Case Report / Olgu Sunumu
doi: 10.5606/phhb.dergisi.2025.50

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Cerebellar plus phenotype in autosomal recessive cerebellar ataxia type 1: An atypical amyotrophic lateral sclerosis-like presentation

Otozomal resesif serebellar ataksi tip 1'de serebellar plus fenotipi: Atipik amyotrofik lateral skleroz benzeri bir görünüm

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ABSTRACT

Autosomal recessive cerebellar ataxia type 1 is a rare neurodegenerative disorder that typically manifests in adulthood. It is characterized by progressive gait ataxia, dysarthria, dysmetria, mild oculomotor impairments, and diffuse cerebellar atrophy observed in brain imaging. This condition primarily affects cerebellar functions, with minimal involvement of other neurological systems. Herein, we reported a case of a 28-year-old female patient who presented with clinical features resembling amyotrophic lateral sclerosis, deviating from the typical autosomal recessive cerebellar ataxia phenotype. The patient had a 10-year history of progressive lower extremity weakness, speech difficulties, and muscle wasting. Neurological examination revealed spastic and hypophonic speech, muscle wasting, fasciculations, spasticity, and limb ataxia. Brain magnetic resonance imaging showed pancerebellar atrophy, and electromyography indicated widespread denervation findings. Genetic testing identified a pathogenic SYNE1 mutation, associated with amyotrophic lateral sclerosis-like symptoms and cerebellar ataxia. This case highlights the importance of recognizing atypical presentations in neurodegenerative diseases, particularly hereditary ataxias.

Keywords: Amyotrophic lateral sclerosis, ataxia, neurodegenerative diseases.

ÖZ

Otozomal resesif serebellar ataksi tip 1, genellikle erişkin dönemde ortaya çıkan, nadir görülen bir nörodejeneratif hastalıktır. İlerleyici yürüme ataksisi, dizartri, dismetri, hafif okülomotor bozukluklar ve beyin görüntülemesinde gözlenen yaygın serebellar atrofi ile karakterizedir. Bu hastalık esas olarak serebellar fonksiyonları etkiler ve diğer nörolojik sistemlerin tutulumu genellikle minimaldir. Bu yazıda, tipik otozomal resesif serebellar ataksi fenotipinden farklı olarak amiyotrofik lateral skleroz benzeri klinik özelliklerle başvuran 28 yaşında bir kadın hasta sunuldu. Hastada 10 yıldır giderek artan alt ekstremite güçsüzlüğü, konuşma güçlüğü ve kas erimesi öyküsü mevcuttu. Nörolojik muayenede spastik ve hipofonik konuşma, kas atrofisi, fasikülasyonlar, spastisite ve ekstremitelerde ataksi saptandı. Beyin manyetik rezonans görüntülemede panserebellar atrofi izlendi ve elektromyografide yaygın denervasyon bulguları mevcuttu. Genetik analizde amyotrofik lateral skleroz-benzeri semptomlar ve serebellar ataksiyle ilişkili patojenik bir SYNE1 mutasyonu tespit edildi. Bu olgu, özellikle herediter ataksilerde, nörodejeneratif hastalıkların atipik klinik tablolarının tanınmasının önemini vurgulamaktadır.

Anahtar sözcükler: Amyotrofik lateral skleroz, ataksi, nörodejeneratif hastalıklar.

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Received / *Geliş tarihi:* October 08, 2025 Accepted: / *Kabul tarihi:* November 02, 2025 Published online: / *Online yayın tarihi:* December 08, 2025

Citation:
Saltoğlu T, Kurtkaya Koçak Ö, Sücüllü Karadağ Y. Cerebellar plus phenotype in autosomal recessive cerebellar ataxia type 1: An atypical amyotrophic lateral sclerosis-like presentation. Parkinson Hast Harek Boz Derg 2025;28(2-3):20-23. doi: 10.5606/phhb.dergisi.2025.50.

Autosomal recessive spinocerebellar ataxias (ARCAs) are a diverse group of neurodegenerative disorders. These disorders can manifest as either pure or mixed cerebellar syndromes and are associated with a variety of symptoms, including cognitive impairment, oculomotor dysfunction, pyramidal and extrapyramidal signs, and peripheral neuropathy.[1] Autosomal recessive cerebellar ataxia type 1 is an adult-onset condition primarily affecting the cerebellum, presenting with gait disturbances, dysarthria, dysmetria, subtle oculomotor abnormalities, and widespread cerebellar atrophy visible on brain imaging. This disorder is linked to mutations in the SYNE1 (spectrin repeat-containing nuclear envelope protein 1) gene, which encodes a synaptic nuclear envelope protein.[2] It is most commonly observed in Quebec, Canada, with only a small number of cases reported in other countries, including Japan and Saudi Arabia.[3] A multicenter study on SYNE1 mutations revealed that in 50% of patients, the disease initially presents with noncerebellar symptoms, including motor neuron features resembling amyotrophic lateral sclerosis (ALS). Almost all patients exhibit a "cerebellar plus" phenotype, with motor neuron disease being the most commonly associated condition.[4] Herein, we present a case of a female patient exhibiting both cerebellar ataxia and ALS-like symptoms associated with a novel deletion mutation in the SYNE1 gene. This represents one of the rare clinically and genetically confirmed cases from Türkiye, emphasizing the importance for clinicians in this region to consider SYNE1 mutations when encountering such a unique phenotype.

