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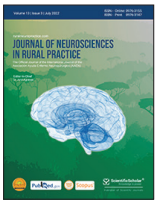

Case Report

Spinocerebellar ataxia 46 in a young female

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ABSTRACT

Spinocerebellar ataxias (SCAs) are a group of both clinically and genetically heterogeneous neurodegenerative disorders. SCA 46 is a rare autosomal dominant ataxia initially described in a Dutch family, clinically characterized by ataxia, peripheral neuropathy, cerebellar dysarthria, and varied oculomotor abnormalities. SCA 46 has recently been discovered to be associated with a mutation in phospholipase D 3 gene.

Keywords: SCA 46, PLD3 gene, Autosomal dominant inheritance

INTRODUCTION

Spinocerebellar ataxias are generally divided into early onset recessive ataxias and late onset dominant ataxias based on the age of onset.We report a rare case of a young female presenting with autosomal dominant cerebellar ataxia associated with sensorineural hearing loss,peripheral neuropathy and mutation in phospholipase D3 gene.

CASE

A 20-year-old female born out of non-consanguineous parentage presented to us with complaints of unsteadiness of gait and weakness of all four limbs. At the age of 13 years, she initially developed defective hearing in both her ears associated with tinnitus, which gradually worsened over the years. About 4 years later, she developed progressive unsteadiness of gait during standing and walking, associated with the clumsiness of hands. She denied the aggravation of unsteadiness in the dark.

For the past 2 years, her speech had gradually become slurred and she also developed gradually progressive flail weakness in both her lower limbs followed by upper limbs. Due to the weakness, she had a severe limitation in the performance of her daily activities and had eventually become completely wheelchair-bound. She also had sensory disturbances over both her legs and hands. Her childhood medical history and family history were unremarkable.

On examination, her cognitive functions were intact. She had scanning dysarthria. Ophthalmological testing showed reduced visual acuity in both eyes and on fundoscopic examination, she was found to have bilateral temporal pallor suggestive of early optic atrophy. Oculomotor examination demonstrated bilateral horizontal gaze-evoked nystagmus. She had bilateral sensorineural hearing loss.

She had symmetrical distal more than proximal weakness (1/5 and 3/5 grading, respectively) in both upper and lower limbs with bilateral wrist drop and foot drop. All deep tendon reflexes were absent and plantar reflex showed no response bilaterally. She had a glove and stocking type of sensory loss. Examination for cerebellar signs showed titubation, truncal ataxia, scanning dysarthria, and bilateral horizontal gaze-evoked nystagmus.

Her routine hematological and biochemical investigations were found to be normal. Other parameters such as lipid profile, thyroid profile, serum creatine kinase levels, lactate levels, pyruvate levels, vitamin B12 levels, vitamin E levels, and anti-tissue transglutaminase levels were all within normal limits. The cerebrospinal fluid analysis detected no abnormality. Human immunodeficiency virus enzyme-linked immunosorbent assay, venereal disease research laboratory for syphilis, and autoimmune screen were all negative. Cardiac status was stable with normal echocardiography. Nerve conduction studies showed evidence of severe sensorimotor axonal polyneuropathy. Visual-evoked potential testing demonstrated prolonged P100 latencies in both eyes. Magnetic resonance imaging of the brain revealed diffuse cerebellar atrophy [Figures 1 and 2].

Nerve biopsy from the sural nerve showed features suggestive of acute on chronic axonal neuropathy and muscle biopsy showed neurogenic changes with no distinct

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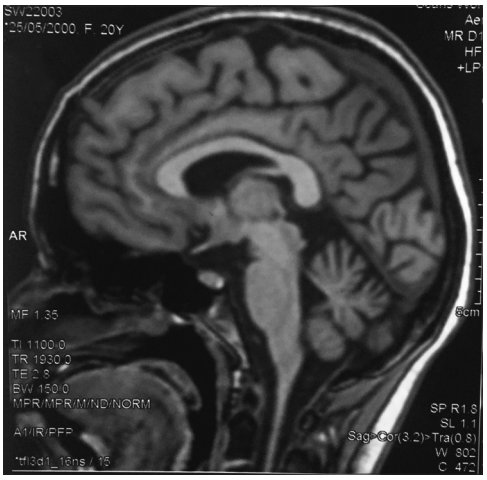

Figure 1: T1 sagittal image of brain showing diffuse cerebellar atrophy.

