Autosomal Dominant Optic Atrophy Plus Syndrome

**EDUCATIONAL OBJECTIVES:** Upon completion of this case study, participants will acquire skills to 1) Recognize the spectrum of clinical phenotypes linked to the optic atrophy 1 (OPA1) gene, 2) Identify and differentiate common forms of hereditary optic neuropathy, and 3) recognize the neuromuscular manifestations of OPA1 mutations.

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EMG CASE: 
Autosomal Dominant Optic Atrophy Plus Syndrome

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and Margherita Milone, MD, PhD

Case Information

<table>
<thead>
<tr>
<th>Presenting Symptom(s):</th>
<th>Visual impairment, spastic paraparesis, numbness, and intestinal dysmotility</th>
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<tbody>
<tr>
<td>Case-specific Diagnosis:</td>
<td>Autosomal dominant optic atrophy (DOA) plus syndrome (OPA1)</td>
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<tr>
<td>Appropriate Audience:</td>
<td>Residents, fellows, and practicing physicians</td>
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<td>Level of Difficulty:</td>
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1. HISTORY

A 58-year-old man was referred to the neuromuscular clinic for evaluation of visual loss and progressive gait dysfunction. According to his mother, he was a "stiff infant". However, he had no feeding or breathing difficulty. He had normal motor development. He was noted to have impaired vision at age 6 years and was diagnosed with bilateral optic atrophy. He was physically very active and able to keep up with his peers, but as teenager he seemed "uncoordinated." By the end of high school, he became legally blind. He never had ocular pain. In his late 20s, he developed progressive leg stiffness and weakness resulting in severe gait dysfunction and several falls. This was followed by onset of speech difficulty and dysphagia. Around age 40, he started complaining of numbness, tingling, and burning sensation in the feet, and five years ago, he started experiencing bilateral hand numbness. He denies upper extremity weakness. For several years he has been suffering from alternating constipation and diarrhea, and in the 18 months preceding this evaluation, he had lost 30 lb unintentionally. He has no symptoms suggestive of orthostatic hypotension or sphincteric disturbances. His cognitive functions remain intact allowing him to work and handle the family's finances with no difficulty.

Family history is noticeable for "color blindness" in the maternal grandmother and in a sister. His mother was wearing glasses but healthy until dying at age 84; his 84-year-old father is doing well.
The patient brings an extensive medical documentation that excludes acquired inflammatory, metabolic, and infectious etiologies for his neurological symptoms, including a normal cerebrospinal fluid examination.

Based on the available history, the most likely diagnoses are:

A. Autosomal dominant optic atrophy (DOA) plus syndrome.
B. Leber hereditary optic neuropathy (LHON).
C. Hereditary spastic paraplegia 11 (SPG11).
D. Leigh syndrome (subacute necrotizing encephalomyelopathy).
E. Optic atrophy type 3-linked disorder.

2. COMMENTARY

The patient has symptoms suggestive of a multisystem neurological disorder. The clinical history of progressive neurological symptoms since childhood and lack of evidence for autoimmune and infectious diseases suggest the possibility of a genetically determined disorder. The visual loss and the additional neurological symptoms raise the question of a mitochondrial disorder. The reported "color blindness" on the maternal side questions hereditary dyschromatopsia.

Autosomal DOA and LHON are the most common causes of optic atrophy, pathologically characterized by retinal ganglionic cell loss, and are both mitochondrial disorders. DOA results in a childhood painless visual loss which can be accompanied by a broader phenotype (e.g., peripheral neuropathy, myopathy, progressive external ophthalomoplegia, hearing loss in various combination) signaling involvement of both central and peripheral nervous systems (DOA plus). The myopathy is usually proximal and accompanied by cytochrome c oxidase negative fibers on muscle biopsy. The progressive external ophthalomoplegia can be the only neuromuskular manifestation of the DOA plus and has a later age of onset. The peripheral neuropathy is usually length-dependent and has predominant sensory involvement. DOA and DOA plus are caused by mutations in the optic atrophy 1 (OPA1) gene. LHON manifests in the second to third decade of life with subacute painless monocular central visual loss, followed by similar symptoms in the contralateral eye within a year of disease onset. Extra-ocular manifestations, such as peripheral neuropathy and ataxia, are extremely rare in LHON but have been reported. In a series of 45 LHON patients, nine had clinical and electrophysiological evidence of predominantly sensory axonal neuropathy. LHON is maternally inherited and caused by homoplasmic point mutations in complex I subunit genes of the mitochondrial DNA.

