

Complex spastic paraplegia as a neurological phenotype in an opa1 patient

Ana Beatriz Cardoso Vanni¹ , Ana Clara Pelicer Pessoni¹ , Henrique Bornelli de Castro¹ , Gustavo Novelino Simão¹ , Zumira Aparecida Carneiro¹ , Charles Marques Lourenço¹ 

ABSTRACT

Introduction: Autosomal dominant optic atrophy (ADOA) is one of the most common forms of inherited optic atrophies and is caused by mutations in the OPA1 gene. Patients affected by this disease usually present visual loss in the first decade of life, and may present extra-ophthalmologic manifestations over the years, configuring a syndrome called OPA1 plus or ADOA-plus. **Objectives:** to report the case of a patient with ADOA-plus syndrome, establishing correlations with cases described in the literature, **Case report:** a 30-year-old female patient was referred for evaluation of progressive optic atrophy associated with symptoms of peripheral neuropathy. At two years of age, she was diagnosed with partial visual loss during a childcare visit. She reported no other associated symptoms during childhood and adolescence. At the age of 20, she presented with difficulty walking, lower limb weakness, and poor balance. At 25, after extensive investigation, a pathological mutation in the OPA1 gene was identified through exome sequencing, confirming the diagnosis of ADOA-plus, and treatment with Coenzyme Q10 was initiated. Currently the patient reports sensory ataxia, progressive decrease in visual acuity, fasciculations and cramps in the lower limbs, dysphagia and dyspnea. **Discussion:** Many patients with ADOA-plus present sensorineural deafness as the most common extra-ophthalmologic symptom, in addition to parkinsonism and dementia, ataxia and ptosis. The patient reported is a case of optic atrophy associated with peripheral neuropathy, ataxia and myopathy. Due to the wide clinical variability of this disease, OPA1 mutations should be investigated in cases of progressive spastic paraparesis associated with optic atrophy, since the possibility of treatment with Coenzyme Q10.

Keywords: Hereditary optic atrophies, Optic nerve diseases, Ataxia, Coenzyme Q10.

1. School of Medicine. Estácio de Ribeirão Preto University Center, Ribeirão Preto, (SP), Brazil

INTRODUCTION

Mitochondrial optic neuropathies are divided into acquired and hereditary; the hereditary ones form a heterogeneous group of diseases, which are characterized by moderate to severe symmetrical bilateral central visual loss, dyschromatopsia, and optic disc pallor¹. Optic atrophy can be characterized as an isolated event or be part of a systemic picture. The most common forms of inherited optic atrophies are Leber's hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA).⁵ Optic atrophy type 1 (OMIM #165500), caused by mutations in the OPA1 gene, is the disease responsible for the largest share of ADOA cases.²

More than 200 pathological mutations in the OPA1 gene have been identified and new mutations continue to be described.³ The human OPA1 gene is a nuclear gene consisting of 30 exons on chromosome 3q28-q29⁴. The protein produced by the gene is a GTPase required for fusion of the inner membrane of mitochondria and maintenance of mitochondrial architecture (Figure 1). Loss of function of this protein, therefore, leads to mitochondrial fragmentation and eventually apoptosis of the retinal ganglion cells.⁸

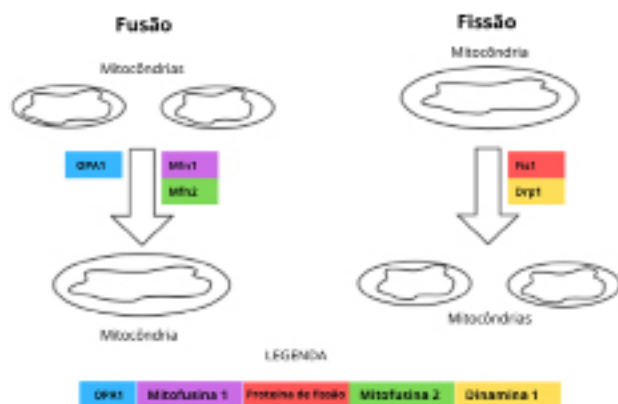


Figure 1. Dynamics of mitochondrial inner membrane fusion carried out by the fusion proteins OPA1, Mitofusin 1 (Mfn1) and Mitofusin 2 (Mfn2) and fission of the same, carried out by the fission protein (Fis1) and Dynamin 1 (Drp1).

Source: The authors (2020).

