Spinocerebellar Ataxia 15: The First Reported Case of SCA15 in Asia secondary to ITPR1 Gene Mutation

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ABSTRACT

Background

Spinocerebellar Ataxia (SCA) represents a rare and heterogeneous group of neurodegenerative disorders, typically characterized by the progressive loss of coordination of movement, resulting primarily from cerebellar dysfunction. This case report discusses the history, clinical presentation, and diagnostic findings of a patient who exhibited symptoms suggestive of SCA. Given the notable familial pattern, further evaluation was undertaken using genetic testing. The objective of this paper is to present the clinical, genetic findings, and inheritance pattern of a patient and her family with SCA.

Case Presentation

Our case is a 36-year-old Filipino female with progressive cerebellar dysfunction for over a decade. Cranial Magnetic Resonance Imaging (MRI) revealed bilateral cerebellar atrophy. Genetic testing identified a Variant of Uncertain Significance (VUS) in the inositol 1,4,5-triphosphate receptor type 1 (ITPR1) gene, a finding consistent with Spinocerebellar Ataxia type 15 (SCA 15). This represents the first reported case of SCA 15 in the Philippines and in Asia.

A detailed pedigree assessment revealed that 18 immediate and extended family members had similar symptoms suggestive of hereditary ataxia. Ten relatives had already passed away, and four could not be contacted for further evaluation. Three available family members were examined and likewise demonstrated comparable cerebellar findings, supporting a familial pattern of the disease.

Conclusion

The findings from this case series suggest that SCA 15 may be present in Filipino families, with an autosomal dominant (AD) inheritance pattern. While no data on the prevalence or incidence of SCA15 in the Philippines currently exists, this report calls attention to the need for further research and genetic studies within the Filipino population.

Introduction

Spinocerebellar Ataxia (SCA) represents a rare and heterogeneous group of neurodegenerative disorders, typically characterized by the progressive loss of coordination of movement, resulting primarily from cerebellar dysfunction.[1] Hereditary cerebellar ataxia (HCA) is further classified based on its mode of inheritance. Individuals with early-onset ataxia (age <25 years) and unaffected parents are more likely to have an autosomal recessive (AR) inheritance pattern, whereas a familial history spanning multiple generations is suggestive of autosomal dominant (AD) ataxia.[1] The prevalence of AD-HCA has been reported to range up to 5.6 per 100,000, while AR-HCA is observed in up to 7.2 per 100,000. The global average is approximately 2.7 per 100,000 for AD-HCA and 3.3 per 100,000 for AR-HCA.[2]

In other Asian countries, SCA3 was found to be the most common subtype in China, Thailand, Taiwan, Singapore, and Malaysia, while SCA2 was most prevalent in

India and South Korea. In Japan, both SCA6 and SCA3 were common, with DRPLA (Dentatorubral-pallidoluysian atrophy) being relatively frequent. SCA1 was the most frequently observed genetic subtype in a study from Sri Lanka and also reported in Mongolia. Four families from Cambodia were diagnosed with SCA3, and in Hong Kong, SCA1, SCA3, and DRPLA were identified in a small cohort. Specific subtypes were notably prevalent in certain regions due to founder effects, such as SCA31 in Japan's Nagano district and SCA12 in Northern India. In Thailand, SCA17 was relatively common alongside SCA3, SCA1, and SCA2. High numbers of SCA patients without a known genetic etiology were observed. The median proportions of SCAs with unknown genotypes varied across countries: 33.3% in Chinese studies, 23.4% in Japanese studies, 38.5% in Indian studies, 30.5% in Korean studies, 57% in Thai studies, and 38% in Taiwanese studies.[5]

The clinical manifestations of SCAs are often overlapping, with symptoms such as ataxia, dysarthria, dysphagia, tremors, and imbalance, all of which tend to worsen progressively. Given this, genetic testing is essential for confirming the diagnosis. In the majority of cases, symptoms emerge between the ages of 30 and 50, often accompanied by progressive cerebellar atrophy.[1] SARA (Scale for the Assessment and Rating of Ataxia) scoring, which is a tool for assessing ataxia, is being utilized to assess for the rehabilitation index for gait ability and independence in the performance of daily living activities.[3]

This case report examines the clinical course of our patient, who had a mutation in the inositol 1,4,5-triphosphate receptor type 1 ITPR1 gene. It is the first reported case of SCA15 in the Philippines and Asia secondary to a mutation in ITPR1 gene.

