Atypical Ataxic-Spastic Syndrome with *SYNE1* Variant Association

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INTRODUCTION

The spectrin repeat-containing nuclear envelope protein 1 (*SYNE1)* gene encodes a family of structural proteins crucial for linking the nuclear envelope to the cytoskeleton [1]. **Mutations in *SYNE1*** have been linked to a form of slowly progressive autosomal recessive cerebellar ataxia, also known as autosomal recessive spinocerebellar ataxia type 8 (ARCA1/SCAR8) [2]. This condition predominantly causes **cerebellar ataxia** with moderate **extra-cerebellar symptoms** [2]. Typically, brain magnetic resonance imaging (MRI) reveals cerebellar atrophy, but cases with **heterogeneous brain MRI** findings have been reported, making diagnosis challenging [1].
We present a case of SCAR8, with an emphasis on the patient's progressive neurological deterioration over eighteen months and peculiar brain imaging findings.

CASE PRESENTATION

This 42-year-old gentleman with a history of delayed psychomotor development, childhood-onset hearing loss, and moderate intellectual disability, presented with acute onset **dizziness**, **speech hesitancy**, and **ambulatory difficulties** (SARA:6/40). No neurological disorders were reported on the family history and his parents had a non-consanguineous marriage.
Extensive investigations to rule out metabolic causes and other autoimmune/paraneoplastic potential conditions were performed. Notably, brain MRI findings showed **bilateral thalamic** and **midbrain hyperintensity** (Figure 1). Whole-exome sequencing (WES) followed by targeted Sanger sequencing pinpointed a homozygous likely pathogenic missense **variant** in the ***SYNE1* gene** (**NM_033071, exon 13:c.G1162A:p.D388N, rs146366996**), consistent with a diagnosis of SCAR8.
Over the ensuing eighteen months, the patient presented **a progressive worsening** of ataxic and spastic symptoms, alongside marked dysarthria and dysmetria, and occasional dysphagia for solids (SARA:28/40). No significant variations were observed on the 18-month follow-up brain MRI after thiamine supplementation.

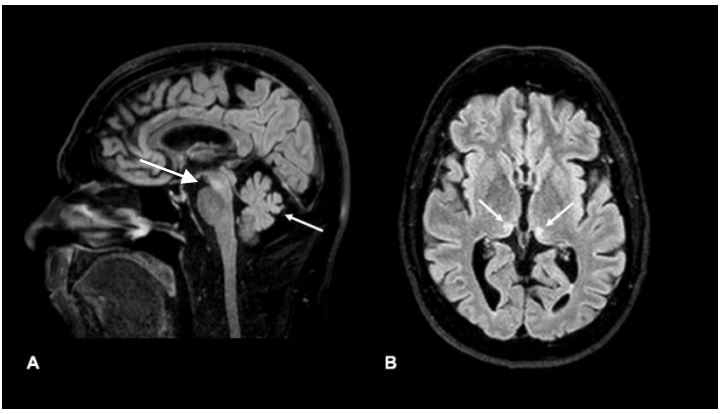

Figure 1.
Brain MRI showed mild cerebellar atrophy, and **hyperintensity** of the **midbrain** (A) and **thalami bilaterally** (B) in sagittal and axial FLAIR sequences, respectively.

DISCUSSION

This case highlights the importance of grounding diagnostic decisions in clinical evaluation, especially when genetic findings are identified in a phenotype that raises suspicion for hereditary ataxia. It also underscores the need for continued research into potential modifying genetic factors, the **evolving phenotypic spectrum of *SYNE1*-associated disorders**, and targeted therapeutic approaches.
The patient's presentation with bilateral thalamic and midbrain hyperintensity is noteworthy. While these lesions are not commonly associated with *SYNE1* disorders in the existing literature, this finding raises the possibility of either a previously unrecognized aspect of the condition or an incidental observation.
No previous studies have explicitly identified our *SYNE1* variant as pathogenic, and its role remains uncertain in the absence of direct functional studies or further clinical evidence.

REFERENCES

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