Hereditary spastic paraplegia (SPG) is clinically and genetically heterogeneous and can present as pure lower limb spasticity and weakness or with additional neurological and non-neurological manifestations (complex SPG). SPG11 is the most frequent autosomal recessive SPG and is caused by mutations in the KIAA1840 gene that encodes for spatacsin, a cytoplasmic protein of unknown function. SPG11 is the SPG most frequently associated with thin corpus callosum and in the complex variant can be accompanied by macular dystrophy, amyotrophy, and mental retardation (Kjellin syndrome). Dysarthria, nystagmus, or upper limb involvement can occur. SPG11 manifests more frequently in childhood than in adulthood. Cognitive impairment and thin corpus callosum are reliable predictors of SPG11.

Leigh syndrome (subacute necrotizing encephalomyelopathy) can present similarly with a mixture of progressive visual loss, spasticity, and neuropathy. It typically presents in infancy or
early childhood, although late childhood and adult onset has been reported. However, developmental delay or psychomotor regression, ataxia, dystonia, external ophthalmoplegia, seizures, and lactic acidosis are much more common manifestations than the visual loss. In addition, brain magnetic resonance imaging (MRI) shows abnormal white matter signal in the basal ganglia. Leigh syndrome is genetically heterogeneous and mutations have been identified in both nuclear- and mitochondrial-encoded genes involved in energy metabolism.

Optic atrophy type 3 is an autosomal dominant disorder caused by mutations in OPA3. The optic atrophy manifests early in life and is often accompanied by cataract. Type III 3-methylglutaconic aciduria is an allelic disorder inherited with an autosomal recessive pattern, presents with early-onset bilateral optic atrophy, later-onset spasticity, extrapyramidal dysfunction, and cognitive deficit, and is characterized by urinary excretion of 3-methylglutaconic acid.

The neurologic examination should be complete due to the multiple symptoms suggestive of multisystem neurological disease.

3. PHYSICAL EXAMINATION

Mental status is normal. Cranial nerve examination reveals pale optic discs and markedly reduced visual acuity (the patient is able to count fingers if placed very close to his eyes), mild bi-facial weakness, and spastic dysarthria. The rest of the cranial nerve examination is normal, including extra-ocular movements and hearing. Motor examination shows mild-to-moderate distal upper limb weakness and associated mild muscle atrophy, moderate distal-more-than-proximal lower limb weakness, and asymmetric lower limb spasticity. He has asymmetric hyperreflexia (biceps, brachioradialis, and triceps reflexes were hyperactive on the right side) but absent Achille's reflexes and absent plantar responses. Sensory examination shows a distal symmetric length-dependent pan-modality (light touch, pain, temperature, vibratory and joint position sense) in the lower limbs. He has a mild and slightly asymmetric sensory loss distally in upper limbs mainly involving the right hand (mild decrease in superficial pain up to the wrist and vibration sense at the interphalangeal joints). He has no dysmetria on finger-to-nose; lower limb coordination is compatible with his degree of muscle weakness and spasticity. He is unable to stand independently, but he is able to take a few steps with his walker exhibiting a spastic and steppage gait.

Based on the available history and physical examination, the differential diagnosis can be rearranged as follows:

A. Autosomal DOA plus syndrome.
B. Hereditary SPG11.
C. LHON.
D. Leigh syndrome.
E. Optic atrophy type 3-related disorder.

4. COMMENTARY II

Leigh syndrome and OPA3-related disorders are less likely on the basis of the normal mental status. LHON is unlikely due to the insidious and childhood onset of visual loss and the prominence of extra-ocular manifestations. SPG11 also is unlikely because, when associated with visual symptoms, it is usually accompanied by cognitive deficits.
Electrophysiological evaluation should be directed toward the search of a peripheral neuropathy and possible associated subclinical myopathy.

5. ELECTROPHYSIOLOGIC DATA

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<td>5.7 (N&gt;6.1)</td>
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NEEDLE ELECTROMYOGRAPHY

INSErTional activity: N, sust, unsust
FIB: 0, 1+, 2+, 3+, 4+
OTHer: 0 or fascic, myotonia, myokymia
EFFort: N, decre
RECruitment: N, inc or dec 1+, 2+, 3+, 4+
AMPplitude: N, inc or dec 1+, 2+, 3+, 4+
DURation: N, inc or dec 1+, 2+, 3+, 4+
POLyphasia: N, inc or dec 1+, 2+, 3+, 4+

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5. DIAGNOSTIC IMPRESSION

The patient brings results of numerous investigational tests. Brain and orbit MRI show atrophy of the optic nerves and optic chiasm and mild generalized cerebral and cerebellar atrophy. MRI of the cervical spine reveals minimal spinal cord atrophy with no signal change. Screening for common mitochondrial DNA (mtDNA) mutations, including those associated with LHON, is negative. Creatinine kinase, lactate, pyruvate, liver enzymes, and vitamins B12 and E are normal. Genetic inborn error of metabolism screening is normal. Needle electromyography/nerve conduction study results (data shown above) show a predominantly axonal sensorimotor peripheral neuropathy. Electrocardiogram and echocardiogram are normal. Motility studies reveal normal gastric emptying, above average small bowel transit rate, and decreased colonic transit at 24 and 48 hours.

