Mutation, metal and misfiring immunity: A case of spinocerebellar ataxia 45 with autoimmune and Wilsons crossroads

By Anuhya Chadalawada

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Mutation, metal and misfiring immunity: A case of spinocerebellar ataxia 45 with autoimmune and Wilsons crossroads

Anuhya Chadalawada, Lakshmi Narasimhan Ranganathan, Rithvik Ramesh, Sundar Shanmugam, Philo Hazeena

[1]Department of Neurology, Sri Ramachandra Institute of Higher Education and Research Porur, Chennai, India

Corresponding author:
Anuhya Chadalawada
E-mail: anuhya.chad@gmail.com

ABSTRACT

Spinocerebellar Ataxia type 45 is a rare autosomal dominant neurodegenerative disorder caused by FAT2 gene mutations primarily affecting the cerebellum. Until now only six cases were described worldwide, including one from India. They presented predominantly with late onset cerebellar ataxia. We present a unique case of 45-year-old female with FAT2 gene mutation, presenting with cerebellar ataxia, proximal weakness and extra pyramidal symptoms. Her investigations revealed ATP7B mutation linked to Wilson disease, and ANA, Ro-52 positivity additionally. This case describes the complex genetic and autoimmune overlap and possible SCA 45 phenotypic spectrum.

Keywords: spinocerebellar ataxia type 45, FAT2 gene, ATP7B, Ro-52.

Abbreviations:

ANA – anti nuclear antibody

SCA – spinocerebellar ataxia

BACKGROUND

Spinocerebellar ataxia is a group of autosomal dominant, genetically and phenotypically heterogeneous neurodegenerative disorders, presenting with cerebellar dysfunction. Until now over 50 subtypes of SCA have been described [1]. SCA 45 is due to heterozygous mutation in FAT 2 gene, whose protein primarily localizes to parallel fibers of cerebellum. Until now, six cases were described worldwide including one from India. Predominantly these 6 cases were phenotypically characterized by late onset cerebellar dysfunction and 1 among which presented as CANVAS. Here we describe a 45-year-old patient with FAT 2 mutation presenting with cerebellar dysfunction along with proximal myopathy and extrapyramidal symptoms.

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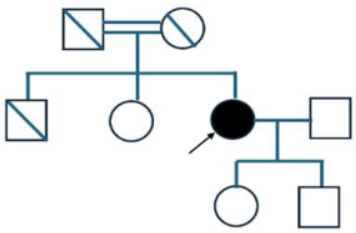
CASE REPORT

A 45-year-old female presented with a 5-year history of insidious onset gradually progressive weakness of her proximal lower limbs characterized by difficulty in climbing stairs and getting up from squatting position. This weakness was uncharacterized with no wasting, twitching or muscle tightness and progressed to subsequently involve truncal and neck muscles. There was no history to suggest distal lower limb or upper limb weakness. A few months after the onset of weakness, patient noticed unsteadiness and swaying while walking, which worsened on walking over uneven surfaces. For the last 1 year, she developed tremulousness of bilateral upper limbs when reaching for an object along with slurred speech and slowness of activities. There was no history of prior drugs intake and exposure to heavy metals. She had respiratory tract infection 5 years ago for which CT-Thorax done revealing linear fibrosis with traction bronchiectasis in left upper lobe. Her family history was significant for a 3rd degree consanguinity, Parkinsonism in her father, and Wilson disease in her brother (Figure 1).



