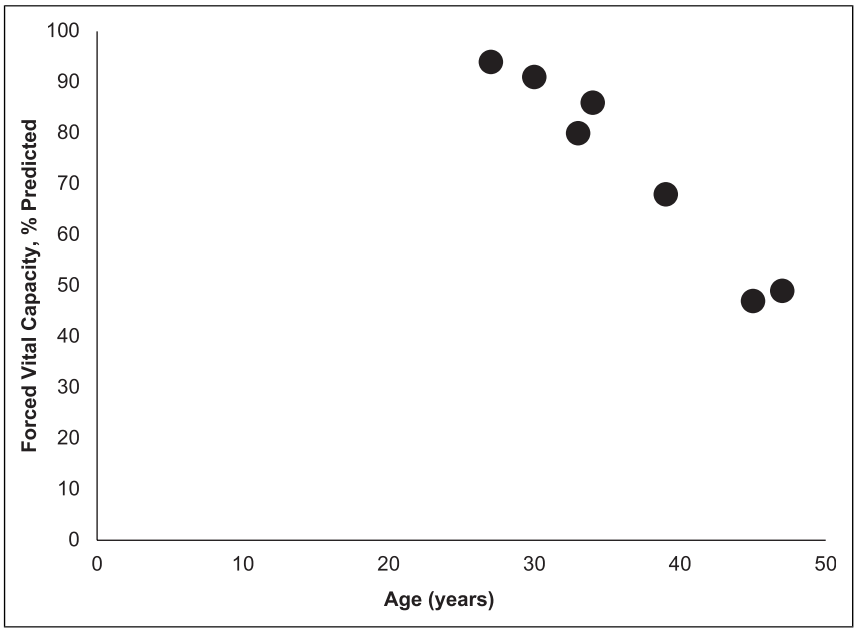

Fig. 2. Forced vital capacity by age. Not plotted here are the mean inspiratory and mean expiratory pressures. At age 45 years, for example, these pressures were 26 cm H20 and 27 cm H20, respectively.

Extensive genetic and biochemical testing was normal over the years of follow-up. In 2021 when she was 49 years old, research-based genetic testing on the patient and her parents through the Inherited Neuropathy Consortium using the GENESIS platform [9] identified a previously reported de novo pathogenic variant c.115_117del (chr9: 94874785_94874787del, p. Leu39del) in *SPTLC1* that was confirmed through commercial diagnostic laboratory testing (Invitae).

Discussion

We describe a 51-year-old female with early onset alS due to a c.115_117del variant of *SPTLC1* who has been followed for 30 years. This is a recurring mutation; at least 7 additional cases from 4 families with JALS have been reported with this *SPTLC1* variant [5, 8]. There is striking phenotypic variation among the individuals with this genotype, summarized in Table 1. Our case was older at presentation than the other cases (22 years vs. 3–16 years of age), and the patient reported here is currently older than any of those reported. While most previously reported cases started with lower extremity weakness or abnormal gait, our patient presented with upper extremity weakness [5, 8]. Loss of ambulation occurred as early as age 10 years in reported cases, while one individual was walking short distances at 34 years of age (case 7, Table 1). Our patient did not lose the ability to walk without assistance until age 45 years. Respiratory involvement is rare among those reported with this variant, although it has been seen in patients with other *SPTLC1* genotypes. The patient reported here had her first abnormal FVC measured at age 39 years. All previously reported cases with the same genotype were younger than 39 years, and only one had low FVC. It is of interest that case 7 in Table 1, with a phenotype most similar to the present case, took Riluzole starting at age 15 years [5].

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Table 1. Clinical features in current and reported cases of juvenile amyotrophic lateral sclerosis due to *SPTL1C* variant c.115_117del, p.(Leu39del)

Case name listed in literature [reference number]	Age at report, years	Sex	Age at onset or presentation, years	Initial symptom	Age at loss of ambulation, years	Respiratory insufficiency
Current case	51	F	22	Arm weakness	45	+
Patient 5 [5]	13	M	3	Falls	10	–
Patient 4 [5]	28	M	8	Toe walking	17	+*
Patient II-1 [5]	27	F	16	Upper extremity discoordination	19	–
Patient II-2 [5]	25	F	14	Abnormal gait	23	–
Patient II-3 [5]	21	M	10	Abnormal gait	14	–
Patient II-4 [5]	19	F	6	Abnormal gait	13	–
Case 4 [8]	34	F	15	Arm and leg weakness	–	–

*FVC abnormal, but no support needed.

Pathogenic variants in *SPTLC1* also cause HSAN1, an autosomal dominant disorder that presents in teens through adulthood with sensory loss [7]. *SPTLC1* variants associated with JALS are clustered in the second exon [10], while those associated with neuropathy are more broadly distributed [6]. A severe childhood HSAN1 phenotype with systemic features such as growth failure, intellectual disability, and cataracts has been associated with missense variants affecting serine 331 [11]; case 3 reported by Johnson et al. [8] as JALS-Plus (p.Ser331Tyr) likely has this phenotype.

