Short Report

Bilateral Vestibulopathy Aggravates Balance and Gait Disturbances in Sensory Ataxic Neuropathy, Dysarthria, and Ophthalmoparesis: A Case Report

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Abstract

In patients with a triad of sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO), the presenting features are mainly ataxia or ptosis. SANDO patients often have impaired balance and gait, which is not surprising considering the combination of sensory ataxic neuropathy, and additional symptoms like cerebellar ataxia and limb girdle weakness. We describe a SANDO patient who noticed an increasingly impaired balance and gait, without any dizziness. Neurological investigation revealed an external ophthalmeplegia and a cerebellar ataxia; the head impulse test was not reliable because of eye movement disorders. The caloric reflex tests showed lack of responses on both sides, compatible with severe bilateral vestibulopathy. Making the diagnosis of bilateral vestibulopathy in SANDO patients may have implications for the management of the patient, because specific vestibular rehabilitation can improve gaze and postural stability.

Key Words: SANDO, bilateral vestibulopathy, balance, ataxia

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INTRODUCTION

In 1997, 4 patients were described with a triad of sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO), which has long been considered as part of the chronic progressive external ophthalmoplegia (CPEO) spectrum.[1] However, a recent study showed that the combination of progressive external ophthalmoparesis and sensory ataxic neuropathy (SAN) is associated with a specific genetic profile. Compared to CPEO patients without SAN, SANDO patients have a much higher frequency of multiple mitochondrial DNA (mtDNA) deletions.[2] Multiple mtDNA deletions are generally caused by mutations in mtDNA maintenance genes, in the case of SANDO mostly in the polymerase gamma 1 (*POLG*) and Twinkle helicase (*C10orf2*) genes. Because of this specific genetic profile, SANDO is increasingly being recognized as a distinctive mitochondrial phenotype.

The presenting features in SANDO are mainly ataxia (67%) or ptosis (24%).[2] Mean age at onset is 32 years, though the range is considerable (5–73 years). In addition to the 3 key clinical features making up the acronym, additional symptoms include cerebellar ataxia, limb girdle weakness, diabetes, seizures, cognitive impairment, and dysphagia.

SANDO patients often have impaired balance and gait, which is not surprising considering the combination of SAN, cerebellar ataxia, and limb girdle weakness. In our personal experience however, gait and balance are more profoundly impaired than in patients with similar degrees of neuropathy, ataxia, or muscle weakness.[3,4]

In this report we describe a SANDO patient with severe bilateral vestibular loss. We hypothesize that in this particular patient, bilateral vestibular loss might have aggravated the already impaired balance and gait.

Balance and Gait Disturbances in SANDO

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CASE REPORT

A 54-year-old man first noted ptosis at the age of 34. Over the years he developed several other symptoms including an external ophthalmoplegia, generalized mild muscle weakness, a length-dependent sensory deficit, areflexia, and mild cerebellar ataxia. Hearing and visual acuity remained unaffected.

Several investigations had been performed in the years following the first presentation. Electromyogram revealed absence of sensory response in both arms and legs and neurogenic motor units, more profoundly in distal than in proximal muscles. Head magnetic resonance imaging showed both cerebellar and cerebral atrophy. Electrocardiograms were always normal.

At age of 36 a muscle biopsy was taken from the right quadriceps. Muscle histology was unremarkable. Assessment of the mitochondrial respiratory chain enzymes revealed a moderately decreased complex III activity (68% of the lower normal limit), and a complex I activity around the lowest reference value, whereas complex II and citrate synthase activities were well above the mean of the reference value.[5,6] Genetic investigations revealed multiple mtDNA deletions, which were associated with 2 compound heterozygous mutations c.1399 G > A (p.Ala467Thr) and c.2243 G > C (p.Trp748Ser) in the *POLG* gene (NM_002693). This combination of mutations has been described before in SANDO patients.[2,7]

Two years ago, at the age of 52, the patient noticed increasingly impaired balance and gait, without any dizziness. During fast movements he experienced a blurred vision. He had never been treated with ototoxic medication, aminoglycosides in particular, nor was he using any other medication.

Neurological examination revealed a ptosis on both sides. Eye movements were restricted in horizontal plane; the head impulse test was not reliable because of eye movement disorders. Diffuse weakness was noted in arms and legs; distal sensation in arms and legs was reduced, areflexia was present. There was an uncertainty in walking; Romberg was positive. All other coordination tests were intact.

An audiogram was normal for his age. A new head magnetic resonance imaging confirmed the previous findings of generalized cerebral and cerebellar atrophy, without any abnormalities in the cerebellopontine region.

The caloric reflex tests showed lack of responses on both sides, compatible with severe bilateral vestibulopathy (BV).

Vestibular rehabilitation has been started, with little improvement so far.

DISCUSSION

BV is defined as a bilateral loss of the labyrinthine function and/or the superior vestibular nerve, and might be caused by ototoxic medication (aminoglycosides in particular), Meniere's disease, and several neurodegenerative disorders. To our knowledge, this is the first report of BV in a patient with SANDO, or more specifically, in a patient with a genetic defect in *POLG*.

The clinical presentation of BV can vary significantly. Almost all patients experience decreased gait, especially in the dark or on uneven surfaces. Patients complain about blurred vision during fast head movements (*oscillopsia*), and sometimes about dizziness during fast head movements as well. Finally, patients might experience difficulties with spatial orientation. Dizziness and ear symptoms are less common. Gait is often impaired and patients are generally unable to perform tandem gait. The head impulse test is abnormal in half of the cases. A quarter of BV patients have signs of polyneuropathy and/or cerebellar dysfunction.[8]

BV is a symptom rather than a disease. No cause can be found in half of the patients.[9,10] The prevalence of BV is low, and thus there is often a long diagnostic delay. The course depends mainly on the underlying disease.

The workup of a suspected BV requires caloric and rotatory chair tests. The former

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reveals vestibular hypofunction or areflexia on both sides, the latter, absence of post-rotatory nystagmus after the chair is suddenly stopped.

As in unilateral vestibular loss, vestibular rehabilitation is the treatment of choice in BV.[11,12]

Improved gaze and postural stability is reported in 35%–50%.

In our patient the diagnosis of BV was made more than 20 years after disease onset. One possible explanation is that BV did not develop until late in the course of the disease. However, there is also a possibility that BV had gone unnoticed, because impaired balance and gait may very well have been attributed to other symptoms such as SAN, ataxia, and muscle weakness. This raises the question as to whether the association between BV and SANDO in our patient is coincidental, or that BV is yet another symptom of the already expanding phenotype of *POLG* mutations.

In favor of a causal relationship is the fact that vestibular dysfunctions have previously been associated with other mitochondrial disorders, more particular in some of the patients carrying the mtDNA mutation m.3243A>→G or the m.1555A>→G mutation. The m.3243A > G mutation is associated with mitochondrial phenotypes such as mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes, maternally inherited diabetes and deafness, CPEO, Leigh syndrome, focal segmental glomerolosclerosis, and a variety of overlap syndromes. Moreover, the m.3243A>→G mutations is associated with dysfunction of both the superior and inferior vestibular systems.[13] The m.1555A > G mutation is associated with aminoglycoside induced deafness and vestibular loss. However, there are also reports of patients carrying the m.1555A > G mutation with saccular and inferior vestibular nerve dysfunction, despite never having been exposed to aminoglycosides.[14]

In conclusion, this is the first report of BV in a patient with SANDO caused by *POLG* mutations. Making the diagnosis of BV in SANDO patients may have implications for the management of the patient, because specific vestibular rehabilitation can improve gaze and postural stability.

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