(Figure 1): Pedigree chart of the patient

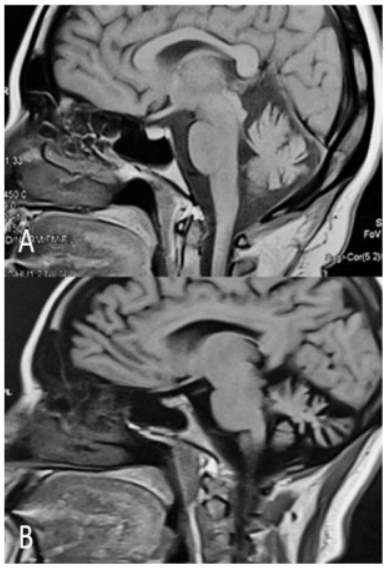
On cognitive testing, the patient scored 28/30 on the MOCA, while cranial nerve examination displaying a dysarthria speech, along with gaze-evoked nystagmus (more pronounced on the right than the left). Spinomotor examination showed cogwheeling rigidity, with normal muscle bulk and strength in the upper limbs, while the lower limbs had proximal power rated at 4/5 and distal power at 5/5 bilaterally with absent ankle reflexes bilaterally and bilateral flexor plantar responses. Finger-to-finger and finger-to-nose testing were impaired on both sides, and the patient was unable to perform tandem walking. Extrapyramidal examination, revealed a mask-like facial expression, an accommodative glabellar tap response, bradykinesia in both upper and lower limbs, kinetic tremors, and no cogwheel rigidity (UPDRS-38). The patient's gait was broad-based with evident ataxia (SARA score 20).

Considering the age, duration, family history and insidious nature of progression, Differential diagnosis included hereditary, Spinocerebellar ataxia –possibly AD, Wilson (In view of young onset tremors along with family history) and autoimmune mediated considering two different system's involvement. Hemogram, liver and renal panel were normal. TSH was elevated. Initially her Brain magnetic resonance imaging (MRI) revealed generalized mild cerebellar atrophy (Figure-2). ANA done initially - 2 positive with no specific pattern, Serum CPK was normal, Ro-52, CENP, DFS-70 -strongly positive. EMG and NCS were normal.

Patient was treated with pulse steroids after which she appeared to improve symptomatically. Subsequently the patient had static course until 2022. In view of worsening symptoms, repeat EMG and NCS done showing myopathy changes with early recruitment pattern especially in proximal muscles, no evidence of neuropathy. Repeat CPK was normal and ANA -3 positive (homogenous and centromere). Serum C3 and C4 levels were in normal range. Her Ceruloplasmin levels, 24-hour urinary copper excretion were normal. Serum copper was elevated. KF ring was negative.

Considering dominant inheritance pattern, spinocerebellar ataxia panel (1, 2, 3, 6, 7, 12) was sent, which was negative. Whole Exome sequencing done revealed- 1. A heterozygous c.3236delinsTT (p.Cys1079PhefsTer2) likely pathogenic variant in the ATP7B gene and a heterozygous c.10001C>A (p.Ala3334Asp) variant of uncertain significance in the FAT2 gene.

Patient was initiated on Zinc therapy along with symptomatic and occupational, speech therapy and is under follow-up.



(Figure -2): MRI-Brain sagittal sequences of the patient showing progressive cerebellar atrophy A) done in 2019 B) done in 2023.

DISCUSSION

We present a case of a middle-aged female with insidious onset, progressive, proximal weakness, cerebellar ataxia and extrapyramidal symptoms. Her investigations revealed three abnormalities. Genetic testing revealed two heterozygous mutations: one in the FAT2 gene associated with Spinocerebellar Ataxia type 45 (SCA45), and another in the ATP7B gene linked to Wilson's disease. Additionally, the patient demonstrated persistent antinuclear antibody (ANA) positivity with Ro-52 antibodies, suggesting an autoimmune component.

The FAT2 gene encodes a cadherin-related protein predominantly expressed in cerebellar granule cells, particularly in parallel fibers [2]. Mutations in this gene have been implicated in SCA45, a rare autosomal dominant cerebellar ataxia characterized by late-onset cerebellar dysfunction. To date, only six cases have been reported worldwide, including one from India, making this the second case from the country and the seventh globally.

Heterozygous missense variation in exon 15 of FAT 2 gene (c.10001C>A) resulting in replacement of alanine by aspartic acid at 3334 codon. Although, this variant is predicted to be damaging according to SIFT and PolyPhen, its presence at a non-conserved position and rarity, been classified as uncertain significance [3].

