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HURDLES IN DIAGNOSIS OF FAMILIAL AMYOTROPHIC LATERAL SCLEROSIS WITH ANTICIPATION CATASTROPHE ACROSS THREE GENERATIONS: A CASE REPORT

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ABSTRACT

Familial amyotrophic lateral sclerosis (F-ALS), a rare hereditary variant of ALS, is characterized by a genetic predisposition to the disease. In this case report, we reveal a compelling instance of F-ALS within a three-generation family, involving a grandfather, son, and grandson, all manifesting early-onset symptoms and progressive upper and lower motor neuron findings. The clinical diagnosis was confirmed through electromyography fulfilling El Escorial criteria of ALS. Our investigation highlights the familial connection in this case, emphasizing the hereditary aspect of ALS. This report underscores the significance of considering familial ALS in cases of successive generational involvement with early onset, a phenomenon called anticipation, shedding light on the necessity for further research to unravel the genetic basis by mutation analysis, which may have implications for future treatment.

KEY WORDS:

Familial ALS, Amyotrophic lateral sclerosis, Three-generation case, Early-onset ALS, Anticipation

INTRODUCTION

Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's Disease, is a complex neurodegenerative disorder. It has long captivated attention of neurologist community due to its multifaceted nature, marked by motor neuron degeneration, progressive muscular weakness, and ultimately, significant disability.[1] While the majority of ALS cases, approximately 90%, are of sporadic origin, a unique subset comprising 10% is recognized as familial ALS (F-ALS). F-ALS, as the name suggests, occurs within families and is associated with an inherited genetic predisposition. [2]

'Anticipation', a term defined as early and severe presentation of a disease in successive generations within a pedigree, is a feature typically associated with hereditary neurodegenerative disorders such as Huntington's disease, also emerges within the context of ALS.[3] This lineage emphasis upon early-onset symptoms in successive generations, reflecting an unusual presentation of F-ALS, which notably contrasts with the more common late-onset sporadic cases. The inheritance pattern is evident, with manifestations spanning from the grandfather to the grandson. This case serves as an illustrative and challenging portrayal of the interplay between genetics, familial aggregation, and the devastating clinical course of ALS.

CASES PRESENTATION

Case 1

A 70-year-old man resident of a remote village in Sindh, with a history of hypertension and diabetes, presented with one year history of progressive asymmetrical all four limb weakness and three month history of unrelenting muscle twitches in multiple areas of body. The weakness began in the lower limbs, initially left leg then right leg after a month, eventually involved upper limbs as well, affecting his ability to walk, dress, and perform fine motor tasks. He experienced significant weight loss. There were no bulbar and psuedobulbar symptoms.

The clinical examination revealed mild to moderate cognitive decline with MMSE of 23/30. There were visible fasciculations in the tongue, chin, right lower back, shin of both legs and right arm. Motor system examination showed reduced bulk in all four limbs, gross wasting was appreciated. Tone was reduced in all four limbs, power 3/5 in left lower limb and 4-/5 in right lower limb, and 4-/5 in both upper limbs with weak grip bilaterally. Reflexes were +3 in upper limbs and +1 in lower limb, plantars were bilaterally up going. Sensory, cerebellar, and cranial nerve assessments were unremarkable. Patient was admitted and extensive workup was done. Laboratory and radiological parameters including Xrays and MRI whole spine were within normal limits. Nerve conduction studies showed axonopathy, reduced CMAPs and SNAPs with normal amplitude and velocity. Electromyography showed spontaneous activity and fibrillations in left dorsal interossei, brachioradiallis, biceps, geniglosus, thoracic para-spinal muscles and vastus mediallis muscle. A conclusive diagnosis of ALS was established in accordance with the revised El Escorial criteria (Figure 1).[4]

