CASE REPORT

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Slowly Progressive Familial Amyotrophic Lateral Sclerosis: G93C Variant of Superoxide Dismutase 1 Mutation

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Abstract

Amyotrophic lateral sclerosis (ALS) is a fatal neurological disease with an unknown aetiology. In the literature, 5 - 10% of ALS cases are familial. There can be various mutations that cause ALS; the most common are the C9orf72 or SOD1 mutations. In the Asian population, SOD1 mutation is mostly described. We present an unusual variant of the SOD1 mutation, which is characterised by distal motor neuron disease without any bulbar affection and very slow progression. This is the second genetically proven familial ALS among all case reports published and the first reported G93C/G94C variant SOD1 mutation from India.

Key word: Familial ALS, slow ALS , rare ALS, SOD1 mutation, G93C variant.

Introduction

Amyotrophic lateral sclerosis is a disorder of progressive weakness, wasting, and spasticity because of anterior motor horn cell affection. Sporadic ALS aetiology is often unknown, but 5 - 10% of ALS are familial. There is a low incidence of ALS in India as compared to the US[1]. Familial ALS in India is reported to be <5%. The mutation common in the Asian cohort is the SOD mutation, while in the Caucasian cohort, the most common mutation is C9orf72, accounting for 40% of familial ALS[1]. In India, there has been only one case report on familial ALS by Devi *et al*. It showed an L84F mutation in exon 4 of SOD1 with the novel nucleotide variation c255G77 inherited in four members of the family with autosomal dominant inherited ALS[2]. Till now, only 3 case reports from India, have showed a familial pattern, and only one was genetically proven. All cases had a decreased life expectancy, and familial ALS was reported to have more prominent bulbar symptoms than sporadic cases[3].

Case report

A 37-year-old lady presented with gradually progressive asymmetric quadriparesis with wasting of both upper and lower limbs of 5-year duration. The patient first noticed weakness at 32 years of age when she noticed difficulty climbing stairs, standing for long hours, or walking long distances. The symptoms were initially noted in her right leg but involved her left lower limb after 6 months. Gradually, over the next year, she had difficulty getting up in the toilet or from the ground. She started noticing around this time that her legs were thinning out; there was no history of any distal weakness in the form of difficulty wearing a slipper or buckling of the knee or ankle. There were no sensory symptoms. For the past 2 years, she noticed weakness in the distal muscles of her left hand; she had difficulty peeling vegetables, holding her phone, or typing with her left hand. This had progressed and was now affecting the right hand too. For the past year, she has had difficulty buttoning, breaking chapati (Indian bread), or holding a spoon. So far, there was no history of difficulty turning in bed or requiring support for getting out of bed; there was no dysphagia or dysarthria. The patient was able to carry-out her daily activities with support, and her ALS functional score was 35 (Table I). On examination, she had no fasciculations or fibrillations in the tongue; she had fasciculations over both biceps and triceps and quadriceps muscle; there was distal wasting of both upper and lower limbs and polyminimyoclonus in both upper limbs; the power was 4 in both upper limbs in distal muscles; 4/5 in proximal muscles; similarly, 3 in both lower limbs in antigravity muscles; and 4 in other muscles. She had absent reflexes in both lower limbs and bilateral plantars that were extensor; no sensory or cerebellar signs were present.

Table I: ALS functional rating scale-revised in this patient (ALSFRS-R)[14].

Bulbar		Fine motor		Gross Motor		Respiratory	
Speech	4	Handwriting	3	Turn in bed	2	Dyspnoea	3
Salivation	4	Cutting Food	2	Walking	2	Orthopnoea	4
Swallowing	4	Dressing	2	Climbing stairs	1	Respiratory Insufficiency	4