In patients carrying the OPA1 gene mutation, the most obvious clinical manifestation, visual loss, is observed as early as the first decade of life.⁶ However, a small proportion of these patients subsequently present with extraophthalmological manifestations such as hearing loss, ataxia and myopathy.⁷

The extraophthalmologic manifestations, when they occur in patients with a mutation in the OPA1 gene, configure a syndrome, called OPA1 plus, or ADOA + (OMIM #125250)^{3,4}. The age at which visual loss is established does not vary between ADOA and ADOA+, however patients with extraophthalmic manifestations have more severe visual loss³. The other symptoms appear at least a decade or more after the first symptom, and may settle by the fourth decade of life.³

This study aims to report the case of a patient with ADOA+ syndrome, diagnosed with visual loss in childhood and extraophthalmologic symptoms in adulthood, to elucidate the phenotype of the disease and establish correlations with cases described in the literature.

CASE REPORT

A 30-year-old female patient, daughter of non-consanguineous parents, was referred for evaluation of progressive optic atrophy associated with symptoms of peripheral neuropathy.

Their gestational and neonatal history was uneventful. During pregnancy, there was no exposure to teratogenic agents, she was born at term, and was discharged on the second day of life.

From two years of age on, she presented partial visual loss, which in childcare was assessed as progressive partial visual loss associated with divergent strabismus. During childhood and adolescence, the patient reported no health problems.

At the age of 20 he presented difficulty to walk without support in a straight line, weakness in the lower limbs, unbalance to stand, squat and run. From then on, he started neurological follow-up in which tests such as lumbar puncture, unaltered, and blood tests were requested (Table 1).

Family history revealed no similar family cases of optic atrophy or progressive neurological disease. Patient's mother has a history of "infantile paralysis" (sic).

At 25 years of age, she was referred to the tertiary service for neurogenetic follow-up, where a muscle biopsy was performed, showing a discrete irregularity in the diameter of the myofibers, rare hypotrophic fibers, and no inflammatory cell flow. The electroneuromyography was compatible with a sensory-motor axonal neuropathy, the motor component being length-dependent, with signs of activity.

After an extensive clinical and laboratory evaluation that failed to elucidate the patient's condition,

a complete exome sequencing study was carried out, which revealed the presence, in heterozygosity, of the missense variant c.1311A > G ; p (Ile437Met), classified as pathogenic in the OPA1 gene, confirming the diagnosis of Optic Atrophy type 1 plus (ADOA plus). After the diagnosis, an MRI scan was performed (Figure 2), whose findings justified the patient's clinical.

Table 1. Laboratory examinations

	Value	Value of reference
Lactate (rest)	1.3 mmol/L	0.5 – 2 mmol/L
Lactate (effort)	5.8 mmol/L	0.5 – 2 mmol/L
Ionic calcium	1.2 mmol/L	1.12 – 1.32 mmol/L
Sodium	139 mmol/L	135 – 145 mmol/L
Potassium	4 mmol/L	3.5 – 5 mmol/L
CPK	198 U/L	24 – 170 U/L
TGO	22 U/L	< 32 U/L
TGP	15 U/L	< 31 U/L
Uric Acid	4.4 mg/DL	2 – 5 mg/DL
Blood glucose	79 mg/DL	70 – 100 mg/DL
Vitamin B12	252 pg/mL	174 – 878 pg/mL
Magnesium	1.58 mEq/L	1.4 – 2.3 mEq/L

Source: The authors (2020).

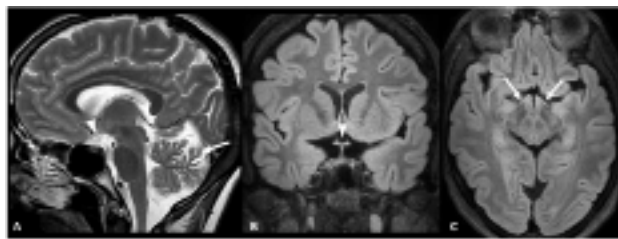


Figure 2. MRI images of the patient, 27 years old, with OPA1. A: Sagittal T2 demonstrating cerebellar (arrow) and optic nerve/chiasma atrophy (arrowhead). B and C: Coronal and axial T2 FLAIR demonstrating mild hypersignal and atrophy of the chiasm (arrowhead) and optic tracts (arrows).

Source: The authors (2020).

Currently, the patient reports sensory ataxia, progressive decrease in visual acuity, fasciculations and cramps in lower limbs, dysphagia, dyspnea on mild exertion, and malaise if prolonged fasting. On physical examination, the patient is oriented in time and space; symmetrical face, divergent strabismus, symmetrical palate elevation, centered tongue;

eumetrics and eudiadochokinesia; osteotendinous reflexes grade 2 in LL and grade 3 in upper limbs; Muscle strength grade 4 in LL and upper limbs (except lower limb grade 4-); hypertonia of plantar flexors, positive Mingazini IIM, bilateral increased plantar arch, flexed toes, ischiotibial weakness, alteration of vibratory sensitivity of LL; atypical gait - needs cane support to walk.

As pharmacological treatment she uses coenzyme Q₁₀ 450mg, three times a day and, as rehabilitation therapy, she does pilates classes every week. An evaluation with the physical therapy team indicated the need for foot orthoses.

