Short Communication

Novel OPA1 mutation featuring spastic paraparesis and intestinal dysmotility

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A 58-year-old man with optic atrophy, spastic paraparesis, axonal sensorimotor peripheral neuropathy and intestinal dysmotility harbors a novel heterozygous missense mutation in the mitochondrial import signal peptide of OPA1. The case underscores the role of OPA1 in the pathogenesis of spastic paraparesis, so far reported only in very few cases, and it adds intestinal dysmotility to the spectrum of adult-onset clinical manifestation of OPA1-associated disease.

1. Introduction

OPA1 (OMIM: 605290) is the leading causative gene of autosomal dominant optic atrophy (DOA), characterized by insidiously progressive bilateral visual loss, optic disc pallor, dyschromatopsia, and centrocecal scotoma [1]. The visual decline usually manifests in early childhood, but there is a pronounced inter- and intra-familial variability in the severity of visual symptoms and some subjects may be asymptomatic [2]. Approximately 20% of OPA1 mutation carriers manifests with a multisystem neurological disorder, the DOA plus phenotype [3]. Bilateral sensorineural hearing impairment in late childhood or early adulthood is a frequent feature, followed by a varying combination of ataxia, myopathy, axonal peripheral neuropathy and progressive external ophthalmoplegia. DOA plus phenotype can also manifest with the clinical phenotype of hereditary spastic paraplegia (HSP) or multiple sclerosis-like picture accompanied by periventricular white matter lesions and unmatched oligoclonal bands in the cerebrospinal fluid. Additional clinical features of DOA plus syndrome include non-insulin dependent diabetes and migraine [3]. Moreover, OPA1 mutations may lead to extracranial organ involvement in the absence of visual symptoms or even optic atrophy [3,4].

OPA1 is a protein located within the inner mitochondrial membrane and plays a key role in mitochondrial fusion. OPA1 pathogenic mutations are scattered through the gene coding regions but concentrate in the GTPase domain and dynamin central region of the protein [5]. Mutations in the GTPase domain carry a higher risk of resulting in DOA plus phenotype [3]. However, mutations in other domains, such as the N-terminal mitochondrial targeting sequence can lead to a multisystem neurological disorder lacking visual symptoms and optic atrophy [4].

Herein, we report the clinical effects of a novel heterozygous missense mutation in the highly basic amino-terminal domain of OPA1.

2. Case report

A 58-year-old male presented for evaluation of visual loss and progressive gait dysfunction. His neurological symptoms manifested at age 6 years, when he was noted to have impaired vision and was diagnosed with bilateral optic atrophy. He was able to keep up with his peers, although “uncoordinated”. In his late 20s, he developed progressive gait dysfunction, followed by speech difficulty and dysphagia. His visual acuity continued to worsen. Around age 40 he started experiencing progressive distal limb numbness, severe constipation sometimes alternating with diarrhea and lack of urge to defecate. In 1.5 years prior to his neurological evaluation he had an unintentional 30 pound-weight loss. His cognitive functions remained intact. Family history was noticeable for “color blindness” in the maternal grandmother; his mother was wearing glasses that corrected her vision but was otherwise healthy until death at age 84.

Neurological examination revealed pale optic discs and markedly reduced visual acuity (he was able to count fingers if placed very close to his eyes), mild bi-facial weakness, spastic dysarthria, mild-to-moderate
distal upper extremity weakness and moderate distal more than proximal lower limb weakness, severe spastic paraparesis, asymmetric hyperreflexia but absent Achilles reflexes, absent plantar responses, and distal pan-modality sensory loss mainly affecting the lower limbs. He was unable to stand independently; he was able to take a few steps with the walker exhibiting a spastic and steppage gait. The rest of his neurological examination was normal, including extra-ocular movements and hearing. He had no pes cavus.