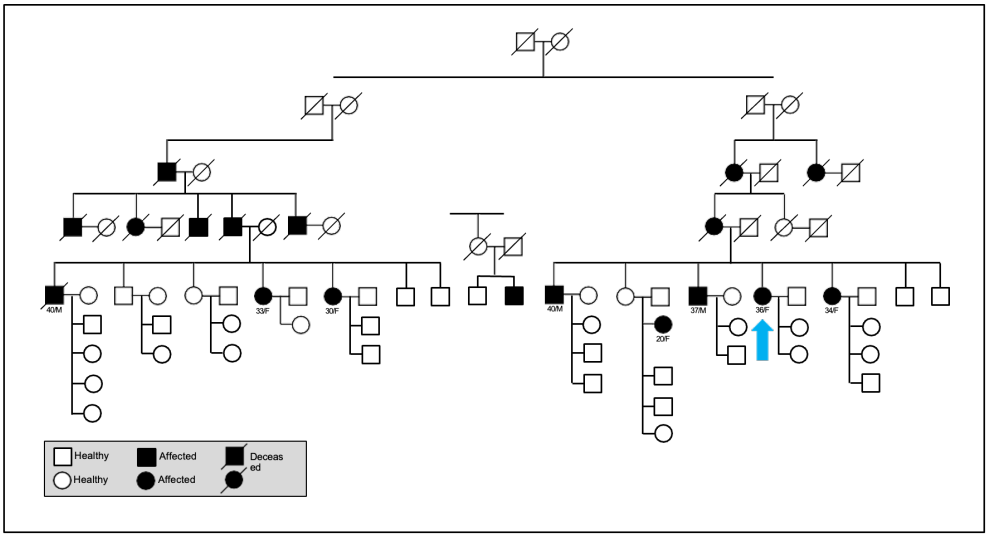
CASE PRESENTATION

Family History of Ataxias

Figure 1 depicts the pedigree chart of this family who resides in the Northern Philippines (Itogon, Benguet). The family tree, meticulously constructed through detailed history taking, includes 18 members, with the youngest being 20 years old. Among the affected relatives, 10 are deceased, the oldest of whom lived to 40 years old. Of the currently symptomatic relatives, only 3 were able to consent to the genetic test, while other family members could not be reached. History and examination of the contacted family members were conducted to assess the presence of symptoms related to the condition.

Our index case, a 36-year-old Filipino female, reported symptoms of

Figure 1. Pedigree chart of the immediate family and distant relatives of the proband patient; the blue arrow identifies the patient in this report.



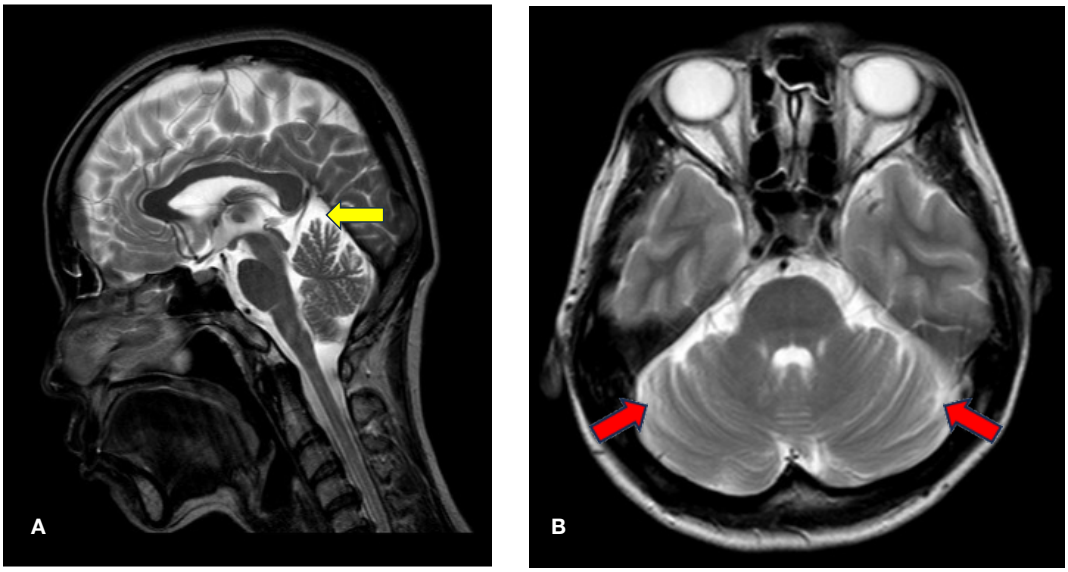
progressive cerebellar dysfunction for over a decade. Her symptoms began with an unsteady gait and dizziness, which progressed to a severe sensation of imbalance, particularly noticeable when playing volleyball. Despite initially ignoring the symptoms, the patient sought medical attention after she began experiencing frequent falls while attempting to look up to hit the ball. SARA score was 7 (gait: 1, stance: 0, sitting: 0, speech: 2, finger chase: 1, nose finger: 1, fast alternating: 1, heel shin: 1). Cranial Magnetic Resonance Imaging (MRI) findings (Figure 2) revealed bilateral cerebellar atrophy, and the patient was diagnosed with cerebellar ataxia. Treatment with Levodopa/Carbidopa 100mg/25mg three times a day resulted in slight symptom relief. However, over time, the patient developed additional symptoms including action tremors of bilateral hands, dysphagia, and scanning speech. She also presented with hypermetric saccades towards the left, abd head titubation while ambulating. Despite medication, the disease continued to progress, suggesting the need for long-term management strategies and ongoing evaluation. The patient eventually consented and underwent genetic testing which identified a Variant of Uncertain Significance (VUS) on the ITPR1 gene.