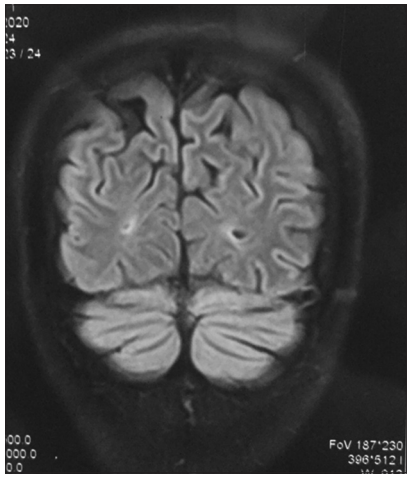

Figure 2: T2 fluid-attenuated inversion recovery image of brain showing diffuse cerebellar atrophy.

ragged red fibers. Frataxin gene mutation testing came out negative and whole mitochondrial genome sequencing detected no abnormality. Clinical exome sequencing detected phospholipase D family member 3 (PLD3) mutation associated with spinocerebellar ataxia (SCA) 46, carrying the c.77T>C; p.Ile26.Thr variant.

DISCUSSION

Our patient, a young lady, had a gradually progressive neurological illness of 7 years duration, beginning with sensorineural hearing loss at 13 years of age, followed by pancerebellar ataxia, scanning dysarthria, and sensorimotor axonal neuropathy as the predominant features. She also had early optic atrophy and gaze-evoked nystagmus on examination. Initially, Friedreich's ataxia and vitamin E deficiency-related ataxia were considered and ruled out.

Mitochondrial disorders with ataxias were considered as a major differential. Mitochondrial ataxias as we know may have a constellation of variable neurological manifestations including neuropathy, diabetes, myoclonus, retinopathy, deafness, ophthalmoplegia, seizures, cognitive disturbances, and psychiatric symptoms. Mitochondrial recessive ataxia syndrome is one such mitochondrial disorder caused due to POLG1 mutations.[1] Whole mitochondrial genome sequencing performed in our patient came out negative and there was no evidence of mitochondrial disease on muscle biopsy.

Van Dijk *et al*., in 1995, described the clinical and electrophysiological findings in a Dutch family affected over two generations with ataxia and polyneuropathy.[2] In their study, Van Dijk *et al*. identified four affected siblings and their deceased father who shared similar phenotypic presentation.

In 2017, Nibbeling *et al*.[3] published follow-up findings from the members of the same Dutch family reported by van Dijk *et al*. In their study, Nibbeling *et al*. used a combination of whole exome sequencing, targeted sequencing, and gene network analysis; re-evaluation of the Dutch kindred by Nibbeling *et al*. revealed a combination phenotype of cerebellar ataxia and sensory neuropathy. Most of the affected members showed dysarthria and variable oculomotor abnormalities such as jerky pursuits, square wave jerks, downbeat nystagmus, gaze-evoked nystagmus, slow saccades, and saccadic dysmetria. All the affected had late disease onset after the fourth decade with the average age of onset being 53.5 years and had a slowly progressive disease course.

In our case by clinical exome sequencing, we were able to identify a PLD3 mutation carrying the c.77T>C; p.Ile26. Thr variant. As discussed above, PLD3 mutation was recently found to be associated with SCA type 46, based on the results of a study by Nibbeling *et al*., in 2017. Our case demonstrated many clinical features consistent with the Dutch kindred described by Nibbeling *et al*., such as cerebellar ataxia with evidence of cerebellar atrophy on imaging, dysarthria, and severe axonal neuropathy. Our patient also had gaze-evoked nystagmus on examination, one of the various oculomotor abnormalities earlier described in the Dutch family.

However, our patient had an earlier onset at 13 years of age and also had severe sensorineural hearing loss as the initial clinical manifestation along with optic atrophy, both of which were not described in the Dutch family. With the phenotypic manifestations of SCA 46 still being not specific and with no formal diagnostic criteria existing, genetic testing is the only possible way to make a confirmative diagnosis. This highlights the need for the advancement of the currently available genetic testing methods to identify new mutation variants and to assess their functional consequences.

CONCLUSION

This case highlights the varied presentation of SCAs and the significance of genetic testing as a part of ataxia evaluation. To the best of our knowledge, this is the first reported case of SCA 46 from India and outside the Dutch kindred described earlier. Our case provides further insight into the clinical phenotype and genotype of SCA 46; also agreeing with the need for further screening to identify new damaging variants in recently identified causative genes of SCAs.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of Artificial Intelligence (AI)-Assisted Technology for manuscript preparation

The author(s) confirms that there was no use of Artificial Intelligence (AI)-Assisted Technology for assisting in the writing or editing of the manuscript and no images were manipulated using the AI.

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