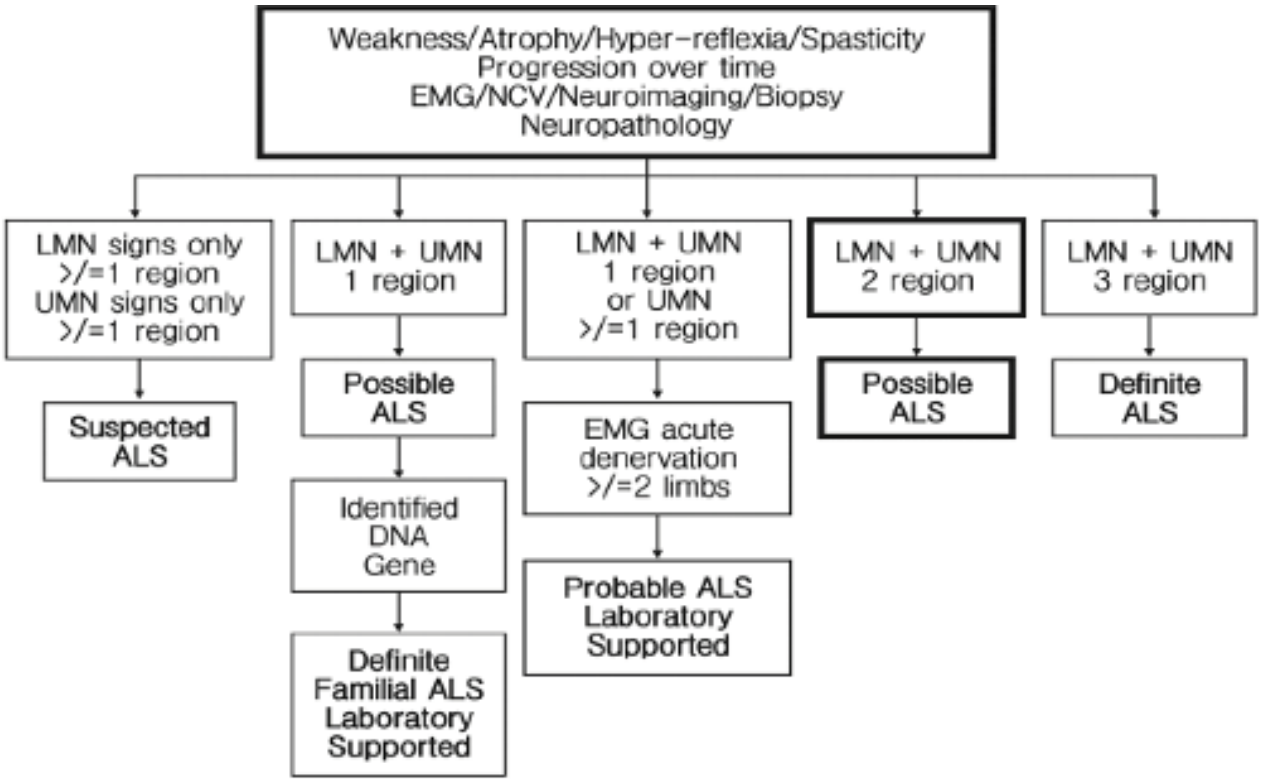

Figure 1: The revised El Escorial criteria
ALS, amyotrophic lateral sclerosis; LMN, lower motor neuron signs; UMN, upper motor neuron signs;Electromyography, electromyography; NCV, nerve conduction velocity

Case 2:
The 51-year old son of index case, a product of interfamily marriage, presented within same time frame with complaints of progressive weakness of all four limbs for six months, asymmetrically involving upper limbs more than lower limbs and generalized body twitching for one month. There were no bulbar symptoms. On motor examination there was reduced bulk with significant thenar and hypothenar wasting, reduced tone, power 3/5 in right upper limb and 4-/5 in left upper limb with weak grip bilaterally. Reflexes were 3+ in upper limbs and 2+ in lower limbs with dowgoing plantars. There were visible fasciculations in both arms and thighs. He also underwent extensive workup and nerve conduction studies revealed reduced CMAPs with normal SNAPs along with signs of denervation and renervation in three body segments (cervical, thoracic and lumbar) on Electromyography, fulfilling El Escorial Diagnostic criteria of Definitive ALS.

Case 3:
The 30-year-old grandson of index case, also a product of interfamily marriage, presented with progressive right leg and left arm weakness for three months and twitching in both legs for 10 days. Patient didn't report any bulbar symptoms. On examination some guttering and thenar wasting was present in left hand, tone was normal in all four limbs, power was 4/5 in left upper limb with weak grip and 4-/5 in right lower limb with +3 reflexes in lower limb and +2 reflexes in both upper limbs, with bilateral flexor planters. Electromyography showed axonopathy with reduced CMAPs and normal SNAPs along with signs of denervation and renervation in two segments (cervical, lumbosacral), fulfilling diagnosis of probable ALS.

A pedigree chart of the index case is demonstrated in Figure 2.

