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A case of rapidly progressive amyotrophic lateral sclerosis associated with *SOD1* mutation (p.D126H variant) following COVID-19 vaccination

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Abstract

Mutations in common amyotrophic lateral sclerosis (ALS) genes have been reported in sporadic ALS. In the current case, we describe a patient without known family history who was found to harbour a *SOD1* mutation (p.D126H variant) and who developed ALS following COVID-19 vaccination. This mutation has only been previously reported once three decades ago in a British family. Although COVID-19 vaccination in itself is unlikely to contribute to the development of ALS, the possibility that vaccination could play a part in triggering the onset of disease in patients with risk variants merits further study.

Keywords: Amyotrophic lateral sclerosis, *SOD1*, D126H, COVID-19 vaccination

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive loss of motor neurons. In up to 10% of patients, ALS is inherited and one of the most common genes being *superoxide dismutase-1* (*SOD1*).[1] We report a patient of Malay ancestry with a *SOD1 p.Asp126His* mutation who developed spinal onset ALS two weeks following coronavirus vaccination.

CASE REPORT

A 37-year-old woman presented with a history of lethargy, fever and left arm pain the day after her second dose of Sinovac-CoronaVac vaccination. By the second week, there was weakness of shoulder abduction, progressing to distal weakness of the hand. Over a period of two months, she continued to progress with difficulties walking and climbing stairs prompting her referral to our Neurology team. On examination, there were no bulbar or respiratory symptoms. Limb examination revealed hypotonia, proximal (MRC 3/5) and distal weakness (MRC 2/5) of left upper limb and mild weakness of the right first dorsal interosseous and abductor pollicis brevis (4/5). The reflexes were reduced, and sensation was intact. In the lower limbs, there was mild weakness of hip flexion (4/5) bilaterally.

MRI of the cervical spine and brain were normal. Nerve conduction studies (NCS) revealed features of a motor neuronopathy with markedly reduced compound muscle action potentials of both median and ulnar nerves with intact sensory studies. Electromyography (EMG) showed active denervation changes in the left infraspinatus, biceps brachii, first dorsal interosseous and abductor pollicis brevis. Initially, a diagnosis of neuralgic amyotrophy was considered. However, her symptoms progressed and five weeks later, she developed swallowing difficulties. Repeat NCS and EMG were suggestive of a motor neuronopathy involving four regions – bulbar, cervical, thoracic and lumbar regions. Taken together with the clinical presentation of disease

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progression, a diagnosis of ALS was established. At this stage, her ALSFRS-R was 10. As she was unable to swallow, an enteral feeding tube was inserted. She also had respiratory muscle weakness with a forced vital capacity of 1.14 L, 37% of predicted value and peak cough flow was 80 L/minute. Although non-invasive ventilation was initiated, she continued to deteriorate and died from respiratory failure and sepsis, six months after the onset of illness. DNA analysis subsequently revealed a heterozygous c.376G>C (p.Asp126His, p.D126H) mutation in *SOD1* (NM_000454.5).

DISCUSSION

Mutation in *SOD1* was first identified in 1993 with links to familial forms of ALS.[2] Since then, > 200 mutations have been reported in the Human Gene Mutation Database (hgmd.cf.ac.uk). In our patient, the p.D126H variant is a missense mutation in exon 5 of the *SOD1* gene. This mutation has not been previously annotated in the current genome database but has been reported in a British family of unknown ethnicity.[3] The proband was 71 years old and had classical ALS with disease duration of 20 months. Recently, a second mutation at codon 126, p.D126N was reported in a family with ALS in France. Both the father and daughter presented with rapidly progressive spinal-onset ALS with a predominantly lower motor neuron phenotype reminiscent of progressive muscular atrophy.[4] Our patient had a young onset at the age of 37 with a rapid progression of 6-month disease duration. She had a heterozygous c.376G>C (p.Asp126His, p.D126H) *SOD1* mutation. The variant shares a SNP ID (rs1568811372) with another reported variant, c.376G>A which causes a different amino acid change; p.Asp126Asn (p.D126N), seen in the French family with ALS, ClinVar accession number RCV001095397.1.[5] The p.D126H mutation has a CADD score of 32, indicating it is in the top 0.1% of deleterious alleles.

Patients with ALS have a heterogeneous presentation. Even within the spectrum of patients with mutations in *SOD1*, their phenotype can vary, including atypical features of sensory involvement and autonomic dysfunction.[6] In Asian populations, mutations in *SOD1* accounts for 30% of familial ALS. The mutation frequency was also seen in up to 1.5% of sporadic ALS.[1] The latter suggests that genetic risk variants may account for sporadic cases of ALS. In the current report, our patient developed ALS following the COVID-19 vaccination. There have been multiple reports of neurological complications following COVID-19 vaccination although a causal link to ALS has not been established. However, there has been increasing evidence to support a multistep process in the development of ALS including an interplay between genetic factors and the environment.[6] It could be hypothesised that in the current case, COVID-19 vaccination together with the presence of *SOD1* p.D126H mutation could have triggered the degenerative process leading to ALS.

DISCLOSURE

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