

Genetically-Proven Spinocerebellar Ataxia 2 In A 41-Year Old Filipina: A Case Report

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Abstract: Introduction. Spinocerebellar ataxia is a group of neurodegenerative disorders characterized by varied clinical presentation of cerebellar dysfunction to cognitive impairment, caused by a CAG trinucleotide repeat expansion. Case presentation. This is a case report of a 41-year old Filipina with a 3-year history of gait imbalance and dysarthria with progression of cerebellar dysfunction overtime associated with cognitive dysfunction, and 3-tier family history of ataxia. On physical examination, there were fasciculations of risorius muscle and tongue with noted atrophy, hyporeflexia and extremity ataxia. Extensive work-up showed normal findings hence exclusion of acquired causes of cerebellar ataxias. The patient was then diagnosed to have Spinocerebellar Ataxia 2 based on the genetic testing and is the first reported in the Philippines. Conclusion. This is the first reported genetically-positive Spinocerebellar Ataxia 2 in the Philippines. The rarity of this disease and scarcity of genetic testing in the country warrants further investigation for treatment advances in the future

Keywords: Ataxia, Ataxin-2, CAG Expansion, Spinocerebellar ataxia 2.

1. Introduction

Spinocerebellar ataxia (SCA) is a group of neurodegenerative disorders associated with mutations in approximately 20 genes, and with a global prevalence of 1:35,000 individuals [1]. SCA is caused by a CAG expansion encoding a polyglutamine tract in the mutant protein. After SCA3, SCA2 is noted to be the second most prevalent type worldwide, accounting for 15% of all cases of SCA [2]. The mean age of presentation is during the third and fourth decade of life clinically presenting with progressive ataxia, dysarthria, tremor, extremely slow saccades, hyporeflexia, and ophthalmoparesis [3,4]. There are a few published case reports of SCA (SCA7, SCA13 and SCA25) afflicting Filipino families and none yet for SCA2. In this study, we present a case of genetically-proven SCA2 in a 41-year old female presenting with gait ataxia and poor saccades.

2. Case Report

The case is a 41-year old female, from Cavite, Philippines, married, college graduate with no comorbidities, initially presenting with a 3-year history of progressive ataxia of gait. A year after, her symptoms now included dysarthria and clumsiness of both hands. Dysphagia, soft high-pitched voice, cognitive dysfunction in short-term memory and attention, and dyspnea on exertion were noted within 2 years from time of first symptom onset. Urinary incontinence and polyuria (15 times in a day) was also noted. Several members of her family (i.e. mother, grandmother, 3 uncles, 2 aunts, and 4 cousins) have the same symptoms (Figure 1) but consanguinity is absent. She has 3 children (19-year old, 12-year old, and 9-year old) who are all asymptomatic. Systemic examination findings are unremarkable. On neurological examination, she has normoproductive speech and poor immediate recall on both mini-mental status examination and Montreal Cognitive Assessment scale. She has negative

ophthalmoplegia, intact saccades and no nystagmus. Fasciculations are noted on the left risorius muscle and tongue, associated with atrophy on the lateral side. Motor and sensory testing showed no deficits. There is dysidiadochokinesia and dysmetria bilaterally, hyporeflexia on deep tendon reflexes and negative Babinski sign, and a wide-based gait, and difficulty in doing tandem walk.

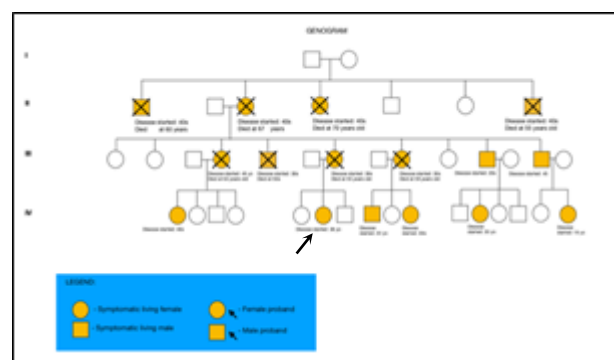


Figure 1: Genogram of index patient. Yellow-filled boxes indicate symptomatic participants. Arrow points to the proband object of this case report.

Extensive work-up for blood chemistry, lumbar puncture and EMG-NCV of all extremities done revealed nonspecific results. MRI of the brain showed moderate to diffuse volume loss involving both cerebellar hemispheres and the pons (Figure 2). Other differential diagnoses (i.e. structural disease, stroke, infectious disease, autoimmune disease, demyelinating disease, psychogenic disorders) were excluded. Furthermore, a hereditary disease with autosomal dominant pattern of inheritance was considered. Genetic studies disclosed an autosomal dominant cerebellar ataxia,

SCA2 as shown in Figure 3.