The early visual loss of insidious onset, the later development of spastic paraparesis, axonal peripheral neuropathy, and gastrointestinal dysmotility, in the absence of cognitive deficits and normal corpus callosum, predict a defect in OPA1. Sequencing of the OPA1 gene detected a heterozygous novel variant c.312A>G resulting in p.Ile104Met. This mutation is predicted to be pathogenic: (1) isoleucine at codon 104 is a branched amino acid that is highly conserved across species, (2) SIFT and PolyPhen-2 algorithms predict that the variant is deleterious, and (3) this variant has not been detected in more than 1000 normal control subjects.

6. COMMENTARY III

OPA1 is the leading causative gene of DOA, which is characterized by insidiously progressive bilateral visual loss, optic disc pallor, dyschromatopsia, and centrocecal scotoma. The visual decline usually manifests in early childhood. However, there is a pronounced inter- and intra-familial variability in the severity of the visual symptoms, and some subjects may be asymptomatic. The younger age of onset of the visual symptoms, the slow progressive course, and the autosomal dominant inheritance of DOA differentiate DOA from LHON.

It has been estimated that up to 20% of OPA1 mutation carriers have a multisystem neurological disorder and this observation led to the term DOA plus, or OPA1 plus, syndrome. Bilateral sensorineural hearing impairment manifesting in late childhood or early adulthood is a frequent feature, followed by a combination of ataxia, myopathy, axonal peripheral neuropathy, and progressive external ophthalmoplegia with onset in the third decade of life or later. In a large cohort (n=104) of patients with OPA1 mutations, nearly a third of patients had an axonal sensory or sensorimotor peripheral neuropathy. The phenotype can mimic autosomal dominant MFN2-
peripheral neuropathy, which accounts for approximately 20% of inherited axonal peripheral neuropathies and causes optic atrophy in a subset of affected subjects. A similar phenotype (axonal peripheral neuropathy and optic atrophy) has been recently described in patients carrying SLC25A46 mutations, but inherited with autosomal recessive trait. All 3 proteins, OPA1, MFN2, and SLC25A46, are involved in mitochondrial dynamics.

DOA plus can also manifest with spastic paraparesis and optic atrophy, or with a multiple sclerosis-like illness featured by optic atrophy, ataxia, periventricular white matter lesions, and unmatched oligoclonal bands in the cerebrospinal fluid. Additional clinical features include non-insulin dependent diabetes and migraine. Of interest, due to the variable penetrance for optic neuropathy, OPA1 mutation carriers may lack visual symptoms and even optic atrophy but still manifest myopathy, progressive external ophthalmoplegia, or peripheral neuropathy.

OPA1 is a ubiquitously expressed dynamin related GTPase protein that has the highest level of transcripts in the retinal ganglionic cells, the loss of which leads to optic neuropathy and visual loss. However, the deleterious effects of OPA1 mutations also affects other central nervous system cells, muscle, and peripheral nerve resulting in a multisystem disease. Mutated OPA1 results in fragmentation of the mitochondrial network and mitochondrial dysfunction. Indeed, patients with DOA and DOA plus syndrome often show evidence of mitochondrial dysfunction in muscle biopsy, as suggested by the presence of cytochrome c oxidase-negative fibers and multiple mtDNA deletions.

More than 200 pathogenic mutations have been reported in OPA1 and most of those that cause DOA plus are located in the GTPase domain of the protein. The patient described here carries a novel OPA1 mutation in the basic domain of the protein within a putative cleavage site of the mitochondrial import signal peptide which is essential for the mitochondrial localization of OPA1.

This patient represents an example of DOA plus manifesting with optic neuropathy, axonal peripheral neuropathy, spastic paraparesis, and gastrointestinal dysmotility, the latter being probably a manifestation of visceral mitochondrial myopathy or autonomic neuropathy. Physicians should be aware that although most patients with OPA1 mutations present with early visual loss, neuromuscular manifestations are common in this OPA1-related disease.

7. BIBLIOGRAPHY