Six Patients which were described earlier had prominent clinical features including late onset cerebellar ataxia ranging from 50 to 70 of age of onset. However, one case had CANVAS phenotype and other had associated hearing loss and bullous pemphigoid.

The presence of significant cerebellar features in our case, aligns with the SCA 45 phenotype, along with the autosomal dominant inheritance of mixed phenotypes, making this genetic abnormality the most likely cause of the patients' symptoms. Extrapyramidal symptoms can also be part of SCA phenomenology, as can weakness and given that SCA45 is still not fully characterized due to its rarity, it is possible that extrapyramidal symptoms are part of its phenotypic spectrum.

Although the patients copper levels were elevated, the ATP 7B mutation, detected was heterozygous which is less likely to cause Wilsons disease. The resulting in loss of function variant (p.Cys1079PhefsTer2) is novel, and considered likely pathogenic on comparing to the existing loss of function variants of ATP7B [3]. Genetic reports of her brother would have added

value, but they were not available. The persistent ANA positivity with a homogenous and centromere pattern, along with Ro-52 antibodies, suggests an underlying autoimmune process. Ro-52 antibodies are associated with various autoimmune conditions, including dermatomyositis, polymyositis, and overlap syndromes, which can present with proximal muscle weakness. The initial improvement of symptoms following steroid therapy supports this hypothesis. But the normal CPK levels and EMG, lack of specific myositis antibodies, limited response to steroids, and the nature of her symptom progression suggest that her muscle weakness is less likely due to an autoimmune process and more likely due to genetic reasons. However, in a case described by

CONCLUSIONS

We report a second case of SCA 45 described from India, seventh described worldwide and a second sporadic case with different missense mutations illustrating complex genetic and phenotypic presentation with a possible correlation of patient's extrapyramidal symptoms with her novel pathogenic heterozygous mutation at ATP-7B gene without a complete Wilson disease and ANA, Ro-52 antibody positivity to a possibly autoimmune mediated proximal myopathy. However, given the rarity and limited understanding of SCA 45, patient's phenotype may even represent a part of expanded phenotypic spectrum of SCA 45.

Patient consent: Patient Consent - obtained

Conflict of interest: The authors declare that they have no competing interests

Author's contributions:

Dr Anuhya Chadalawada - data curation, interpretation, drafting

Dr. Lakshmi Narasimhan- Conception and design, data acquisition, interpretation, drafting and validation, supervision

Dr.Rithvik Ramesh- Revising and editing it for critical intellectual content

Dr.Sundar. S - Conception, supervision, final approval.

Dr. Philo Hazeena: review and editing, supervision, final approval

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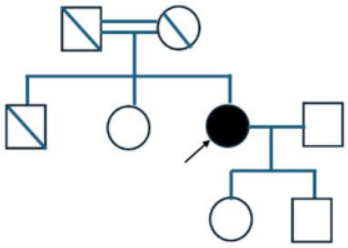
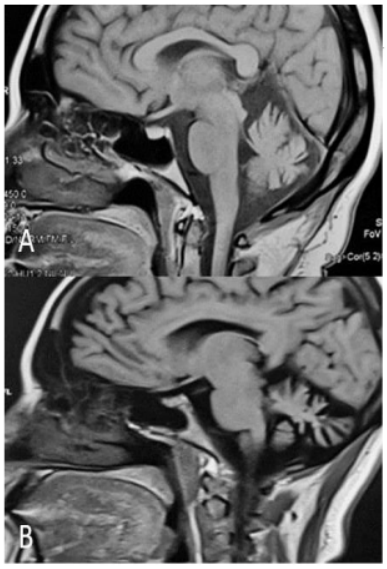
FIGURES, TABLES AND SCHEMES



(Figure 1)- Pedigree chart of patient



(Figure 2) - MRI-Brain sagittal sequences of the patient showing progressive cerebellar atrophy A) done in 2019 B) done in 2023.

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