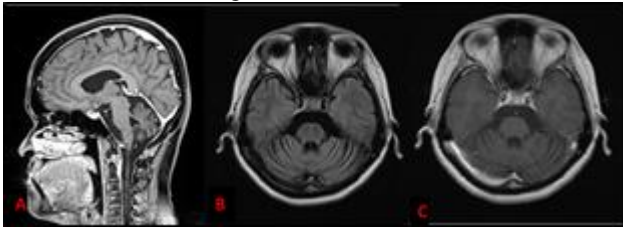


Figure 2: Magnetic resonance imaging, plain study, of the brain of the index patient. (A), Sagittal T1-weighted image showing cerebellar and pons atrophy. (B), Axial T1-weighted image showing partial "hot cross-bun sign" on the pontine region and cerebellar atrophy. (C), Axial T2-FLAIR weighted image showing cerebellar atrophy. FLAIR (fluid attenuated inversion recovery)

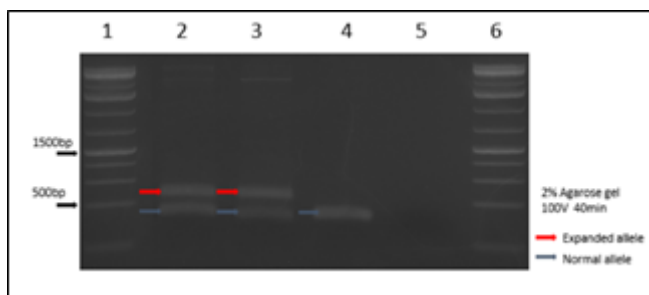


Figure 3: Genetic testing results of index patient. Lane 1 and lane 6 are size markers (1kb ladder), lane 2 is specimen of patient, lane 3 is positive control, lane 4 is normal control and lane 5 is negative control. Since abnormal repeat expansion was found as same as ATXN2, it is considered that there is a strong possibility that SCA2 is the cause of the disease.

3. Discussion

SCA2 is caused by an expansion of a CAG repeat at ATXN2 with 32-33 glutamines in Ataxin-2 [5]. Ataxin-2 is a ubiquitously expressed protein in Purkinje neurons, midbrain, medulla, large neurons in substantia nigra and trochlear neurons. Its function is still unknown and studies on knock-out Ataxin-2 rats are viable, suggesting that it is not essential in development despite its widespread expression [6]. It is hypothesized that it functions in RNA processing, regulation of calcium release from endoplasmic reticulum, and assembly of stress granules and endocytic trafficking of epidermal growth factor receptor. The CAG expansion in the ATXN2 gives rise to an abnormal polyglutamine sequence in the Ataxin-2 protein, resulting in a gain of a toxic function that leads to oligomerization in neurons [7]. Studies show that unequivocal diagnosis of SCA2 depends on the molecular test, the combination of early saccade slowing, hyporeflexia, severe tremors and myoclonus is suggestive of a clinical diagnosis [8]. As the disease becomes florid, cerebellar symptoms become constant with associated abnormal eye movements (slow saccades and supranuclear ophthalmoplegia) and peripheral neuropathic signs (decreased or absent reflexes and vibration sense) [9]. The patient initially presented with elaborate cerebellar dysfunction (gait ataxia, dysmetria, dysarthria), and lower motor neuron signs (fasciculations and tongue atrophy). Contrariwise, dysphagia and sphincter disturbances are prominent in late stages of the disease [10]. Additionally,

cognitive defects occur in one-fourth of patients during the moderate stage of the disease and affect domains including executive function, verbal memory and visuo-spatial abilities [11,12]. Retrieval memory has been affected in the patient. Lower motor neuron signs (fasciculations and atrophy) and cramping pains are uncommon in this SCA type [9]. Interestingly, the most frequent ATXN2 repeat length is 22 repeat consisting of the (CAG)₈CAA(CAG)₄CAA(CAG)₈ trinucleotide sequence. These CAA codons do not alter the amino acid residue but can result in branched structures at the nucleic acid level which correlates to produce more heterogenous clinical phenotype resembling a multitude of parkinsonian and neurodegenerative disorders, including progressive supranuclear palsy, multisystem atrophy and amyotrophic lateral sclerosis [14]. The disease progresses to the use of assistive devices 12-25 years after the disease onset [13]. The mean progression rate is 1.49 per year at the Scale for Assessment and Rating of Ataxia with earlier age at onset being associated with faster progression [14]. As with variable presentation of this disease, there is still no definite treatment. Furthermore, management mainly consists of symptomatic treatment and rehabilitation. Dopaminergic and anticholinergic treatments decrease extrapyramidal symptoms, whereas painful muscle contractions can be alleviated by magnesium, quinine, mexiletine or high doses of vitamin B [14]. Rehabilitation does not stop disease progression but can improve motor performances and even speech [2]. The symptomatology in the patient (more florid and faster progression) did not follow the natural course of SCA2 as described in published literatures. Whether there is a difference in the symptomatology of SCA in Asian versus Caucasians is still unknown. Moreover, the exact natural history of the disease has not been established yet hence a need to investigate and explore the different manifestations of this disease so as to develop avenues for treatment especially in the presymptomatic stage.

4. Conclusion

The patient presented with florid signs of cerebellar dysfunction, urinary disturbances and cognitive defects involving memory without ocular involvement. Literature on hereditary spinocerebellar ataxias, mainly SCA2 are limited and involve patients who came from a European or Cuban descent. In fact, there has been limited data regarding SCA affecting Filipinos. Genetic studies should be explored and recommended in such patients presenting similarly to aid not only in diagnosis but in counseling of other family members as well.

5. Acknowledgements

I extend my sincerest appreciation to Dr. Hiroshi Doi, MD, PhD and Dr. Shingo Ikeda, MD, of Yokohama City University, Japan for providing genetic data on this patient.

6 References

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