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BRIEF REPORT

SOD1-ALS mimicking an inflammatory neuropathy: a case report

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Abstract

We present the case of a 36-year-old patient with a rapidly progressing SOD1-ALS, who was initially diagnosed as inflammatory acute motor axonal neuropathy due to contrast-enhancement of the lumbar spinal cord and a pure secondary motor neuron phenotype. Since the initiation of tofersen, disease progression and neurofilament levels impressively declined.

Keywords: Amyotrophic lateral sclerosis, ALS, SOD1 mutation, MRI, contrast enhancement

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease leading to muscle weakness and eventually death through respiratory failure. Around 50 genes have been linked to ALS and pathogenic variants occur most frequently in the *C9ORF72*, *SOD1*, *FUS*, and *TARDBP* genes (1). *SOD1* mutations were the first to be linked to ALS and have been used as gold standard animal model for studying disease pathomechanisms. Most studies argue for an underlying toxic gain of function mutation. The disease-modifying antisense oligonucleotide tofersen leads to a degradation of *SOD1* mRNA and has shown beneficial results in clinical trials and post marketing registry studies (2). However, treatment effects seem to be strongly dependent on the remaining function at treatment initiation. It is therefore necessary to identify *SOD1* mutations in ALS patients as soon as possible. This identification is hindered by a heterogenic phenotype of patients with *SOD1* mutations (3,4), which sometimes hampers the distinction from ALS mimics – particularly as cases often present with pure secondary motor neuron symptoms. In this report, we present the case of a 36-year-old woman with SOD1-ALS initially treated as acute motor axonal neuropathy (AMAN), who greatly benefits during tofersen treatment.

Case report

One week after a febrile respiratory infection, the 36-year-old patient experienced back pain and a paralysis of her right leg which lead to an inability to climb stairs within four weeks. Diagnostics revealed a peripheral paresis with extinguished tendon reflexes, axonal nerve damage in motor neurography, spontaneous activity in electromyography, and MRI contrast enhancement without thickening of the lumbar spinal cord and the corresponding nerve roots (Figure 1A). A slightly increased protein concentration in the cerebrospinal fluid (CSF, 830 mg/l) in combination with normal cell count was interpreted as cytoalbuminary dissociation and anti-GM1 IgM-antibodies were borderline positive, however not reproducible in repeated measurements. The patient was treated with glucocorticoids under the assumption of an AMAN. Despite therapy, muscle weakness continuously progressed to a tetraparesis, respiratory insufficiency and ubiquitous fasciculations. Another cycle of glucocorticoids (two months after symptom onset) and, due to worsening of the symptoms, four cycles of immunoglobulins (six and eight months after symptom onset) were administered without relevant effect. Eventually, therapy was escalated to cyclophosphamide, but clinical findings aggravated and MRI contrast enhancement persisted

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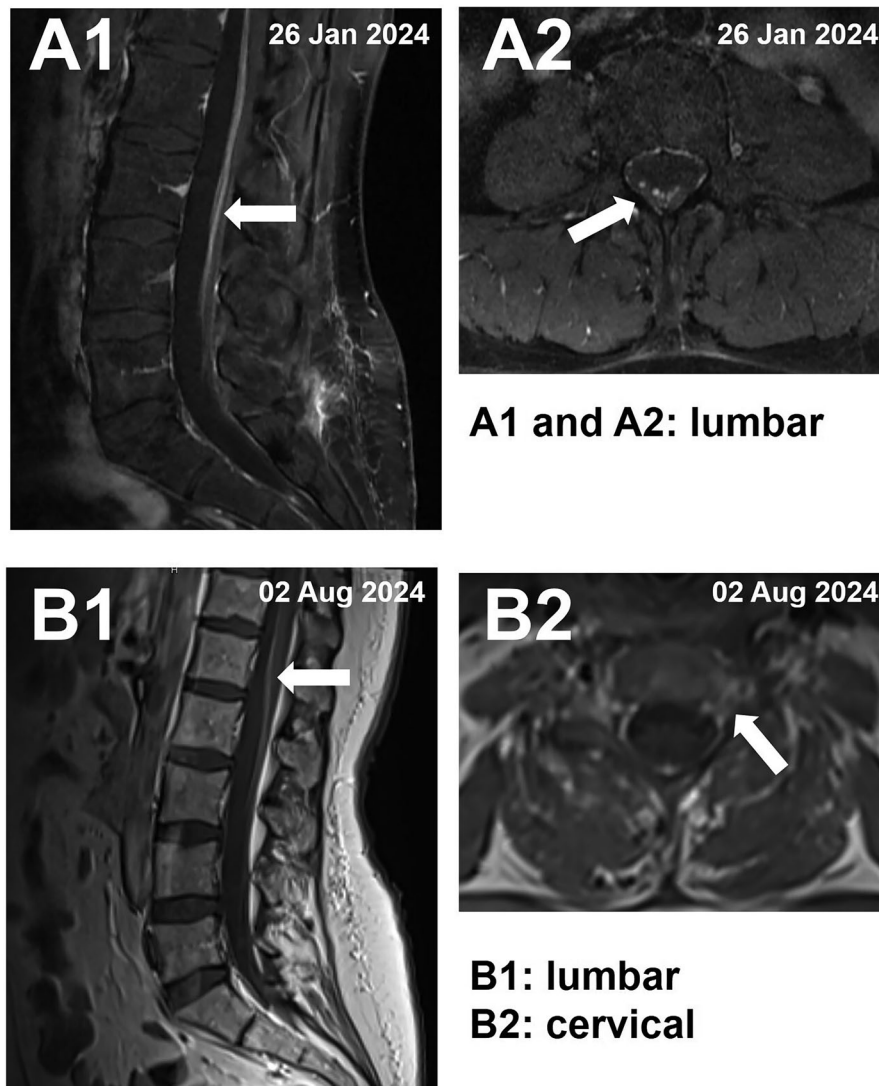