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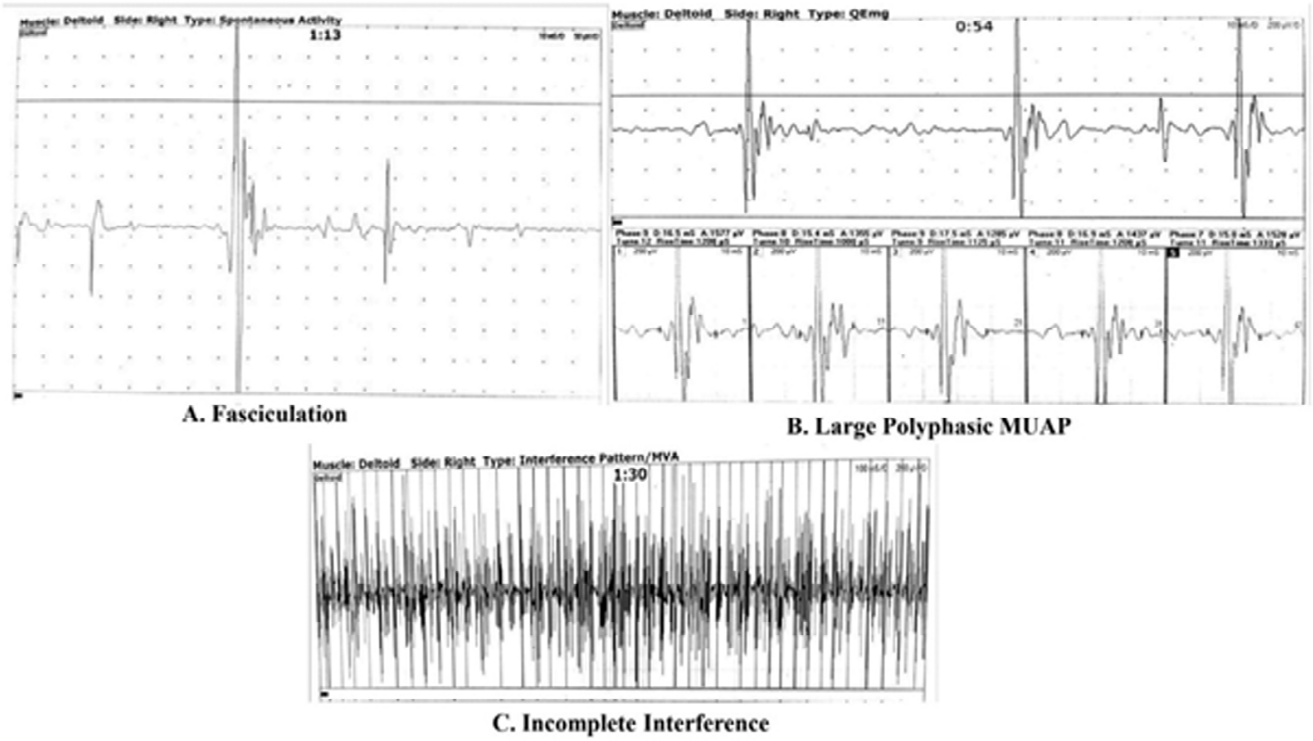

Fig. 1: *Electromyographic pattern of the patient.*

Her NCV was suggestive of motor axonal affection in both upper and lower limbs, there was no affection of sensory nerves, CPK level was normal, and EMG was suggestive of a neurogenic pattern (presence of fibrillations, positive sharp waves and fasciculations along with large polyphasic motor unit action potential with increased duration and incomplete interference) (Fig. 1) in three contiguous segments. An electrophysiological diagnosis of possible ALS was kept, according to modified Awaji criteria[4].

She underwent blood investigations and PET scan to determine the mimics of Motor Neuron Disease. Her whole exome sequence was sent because of a strong familial history of similar illness in family members (see pedigree below in Fig. 2), which was suggestive of the 'c.280 G >T (p.Gly94Cys)' variant of the SOD1 gene in exon 4.

