New SOD1 Mutation Causing Rapid Amyotrophic Lateral Sclerosis with Nerve Root Enhancement

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Keywords: Amyotrophic lateral sclerosis; ALS; Lower motor neuron syndrome; Nerve root enhancement; SOD1; Cu/Zn superoxide dismutase; Motor neuron disease; Magnetic resonance imaging; MRI

Expanding genetic knowledge in amyotrophic lateral sclerosis (ALS) has led to over 20 identified causative genes with improved clinical phenotypic characterization and pathophysiological insights.1 Cu/Zn superoxide dismutase 1 (SOD1) gene mutations cause approximately 20% of familial ALS and 1–2% of sporadic ALS with heterogeneous clinical phenotype.1 Therapeutic clinical trials have targeted the presumed pathogenic mechanism of toxic gain of function through antisense oligonucleotides.2 Gene variant classification of novel mutations carries important therapeutic implications. Here, we describe a patient with a novel SOD1 mutation and rapidly progressive lower motor neuron disease with MRI showing smooth ventral nerve root enhancement.

This case involved a 75-year-old right-hand dominant female – originally from Australia, with a past medical history of metastatic esophageal adenocarcinoma with neuroendocrine origin. Left cerebellar brain metastasis and the primary tumor were resected years prior to presentation. Her history also includes a left breast mastectomy for ductal carcinoma in situ and squamous cell carcinoma. Her father had late life polyneuropathy resulting in leg weakness and her paternal grandmother had bilateral leg weakness of unknown etiology.

Over 4 months, the patient’s weakness progressed from onset in the right hand to involvement of the left leg to loss of independent ambulation. Over the next 2 months, she endured week to week decline in limb strength, axial strength, and respiratory function. Prior to death by medical assistance in dying, 6 months from symptom onset, she had severe quadriaparesis with minimal left finger movements and vital capacity under 37% predicted. She denied symptom onset, she had severe quadriparesis with minimal left fin-

neural and coordination testing were normal. Extensive work-up was completed to rule out infectious, malignant, and autoimmune/inflammatory, and paraneoplastic causes. Infectious testing was negative for herpes simplex virus (HSV), enterovirus, HIV, hepatitis B and C, syphilis, Lyme, and West Nile Virus. Fluorodeoxyglucose positron emission tomography (FDG-PET) brain and body showed moderate hypermetabolism at her esophageal anastomosis. Two biopsies of this site showed no tumor recurrence. Cerebrospinal fluid (CSF) cytopathology and paraneoplastic testing were negative, and protein, glucose, and cell count were within normal. Neurophysiologic testing showed reduced motor compound motor action potential (CMAP) amplitudes, fibrillations, positive sharp waves, fasciculations, and polyphasic motor units with reduced recruitment in cranio-bulbar, cervical, and lumbosacral regions without evidence of demyelination or sensory changes. Interestingly, MRI of the lumbar spine demonstrated abnormal smooth enhancement of ventral intradural nerve roots without associated enlargement, which is atypical for motor neuron disease (Figure 1). Cervical or thoracic enhancement was not observed.

Although ALS was suspected, clinical concern for a treatable paraneoplastic inflammatory disorder led to treatment with intravenous immunoglobulin (25 g IV for 5 days), methylprednisolone (1000 mg IV daily for 5 days with subsequent oral prednisone taper), and plasmapheresis without clinical improvement.

Genetic testing was negative for the C9orf72 repeat expansion. SOD1 sequencing identified a single heterozygous variant, c.382G>C, predicted to cause p.(Gly128Arg), using NM_000454.4 as the reference sequence. The variant is also known as rs1568811389 in the Single Nucleotide Polymorphism Database.

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Cite this article: Perera T, Bencsik C, Pfeffer G, and Mobach T. New SOD1 Mutation Causing Rapid Amyotrophic Lateral Sclerosis with Nerve Root Enhancement. The Canadian Journal of Neurological Sciences [https://doi.org/10.1017/cjn.2022.311]

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DOI: 10.1017/cjn.2022.311

https://doi.org/10.1017/cjn.2022.311 Published online by Cambridge University Press
This variant is reported in one other case, describing rapidly progressive motor neuron disease and severe pain syndrome.1 Although the clinical report considered this to be a variant of uncertain significance, our interpretation of the American College of Medical Genetics and Genomics (ACMG) criteria suggests it should be considered as likely pathogenic given it has higher prevalence in affected individuals (two ALS cases with similar phenotype) compared to controls (zero in population databases).2 Additionally, the variant is in the same domain as other established SOD1 mutations that result in altered protein function.3 Lastly, in silico tools predict this variant is pathogenic and this amino acid residue is highly conserved across species.4,5 Another publication assessing SOD1 variants according to ACMG criteria similarly concluded the variant is likely pathogenic.6

Autopsy, completed 1 month after the last clinical examination, supported a final diagnosis of ALS given both upper and lower motor neuron involvement and p62 (a marker for proteins destined for degradation) positive neuronal inclusions in anterior horn cells, primary motor cortex, and brainstem motor nuclei. Notably, neuronal loss, gliosis, and chromatolytic changes were noted in the anterior horn, primary motor cortex, and two cranial nerves. Neurogenic changes of skeletal muscle were observed with type three atrophy. There were no other pathological abnormalities accounting for progressive muscle weakness or evidence of malignant metastases in the ventral nerve roots or other organ systems. Important similarities exist between our case and the previously reported case with this variant, including rapidly progressive disease onset affecting limb musculature. The main difference in the previously reported case is the presence of bulbar paresis and significant neuropathic pain.1 Additionally, autopsy was not completed in their patient.1

Nerve root enhancement has been reported in a handful of other ALS patients; all were associated with rapid disease progression.7–9 Our case is like these cases in that they both show smooth nerve enhancement without nodularity. One study, however, reports volume alterations in nerve roots.9 The pathophysiologic mechanisms are unclear, but proposed explanations include disruption of the blood spinal cord barrier and Wallerian degeneration.7 Gadolinium-enhanced spinal imaging is not routine in the evaluation of suspected ALS. However, when nerve root enhancement is detected, it does not exclude a diagnosis of motor neuron disease, especially in the absence of nodularity or nerve enlargement. Future observations may provide insight into whether nerve enhancement is more commonly seen with rapidly progressive disease. The findings of our report and Holmøy and colleagues allow for the reclassification of the p.(Gly128Arg) variant as likely pathogenic, which will be of benefit in case this variant is detected in future ALS patients.

Acknowledgements. No financial support has been received for this case report. There are no other acknowledgements.

Disclosures. Dr Theodore Mobach serves as a consultant for Biogen as it relates to Tofersen clinical trials NCT02623699 and NCT04856982, Amylyx, and Mitsubishi Tanabe. Dr Gerald Pfeffer has received grants from Muscular Dystrophy Canada, ALS Canada, Canada Foundation for Innovation, and the Kennedy’s Disease Association. He has an unpaid leadership role on the Medical/scientific advisory board for Muscular Dystrophy Canada, for ALS Canada, for Ataxia Canada, and for Cure VCP Inc. All remaining authors have no disclosures or conflicts of interests to declare.

Statement of Authorship. Case reviewed and written by Tefani Perera, Caralyn Bencsik, and Theodore Mobach. Gerald Pfeffer reviewed genetic testing and wrote the genetics section of the case.

References