DISCUSSION

While SCA is rare globally, its prevalence and specific subtypes can vary significantly across different regions, including Asia and the Philippines. The cases described in this series highlight the variable onset and progression of the disease, as well as the importance of recognizing familial patterns of inheritance.

In the Philippines, the prevalence of SCA is not well-documented, but there have been case reports of various subtypes. For instance, a case of genetically-proven SCA2 was reported in a 41-year-old Filipina, marking the first documented case of this subtype in the country.[6] SCA was also well documented in genetically-positive SCA2 in a Filipino family.[7] Other subtypes, such as SCA7, SCA13, and SCA25, have also been reported in other Filipino families.[6] In other Asian countries, the most common subtypes of SCA, in descending order, include SCA3, SCA2, and SCA6. SCA3, also known as Machado-Joseph disease, is particularly prevalent in China, Thailand, Taiwan,

Figure 2. Brain MRI plain and contrast. Image A shows mild atrophy of the cerebellar vermis, more significant in the superior aspect (yellow arrow). Image B shows that the bilateral cerebellar folia are prominent more along the superior cerebellar surface (red arrows).



Singapore, and Malaysia.[5,6,9] SCA2 is most commonly observed in India and South Korea.[5] In Japan, SCA6 and SCA3 are the most frequent subtypes, with DRPLA also being relatively common. with DRPLA also being relatively frequent.[5,6,9] Specific subtypes like SCA31 in Japan's Nagano district and SCA12 in Northern India are prevalent due to founder effects.[5,6] (for intro)

The rarity and heterogeneity of SCA subtypes in Asia and the Philippines underscore the need for comprehensive genetic testing to better understand the distribution and characteristics of these disorders. The index patient underwent sequence analysis and deletion/duplication testing of 424 genes and turned out VUS in ITPR1 gene, which is associated with AD forms of SCA15 and SCA29. The ITPR1 gene is also associated with AD and AR Gillespie syndrome.[8] The diversity in genetic causes often leads to misdiagnosis or patients being grouped with more common ataxias, resulting in inadequate treatment and management. Since genetic testing is not available in the Philippines, physicians are required to send out specimens to other countries. This is compounded by financial difficulties among patients in this third-world country.

While SCA is a rare and heterogeneous group of disorders, understanding the prevalence and specific subtypes of SCA in Asia and the Philippines is essential for accurate diagnosis, management, and potential treatment advancements. Continued research, collaboration, and improved access to genetic testing and multidisciplinary care are crucial to addressing the challenges posed by these rare and heterogeneous neurodegenerative disorders.

CONCLUSION

This case series underscores the importance of a comprehensive family history and a high index of suspicion in diagnosing hereditary ataxias, particularly when multiple family members are affected. Given the progressive nature of the disease, early intervention and management strategies, including pharmacologic therapy and genetic counseling, are essential. Further research into the genetic basis of SCAs is warranted to better understand the pathophysiology and to develop targeted therapies.

RECOMMENDATIONS

It is recommended that genetic testing be considered for families with multiple affected members to confirm the diagnosis and guide management decisions. A multidisciplinary approach is crucial for managing the symptoms of SCA, involving neurologists, geneticists, rehabilitation medicine specialists, physical therapists, and speech therapists to improve the patient's quality of life. Additionally, raising awareness among healthcare providers about the inheritance patterns and clinical manifestations of SCA is important, as it can lead to earlier diagnosis and more effective interventions.

ABBREVIATIONS

AD	Autosomal dominant
AR	Autosomal recessive
DRPLA	Dentatorubral-pallidoluysian atrophy
$HCAITPR_1$	Hereditary cerebellar ataxia
MRI	Magnetic resonance imaging
SARA	Scale for the Assessment and Rating of Ataxia
SCA	Spinocerebellar Ataxia
VUS	Variant of Uncertain Significance

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None.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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