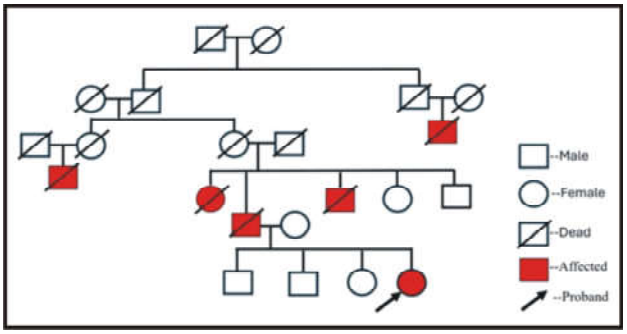

Fig. 2: *Pedigree chart of the patient.*

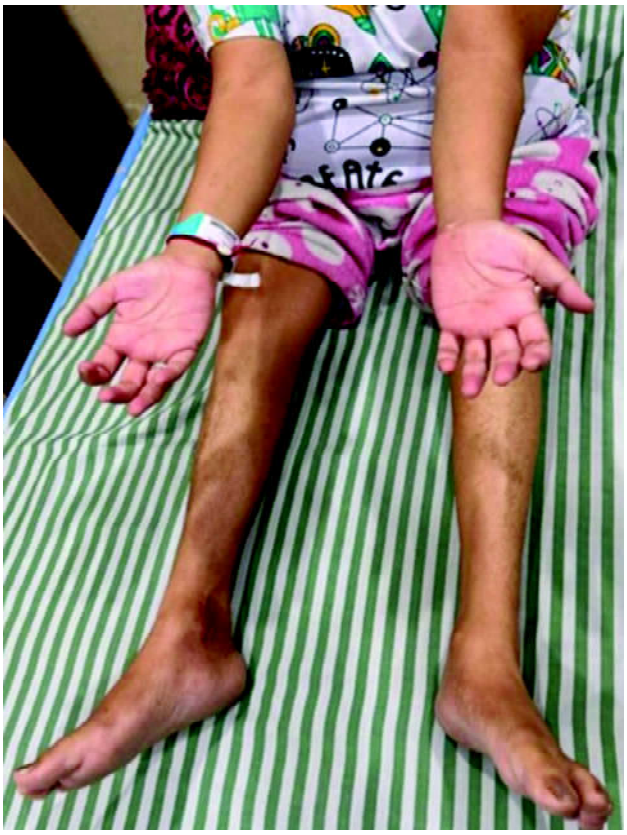

Fig. 3: *Wasting of distal muscles of Upper and Lower limbs.*

Discussion

Amyotrophic lateral sclerosis is characterised by the presence of upper and lower motor neuron features, bulbar involvement, and a poor prognosis. So far, no effective treatment is available for the disease. 5 - 10% of cases may have familial ALS with a predominant autosomal dominant mutation. The frequency of mutations in common ALS-causing genes varies by geographic location; the most common genetic mutation in the Caucasian population is C9orf72, which accounts for >40% of familial and 5 - 20% of sporadic ALS[1-3]. Approximately 20% of familial ALS in the Asian population has mutations in the Cu/Zn superoxide dismutase (SOD1) gene. At least 46 different SOD1 mutations are known to exist, but because the mutations are dispersed throughout the SOD1 structure, their exact molecular mechanism has not been determined[5]. The principle biochemical action of SOD1 is to convert potentially toxic superoxide radicals into hydrogen peroxide, but a toxic gain of mutation for mutant SOD1 causes impaired free radical scavenging[6]. The symptoms in familial ALS are similar to those in sporadic cases involving muscle weakness and atrophy, speech difficulties, swallowing, and respiratory dysfunction due to the progressive degeneration of upper and lower motor neurons[7]. Although familial ALS is generally associated with an earlier age of onset and commonly manifests symptoms in the lower limb, there can be variable disease duration, life expectancy, and clinical progression according to genetic subtypes[3]. The SOD1 mutation generally tends to affect people around 50 years of age[9,10], and there is a tendency to progress with more prominent bulbar symptoms in familial ALS than in sporadic cases.

There are very sparse case reports of familial ALS from India. Only two reports of the SOD1 mutation have been reported till now[11,12]. All cases had an age of onset of around 50 years and an autosomal dominant pattern; there was rapid progression, and the life expectancy was a maximum of 2 years. The median survival in Chinese and Indian studies suggests longer periods of survival compared to Caucasians and an earlier age of onset[9]. Migration studies have also observed similar patterns. In one study of migrants from the Indian subcontinent to the UK, a younger age of onset of patients with lower mortality rates was observed[14].

We have a very unusual presentation of ALS, with the patient relatively preserved even after 5 years of the onset of the illness. The average survival of patients with limb-onset ALS in Asian as well as Caucasian cohorts is 2 years, with 114.8 months of survival reported in an Indian cohort by Devi *et al*[11]. Our patient had survived for more than 5 years and had no bulbar symptoms. Her ALS functional score was 35 out of 40.

Many authors report pathological differences between familial and sporadic ALS, with prominent involvement of the posterior column, spinocerebellar tract, and Clarke's column in familial ALS[7,13]. Our patient had no such complaint involving sensory or cerebellar structures. She had a slower progression of disease as compared to other cases. The patient's father had died at the age of 55 years within 4 years of the onset of disease; her paternal uncle and aunt, suffering from similar illnesses, also died within a few years of the onset of disease. The patient's gradual progression can be explained by the G93C variant which is associated with a less severe disease phenotype, while among other variants, L144S is associated with the least severe form and G41S is associated with the most aggressive form of ALS[7,13]. The G93C mutation is associated with a purely lower motor neuron clinical phenotype and the absence of bulbar involvement. A hint to possible mechanisms in this diversity of phenotypes was provided in a recent report on the selective association of mutant SOD1 with mitochondria of affected tissues in transgenic mouse models of ALS[16].

Conclusion

We hereby present an unusual case of ALS, with autosomal dominant inheritance, asymmetric quadriparesis, and a gradual onset and progression. She had the disease for more than 5 years, but her functional scale was still 35/40, which makes it a unique case with prolonged survival, among all cases reported till now. The case shows a rare variant of Superoxide Dismutase 1 mutation affecting the G93C variant; this variant is commonly associated with slow progression and good survival.

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