Figure 1. MRI findings. Arrows indicate contrast enhancement. Images A1 and A2 stem from the first MRI in 01/2024, images B1 and B2 stem from a follow-up MRI in 08/2024 after immunosuppressive treatment

in the lumbar and cervical region (Figure 1B). As no response to immunomodulatory therapy was observed, diagnosis of ALS was considered. The patient had no family history suggestive of motor neuron disease. During a second opinion in our clinic genetic testing showed a pathogenic variant in the *SOD1* gene (c.217G>A, p.(Gly73Ser), also known as G73S) and ultimately confirmed the diagnosis of ALS. Thereafter, tofersen therapy was initiated as soon as possible (9 months after symptom onset).

After treatment initiation, NfL strongly decreased in both blood and CSF. The clinical presentation stabilized, and the progression rate declined (Figure 2). Besides transient neuropathic radicular leg pain, no relevant adverse events occurred.

Discussion

In this report, the patient was initially (mis)diagnosed as AMAN based on MRI gadolinium enhancement of nerves in the lumbar and cervical

region in combination with mild cytoalbuminary dissociation. Genetic testing finally lead to the correct diagnosis and tofersen was started with a significant effect on both clinical and laboratory biomarkers. This is particularly remarkable, as the respective *SOD1* variant (G73S) is potentially associated with a survival of less than a year (5).

Nerve root enhancement has mainly been described for acute polyradiculoneuropathies such as Guillain-Barré syndrome (GBS) and its variants (6). It has also been described in two cases of ALS: Both Young and Mizuno et al. observed this phenomenon in rapidly progressing patients, the latter in a patient with *SOD1*-ALS (7,8). In the first case, the authors assumed neurodegeneration rather than neuroinflammation, as *SOD1* mouse models show vascular endothelial damage prior to motor neuron degeneration and vascular inflammation (9) and in compressive myelopathy, endothelial damage and neurodegeneration but not inflammation seem responsible for MRI contrast

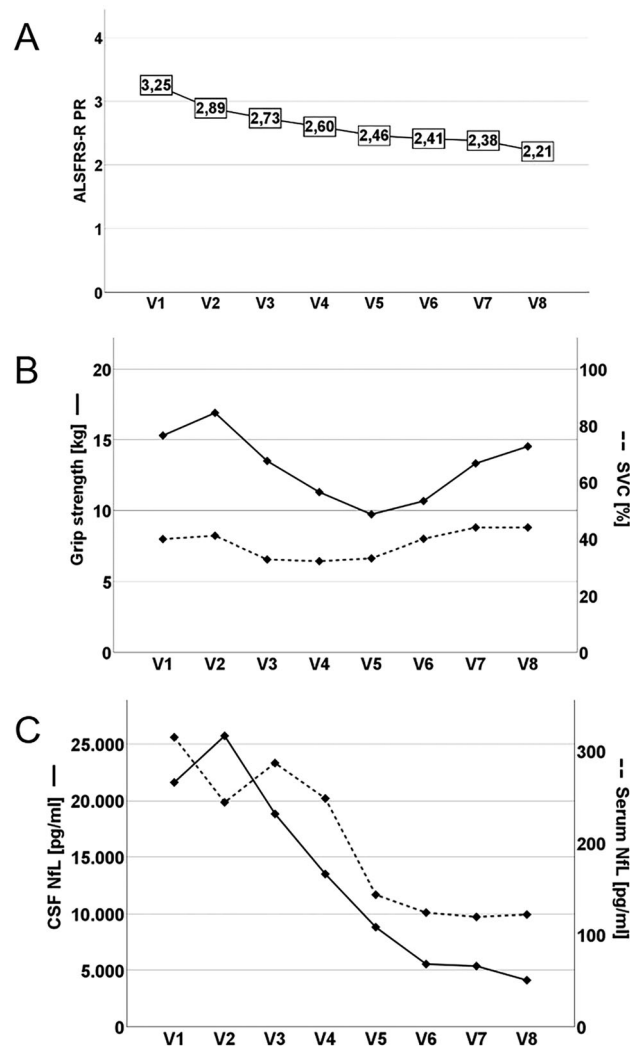


Figure 2. Clinical and laboratory responses under tofersen. (A) ALSFRS-R progression rate (PR) = (48 – ALSFRS-R at examination)/duration from onset to examination (month). (B) Grip strength in kg as measured with KERN dynamometer and forced vital capacity in percentage of predicted SVC as measured by EasyOne Air, ndd. (C) CSF and serum NfL levels as measured with a chemiluminescence detection system (Lumipulse G6000II). V1-8 indicate tofersen applications.

enhancement (10). More in-depth research on the pathophysiology of the enhancement is warranted. Regardless of its origin, MRI contrast enhancement should not distract from an ALS diagnosis in patients with rapid and progressing muscle deterioration considering that both mistaking ALS for immune-mediated neuropathies and vice-versa have relevant consequences on therapy regimens.

Conclusion

We report the case of a patient with SOD1-ALS and a rapidly progressive disease who was mistaken for AMAN due to MRI contrast enhancement and cytoalbuminary dissociation until genetic testing confirmed an ALS diagnosis. Tofersen had a significant effect on clinical and laboratory biomarkers. MRI contrast enhancement has been described in few other cases of ALS and should be considered during differential diagnostics, particularly when nerve roots are not thickened.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, R.G., upon reasonable request.

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