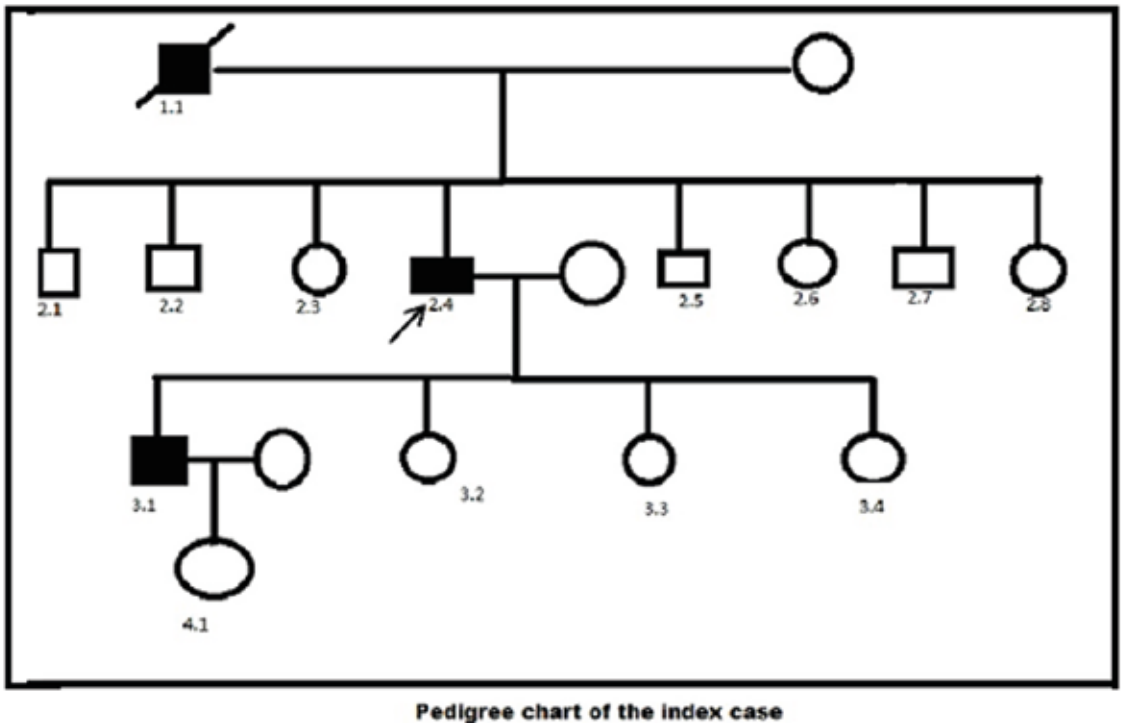

Figure 2: Pedigree chart of the index case

DISCUSSION

Familial ALS is characterized by manifestation of ALS in successive generations, typically following a dominant inheritance pattern with varying degrees of penetrance.[5] In this report, both the initial patient (the index case) and his son were labeled as"definitive ALS" diagnoses in accordance with the El Escorial criteria, amid the involvement of both upper and lower motor neurons across three regions: cranial, cervical, and lumbosacral. While the clinical details of the index case's grandson led to a "probable ALS" diagnosis in line to the El Escorial criteria, this case marks the first documented instance of its kind in Pakistan. Notably, the absence of bulbar symptoms at the onset and the presence of symptoms in the limbs suggest that these patients may have a favorable prognosis with 5-8 years of survival. A small proportion of families have a good prognosis of 5-8 years, while majority are having poor prognosis of less than 2 years.[6] However, genetic testing, a crucial step in confirming genetic mutations, poses a significant hurdle as it's currently unavailable in Pakistan.

Research shows that 40 genes are associated with familial ALS, with four major genes—SOD1, C9orf72, FUS, and TARDBP—accounting for the 70% of familial ALS cases, at least in European populations. Among these, C9orf72 is the most prevalent (around 40%), followed by SOD1 (around 20%). A significant finding is hexanucleotide GGGGCC repeat expansion of the C9ORF72 gene, most commonly reportedmutation in a large number of patients with familial ALS, and this expansion in successive generations is responsible for anticipation.[7] New genes linked to familial ALS are being discovered.[8] Unfortunately, genetic testing, which is the only way to diagnose these mutations, remains unavailable to us.

CONCLUSION

This case series strongly supports link of F-ALS with anticipation, simultaneously it underscores the critical need for genetic testing in the assessment and management of familial ALS (FALS), the main hurdle we faced in our setting. Genetic testing plays a crucial role in predicting patient presentations and deepening our understanding of the disease's genetic roots. This insight can facilitate tailored approaches and of course, genetic counseling, positively influencing patient care.

REFERENCES

1. Rowland LP, Shneider NA. Amyotrophic Lateral Sclerosis. N Engl J Med. 2001;344(22):1688-700.
2. Kulshreshtha D, Singh AK, Maurya PK, Thacker AK. Familial amyotrophic lateral sclerosis from North India: Case report and brief review. Neurol India 2014;62:210-1.
3. Nalini A, Yeshraj G, Veerendrakumar M. Familial amyotrophic lateral sclerosis: First report from India. Neurol India 2006;54:304-5.
4. Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1(5):293-9.
5. Kurland LT, Mulder DW. Epidemiologic investigations of amyotrophic lateral sclerosis. 2. Familial aggregations indicative of dominant inheritance. I. Neurology. 1955 Mar;5(3):182-96. doi: 10.1212/wnl.5.3.182. PMID: 14356347.
6. Chiò A, Logroscino G, Hardiman O, Swingler R, Mitchell D, Beghi E, et al. Prognostic factors in ALS: A critical review. Amyotroph Lateral Scler. 2009;10(5-6):310-23.
7. Gianferrari G, Martinelli I, Simonini C, Zucchi E, Fini N, Carra S, et al. Case report: p.Glu134del SOD1 mutation in two apparently unrelated ALS patients with mirrored phenotype. Front Neurol. 2023;13.
8. Niemann S, Joos H, Meyer T, Vielhaber S, Reuner U, Gleichmann M, et al. Familial ALS in Germany: origin of the R115G SOD1 mutation by a founder effect. J Neurol Neurosurg Psychiatry. 2004;75(8):1186-8.

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