SPTLC1-associated JALS and HSAN1 are biochemically distinct. Variants associated with JALS have a sphingolipid signature of increased sphinganine and circulating ceramide and normal deoxy sphingolipid levels, while those with HSAN1 show increased deoxy sphingolipid levels [10]. Importantly, L-serine, which is used for the treatment of HSAN1, has been shown to exacerbate the biochemical phenotype associated with JALS variants due to their differences in the impact on the SMT metabolic pathway [5]. New therapeutics such as siRNA targeting ALS mutant allele mRNA to normalize sphingolipid levels are a potential treatment approach for this disease [12].

Like the present case, most *SPTLC1*-associated JALS cases that included parental genetic testing are de novo variants. An exception that remains unexplained is autosomal dominant inheritance from a father who had an HSAN1 phenotype [5]. Our case, which is one of the longest documented follow-ups of JALS due to a de novo pathogenic *SPTLC1* variant, adds to our understanding of the clinical course and phenotypic spectrum of this rare disease.

Acknowledgments

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Statement of Ethics

All sites participating in the INC natural history study (protocol 6601) received Institutional Review Board/Ethics Board approval from the University of Pennsylvania for the study. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Aparna Ajjarapu, BA, received funding from the University of Iowa Carver College of Medicine and the Paul D. Wellstone Muscular Dystrophy Specialized Research Center grant (NIH P50NS053672). Shawna M.E. Feeley, MS, LGC has no conflicts of interest. Dr. Michael E. Shy, MD receives support from NCATS and NINDS for the Inherited Neuropathies Consortium (2U54NS065712), a member of the Rare Disease Clinical Research Network (RDCRN). The INC also receives support from the Muscular Dystrophy Association (MDA) and Charcot Marie Tooth Association (CMTA). He has no other disclosures to declare that are relevant to the present manuscript. Christina Trout, RN, MSN has no conflicts of interest. Dr. Stephen Zuchner, MD, PhD has consulted for Applied Therapeutics and Dtx Pharma. He is an unpaid board member of UDN Foundation, TGP Foundation, and the advisory boards for MDA and CMTA. Dr. Steven A. Moore, MD, PhD receives funding from the Paul D. Wellstone Muscular Dystrophy Specialized Research Center Grant (NIH P50NS053672). He has nothing else to disclose. Dr. Katherine D. Mathews receives funding from the Paul D. Wellstone Muscular Dystrophy Specialized Research Center Grant (NIH P50NS053672) and the Centers for Disease Control (U01 DD001248). She serves as an advisory board member for MDA and the FSH Society; is a board member for the Friedreich Ataxia Research Alliance (FARA); receives clinical trial funding from PTC Therapeutics, Sarepta Therapeutics, Pfizer, Reata, Italfarmaco, CSL Behring, AMO Pharma, FibroGen, and Retrotope; and serves as an industry consultant for Sarepta, AskBio, ML Bio, Dyne (no personal compensation).

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Author Contributions

A.A., S.M.E.F., M.E.S., C.T., S.Z., S.A.M., and K.D.M. contributed to the writing, data collection, and data analysis for this research article.

Data Availability Statement

All data generated or generalized during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

References

1 Masrori P, Van Damme P. Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol. 2020;27(10):1918–29.
2 Camu W, Khoris J, Moulard B, Salachas F, Briolotti V, Rouleau GA, et al. Genetics of familial ALS and consequences for diagnosis. French ALS Research Group. J Neurol Sci. 1999;165(Suppl 1):S21–6.
3 Lehky T, Grunseich C. Juvenile amyotrophic lateral sclerosis: a review. Genes. 2021;12(12):1935.

4 Picher-Martel V, Brunet F, Dupre N, Chrestian N. The occurrence of FUS mutations in pediatric amyotrophic lateral sclerosis: a case report and review of the literature. J Child Neurol. 2020;35(8):556–62.
5 Mohassel P, Donkervoort S, Lone MA, Nalls M, Gable K, Gupta SD, et al. Childhood amyotrophic lateral sclerosis caused by excess sphingolipid synthesis. Nat Med. 2021;27(7):1197–204.
6 Wang G, Bieberich E. Sphingolipids in neurodegeneration (with focus on ceramide and S1P). Adv Biol Regul. 2018;70:51–64.
7 Nicholson GA. SPTLC1-Related hereditary sensory neuropathy. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al, editors. GeneReviews((R)). Seattle (WA); 1993.
8 Johnson JO, Chia R, Miller DE, Li R, Kumaran R, Abramzon Y, et al. Association of variants in the SPTLC1 gene with juvenile amyotrophic lateral sclerosis. JAMA Neurol. 2021;78(10):1236–48.
9 Gonzalez M, Falk MJ, Gai X, Postrel R, Schule R, Zuchner S. Innovative genomic collaboration using the GENESIS (GEM.app) platform. Hum Mutat. 2015;36(10):950–6.
10 Lone MA, Aaltonen MJ, Zidell A, Pedro HF, Morales Saute JA, Mathew S, et al. SPTLC1 variants associated with ALS produce distinct sphingolipid signatures through impaired interaction with ORMDL proteins. J Clin Invest. 2022;132(18):e161908.
11 Bode H, Bourquin F, Suriyanarayanan S, Wei Y, Alecu I, Othman A, et al. HSAN1 mutations in serine palmitoyltransferase reveal a close structure-function-phenotype relationship. Hum Mol Genet. 2016;25(5):853–65.
12 Cassereau J, Corcia P, Reynier P. Towards personalized medicine for amyotrophic lateral sclerosis. Trends Endocrinol Metab. 2021;32(11):839–41.