CASE REPORT

A 28-year-old female patient, born to consanguineous parents, had no family history of similar symptoms. The patient presented with a 10-year history of progressive lower extremity weakness, recurrent falls, and speech difficulties. Five years after onset, she developed tongue twitching and muscle wasting. Upon admission, the patient was dependent on a wheelchair. Neurological examination revealed intact higher cognitive functions. The patient's speech was spastic and dysarthric, with a hypophonic quality. Gaze-evoked nystagmus was absent, and both pursuit and saccadic eye movements were normal. Tongue wasting, weakness, and fasciculations were observed, along with muscle wasting and fasciculations in the intrinsic hand and forearm muscles. The lower limbs exhibited spasticity and pure motor weakness, accompanied by exaggerated deep tendon reflexes, bilateral ankle clonus, and extensor plantar reflexes. The jaw reflex was also brisk. Sensory examination was normal. Limb ataxia was evident through impaired performance on the finger-nose-finger test, and the patient demonstrated a spastic-ataxic gait.

The serum electrolytes, thyroid, and parathyroid tests were within normal limits. Levels of serum alpha-fetoprotein, lipid profile, albumin, protein electrophoresis, vitamin E, and copper were all normal. Fundus examination showed no abnormalities. No Kayser-Fleischer ring was observed during the slit-lamp examination.

Magnetic resonance imaging (MRI) of the brain revealed pancerebellar atrophy (Figure 1). No abnormalities were observed in the cervical, thoracic, or lumbar MRI. Nerve conduction studies showed normal motor and

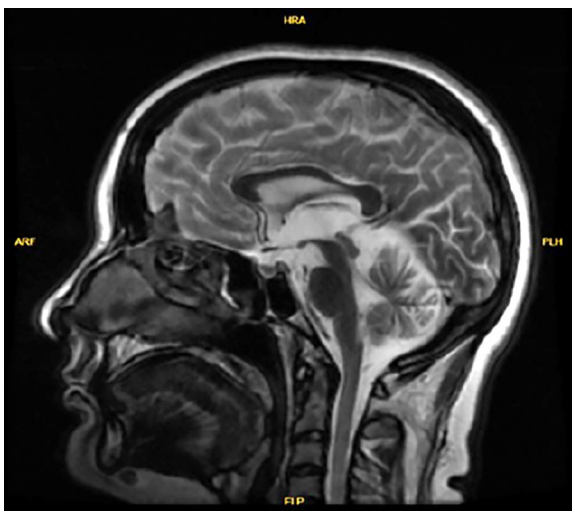

Figure 1. *Magnetic resonance imaging of the brain demonstrates diffuse pancerebellar atrophy, characterized by prominent cerebellar folial widening and volume loss. No abnormalities were detected on cervical, thoracic, or lumbar magnetic resonance imaging.*

sensory conduction velocities and amplitudes. Electromyography revealed fasciculations and chronic denervation, characterized by high-amplitude and long-duration motor unit action potentials, in bulbar and cervical regions and chronic denervation in lumbar segments. These findings were consistent with widespread neurogenic involvement of the motor neurons or their axons, as observed in ALS.

Genetic testing was conducted based on the patient's consanguineous parentage, MRI findings, and speech pattern. A homozygous nonsense mutation was identified in exon 94 of the SYNE1 gene. Sanger sequencing revealed a homozygous C17917C>T (p.Q5973*) (p.Gln5973Ter) mutation in the SYNE1 gene, which has been previously documented and classified as "highly likely pathogenic" in the ClinVar database.[2] This mutation in the SYNE1 gene creates a premature stop codon, consistent with American College of Medical Genetics and Genomics criteria.[5] The result was confirmed using next-generation sequencing (NGS).

Following the diagnosis of ARCA1, genetic testing was conducted on the patient's parents and sister, revealing that all three were heterozygous carriers of the C17917C>T (p.Q5973*) (p.Gln5973Ter) mutation. The family received genetic counseling, and the patient was enrolled in a physical therapy program. Written informed consent was obtained from the patient for publication of this case report.

DISCUSSION

Autosomal recessive cerebellar ataxia type 8 (SCA8), also known as ARCA type 1 (ARCA1) or recessive ataxia of Beauce (MIM 610743), is classified among the ARCAs. It was initially described in 53 French-Canadian families, where affected individuals typically exhibit a clinical profile marked by late-onset, slowly progressive pure cerebellar ataxia. The age of disease onset varies from 6 to 42 years, with a median of 14 years. Advances in high-throughput sequencing technologies have led to the identification of SYNE1 variants causing ARCA1 globally. In about 50% of patients, the initial symptoms are noncerebellar, often resembling ALS-like motor neuron involvement. Almost all individuals exhibit a "cerebellar plus" phenotype, with motor neuron disease being the most commonly associated feature.[4,6] Nearly all SYNE1 mutations are unique to individual cases, requiring the sequencing of all 146 exons for accurate diagnosis.