Brain and orbit MRI showed atrophy of the optic nerves and optic chiasm and mild generalized cerebral and cerebellar atrophy (Fig. 1A–B). EMG and nerve conduction studies demonstrated a moderate length-dependent predominantly axonal sensorimotor peripheral neuropathy. Motility studies showed normal gastric emptying, above average small bowel transit rate, reduced colonic activity and slow colonic transit at 24 and 48 h. Sequencing of all OPA1 exons and flanking intronic regions showed a heterozygous novel variant c.312A>G (p.Ile104Met) in exon 2 that is predicted to be pathogenic. Isoleucine at codon 104 is a branched amino acid that is highly conserved across species; the SIFT and PolyPhen-2 algorithms suggest that the variant is deleterious. In addition, p.Ile104Met was not detected in more than 1000 repetitions; the SIFT and PolyPhen-2 algorithms suggest that the variant is deleterious. We hypothesized that the variant could affect the subcellular localization of OPA1, as the carbohydrate moiety of the N-terminal signal peptide [6] which confers the mitochondrial localization of OPA1. The p.Ile104Met could alter the correct targeting of the OPA1 to the mitochondria, and compromise its role in mtDNA maintenance, assembly and stability of the respiratory chain complexes [7]. All this, in turn, could lead to multisystem cellular dysfunction. Many OPA1 mutations have been associated with cytochrome c-oxidase negative fibers on muscle biopsy and muscle mtDNA multiple deletions [3,4]. We do not know if our patient’s OPA1 mutation results in similar abnormalities or in alteration of the muscle mtDNA content because the patient did not have a muscle biopsy.

Intestinal dysmotility can be a facet of various multisystem mitochondrial disorders, such as MNGIE or POLG-associated disease [8]. However, to our knowledge, the patient’s adult onset (in the 5th decade) intestinal dysmotility, as suggested by the slow small bowel and colonic transit and reduced colonic activity, is a newly observed finding in OPA1-related disease. Gastrointestinal dysmotility, mainly consisting of severe constipation, was previously reported in two young siblings, age 3 and 8 years, with OPA1 mutations [9]. However, these two children, who manifested with a severe neuromuscular phenotype in addition to early-onset optic atrophy, were compound heterozygous for two pathogenic OPA1 mutations. Of interest, despite the severe clinical phenotype, they had no mtDNA multiple deletions or depletion in the muscle. As previously suggested for other mitochondrial disorders, the intestinal dysmotility associated with OPA1 mutations could be the result of a visceral mitochondrial myopathy or of an autonomic neuropathy. This finding expands the spectrum of the late manifestations of DOA plus phenotype.

3. Discussion

Up to 20% of OPA1 mutations result in DOA plus phenotype and most of them are located in the GTPase domain of the protein [3]. Our patient harbors a novel OPA1 missense mutation in the basic domain of the protein and presents with a multisystem disorder featured by optic atrophy, spastic paraparesis, sensorimotor axonal peripheral neuropathy and intestinal dysmotility. Only few cases of DOA plus syndrome have been linked to the OPA1 basic domain [3,4], and none of them had spasticity. In addition, clinical evidence for corticospinal tract involvement is uncommon in OPA1-related disorders. Our patient had no structural, inflammatory or other metabolic abnormality to account for the spastic paraparesis. The mutated isoleucine (p.Ile104Met) is located within the third putative cleavage site (RYLLGSAVG) of the mitochondrial import signal peptide [6] which confers the mitochondrial localization of OPA1. The p.Ile104Met could alter the correct targeting of the OPA1 to the mitochondria, and compromise its role in mtDNA maintenance, assembly and stability of the respiratory chain complexes [7]. All this, in turn, could lead to multisystem cellular dysfunction. Many OPA1 mutations have been associated with cytochrome c-oxidase negative fibers on muscle biopsy and muscle mtDNA multiple deletions [3,4]. We do not know if our patient’s OPA1 mutation results in similar abnormalities or in alteration of the muscle mtDNA content because the patient did not have a muscle biopsy.

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Fig. 1. Brain MRI images. Atrophy of the optic nerves and optic chiasm (A, axial T2) and mild generalized cerebral and cerebellar atrophy (B, sagittal T1 FLAIR).
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