DISCUSSION

Although the expressivity is quite variable, most cases of ADOA in childhood or adolescence present mostly with isolated progressive optic atrophy.¹² Patients who develop extraocular manifestations represent 20% of the cases and are then called ADOA+⁹. These syndromic forms of optic atrophy, caused by OPA1 sequencing variants, have been described with neurosensory deafness as the most common finding¹², in approximately two out of three patients¹⁰. However, although the patient in question presented visual impairment as the first symptom in childhood, so far she has not shown signs of sensorineural deafness.

Also, ADOA+ may be associated, more rarely, with various combinations of symptoms including ptosis, chronic progressive external ophthalmoplegia, peripheral polyneuropathy, ataxia, spastic paraparesis, multiple sclerosis-like and myopathy.¹⁰ In the case presented here, however, the patient does not have ptosis or ophthalmoplegia, but is a case of optic atrophy associated with peripheral neuropathy, ataxia and myopathy.

Although not observed in the patient to date, the association between chronic progressive external ophthalmoplegia and parkinsonism/dementia with subclinical optic neuropathy broadens the phenotypic spectrum of OPA1 mutations, highlighting the association between mitochondrial defects, multiple mtDNA deletions, and selective removal of mitochondria (mitophagy) with parkinsonism.¹³

The ADOA+ phenotype, which is similar to that seen in multisystem mitochondrial disorders, is often associated with missense mutations in OPA1¹⁴, variant found in the reported patient.

Besides these autosomal dominant forms, only a few syndromic cases have been described with compound heterozygous mutations in OPA1, suggestive of recessive or semidominant inheritance patterns.⁹ Recently, recessive mutations in OPA1 have been described, whose phenotype tends to be more severe than that observed in dominant forms of OPA1, and may be associated with cataracts, in addition to optic atrophy. To date, seven patients from four unrelated families have been described with two different OPA1 mutations. However, compound heterozygosity of OPA1 has been found in only three patients from two unrelated families.¹⁴

Since the forms of OPA1 are more associated with dominant inheritance, genetic counseling of families affected by this disease is essential, since the risk of recurrence reaches 50% in the future offspring of these couples. It is important to emphasize, however, that there is intra-familial phenotypic heterogeneity, i.e., the same OPA1 mutation in a family does not necessarily evolve to the same clinical picture (or with the same severity) in all affected.¹⁰

Only a few ADOA+ cases were related to the basic domain of OPA1 and none of them had spasticity. Furthermore, clinical evidence of corticospinal tract involvement is uncommon in OPA1-related diseases¹¹. Interestingly, the patient in question has progressive spastic paraparesis, a clinical phenotype not so common in patients with OPA1 mutation.

The neuroimaging findings found in patients with OPA1 mutations consist of cerebral and cerebellar atrophy, optic nerve thinning, and white matter signal abnormalities, consistent with the findings found in the neuroimaging of the reported patient (Figure 2). In addition to these findings, typical neuroradiological signs of Leigh/Leigh-like syndrome have been described in patients with OPA1. Recently, signs of metabolic stroke very similar to those already described in MELAS syndrome have been reported in some patients carrying the OPA1 mutation. However, it is still too early to tell whether OPA1 investigation should be done in patients with suspected metabolic stroke.¹⁵

As for treatment, it is known that there is no specific therapy approved so far. However, patients seem to benefit from antioxidants, such as coenzyme Q₁₀, which is already used to treat other mitochondrial diseases, such as Leber's Hereditary Optic Neuropathy (LHON).¹⁶ Specifically, Idebenone, a synthetic form of coenzyme Q₁₀, has shown

satisfactory results in stabilizing and improving visual acuity in patients with ADOA,^{17, 18} because it is an essential cofactor for ATP production in the mitochondria, whose functioning dynamics is impaired in this disease.¹⁹

In summary, OPA1 mutations are usually related to optic atrophy with or without sensorineural deafness. However, more and more evidence points to multisystem forms of the disease, which can present in a variety of ways, including peripheral neuropathy. In our patient's case, the combination of spastic paraparesis with peripheral neuropathy would not traditionally make us think of OPA1 mutations, but rather of other genetic forms of spastic paraparesis. Thus, we reinforce that, in the investigation of progressive paraparesis associated with peripheral neuropathy and, particularly, with optic atrophy, it is fundamental to exclude the possibility of a condition caused by mutations in OPA1, since there is a therapeutic possibility with the use of Idebenone/coenzyme Q₁₀.

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Corresponding Author:

Charles Marques Lourenço
charlesgenetica@gmail.com

Editor:

Prof. Dr. Felipe Villela Gomes

Received: mar 08, 2021

Approved: apr 14, 2021