The SYNE1 gene encodes nesprin-1 (nuclear envelope spectrin 1), a very large protein consisting of 8,749 amino acids. It contains two calponin homology domains, 74 spectrin repeats, and a C-terminal Klarsicht/ANC-1/Syne homology (KASH) domain. As a member of the spectrin protein family, nesprin-1 is crucial for maintaining nuclear-cytoskeletal connections. In SYNE1-related disorders, the loss of nesprin-1 function is considered the primary pathological mechanism.[7,8]

Nesprin-1 is a structural protein with diverse functions, which can lead to a variety of clinical manifestations. These include cognitive deterioration, delayed saccades, ophthalmoparesis, brainstem involvement, as well as musculoskeletal conditions such as kyphoscoliosis, pes cavus, and arthrogryposis multiplex congenita syndrome.[9]

Our case presents a distinct cerebellar plus phenotype and is the third such case reported in Türkiye. This report underscores the frequent association of motor neuron involvement with ARCA1. The diagnosis in our case was initially made using Sanger sequencing, but it was also confirmed through NGS.

Since NGS is more cost-effective than Sanger sequencing, it should be considered the preferred method for initial testing. Next-generation sequencing technology allows for the parallel sequencing of millions to billions of short DNA (deoxyribonucleic acid) fragments. When multiple genes are implicated in a disease, such as ataxia, NGS proves to be more affordable and efficient than Sanger sequencing. It is highly accurate, rapid, and cost-effective, making it a valuable tool in

identifying novel genetic mutations through whole genome or whole exome sequencing.[9]

In conclusion, this case represents the third reported instance of the cerebellar plus phenotype in Türkiye, emphasizing that the disease may also manifest with noncerebellar symptoms.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, references and fundings, materials: Ö.K.K.; Design, data collection and/or processing, analysis and/or interpretation, literature review, writing the article: T.S.; Control/supervision, critical review: Y.S.K.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Arias M, Mir P, Fernández-Matarrubia M, Arpa J, García-Ramos R, Blanco-Arias P, et al. Autosomal recessive spinocerebellar ataxia SCAR8/ARCA1: First families detected in Spain. Neurologia (Engl Ed) 2022;37:257-62. doi: 10.1016/j.nrleng.2019.01.014.
2. Noreau A, Bourassa CV, Szuto A, Levert A, Dobrzeniecka S, Gauthier J, et al. SYNE1 mutations in autosomal recessive cerebellar ataxia. JAMA Neurol 2013;70:1296-31. doi: 10.1001/jamaneurol.2013.3268.
3. Swan L, Cardinal J, Coman D. SYNE1-related autosomal recessive cerebellar ataxia, congenital cerebellar hypoplasia, and cognitive impairment. Clin Pract 2018;8:1071. doi: 10.4081/cp.2018.1071.
4. Mademan I, Harmuth F, Giordano I, Timmann D, Magri S, Deconinck T, et al. Multisystemic SYNE1 ataxia: Confirming the high frequency and extending the mutational and phenotypic spectrum. Brain 2016;139:e46. doi: 10.1093/brain/aww115.
5. Amendola LM, Jarvik GP, Leo MC, McLaughlin HM, Akkari Y, Amaral MD, et al. Performance of ACMG-AMP variant-interpretation guidelines among nine laboratories in the clinical sequencing exploratory research consortium. Am J Hum Genet 2016;98:1067-76. doi: 10.1016/j.ajhg.2016.03.024.
6. Gros-Louis F, Dupré N, Dion P, Fox MA, Laurent S, Verreault S, et al. Mutations in SYNE1 lead to a newly discovered form of autosomal recessive cerebellar ataxia. Nat Genet 2007;39:80-5. doi: 10.1038/ng1927.
7. Spagnolo F, Monfrini E, Pinto V, Di Maggio G, De Marco P, Comi GP, et al. Tremulous spastic ataxia in a patient with a homozygous truncating SYNE1 variant. Clin Park Relat Disord 2023;9:100205. doi: 10.1016/j.prdoa.2023.100205.
8. Yoshinaga T, Nakamura K, Ishikawa M, Yamaguchi T, Takano K, Wakui K, et al. A novel frameshift mutation of SYNE1 in a Japanese family with autosomal recessive cerebellar ataxia type 8. Hum Genome Var 2017;4:17052. doi: 10.1038/hgv.2017.52.
9. Nadaf SN, Chakor RT, Kothari KV, Mannan AU. Synaptic Nuclear Envelope Protein 1 (SYNE 1) Ataxia with amyotrophic lateral sclerosis-like presentation: A Novel Synaptic Nuclear Envelope Protein 1 (SYNE 1) gene deletion mutation from India. Ann Indian Acad Neurol 2020;23:539-41. doi: 10.4103/aian.AIAN_448_18.