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Expanding the clinical spectrum of the mitochondrial mutation A13084T in the *ND5* gene

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Our group previously published about a patient with a LS/MELAS (Leigh syndrome/mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes) overlap phenotype associated with a novel mitochondrial mutation in the *ND5* gene.[1] At that time, his 38-year-old mother presented only migraine and asymptomatic bilateral optic atrophy, without other neurologic signs or symptoms. Headache attacks, occurring about twice a month, were localized mainly in the right frontoparietal region, sometimes associated with nausea or vomit or phonophotophobia, and were responsive to nonsteroidal anti-inflammatory drugs. She carried lower levels of heteroplasmy of the same A13084T mutation (57% in lymphocytes and 48% in fibroblasts) compared with her son (82% in blood and 72% in fibroblasts).

At 53 years of age, she was admitted to our hospital to treat the recent worsening of migraine attacks in terms of frequency (up to 12 a month) and severity. Neurologic examination was unremarkable, including manual visual field by confrontation. Ophthalmologic examination revealed visual acuity loss, which onset was not exactly datable. Visual acuity was 20/32 in the right eye (oculus dexter [OD]) and 20/40 in the left eye (oculus sinister [OS]). Fundoscopy confirmed known bilateral optic disc pallor and excavation, with major involvement of the temporal sectors (figure, A). Intraocular pressure was 16 mm Hg bilaterally. Computerized visual field analysis showed a moderate-severe defect in the superotemporal sector in the OD and centrocecal scotoma in the OS (figure, B). No retinal abnormalities were detected at infrared and autofluorescence retinoscopy (figure, C), whereas optical coherence tomography showed a diffused macular ganglion cell layer thinning and a retinal nerve fiber layer atrophy of the temporal sectors bilaterally (figure, D). Visual evoked response to flash stimulation was reduced in amplitude in the OS, with a markedly increased latency, and normal in the OD. Serum lactate was slightly elevated (1.6 mmol/L; normal values <1.3 mmol/mol), and folate levels were mildly reduced (3.5 μg/L; normal range 4.6–18.7 μg/L). The remaining blood tests, including thyroid and liver functions, were otherwise normal. We performed a brain MRI with gadolinium that also included studies of orbits and cerebral vessels. Subcortical white matter carried nonspecific hyperintensities in T2 sequences, but no signs of previous stroke-like lesions were detected. No optic nerve or chiasm abnormalities were seen on scans. Arteries of the circle of Willis were normally represented.

Our findings pointed out to a phenotype similar to Leber hereditary optic neuropathy (LHON), not previously diagnosed because the patient did not perform further evaluations in the past years nor reported ocular symptoms so far. Idebenone (dosage 90 mg trice a day) was added to the treatment with coenzyme Q10 (dosage 50 mg twice a day).[2] Because LHON

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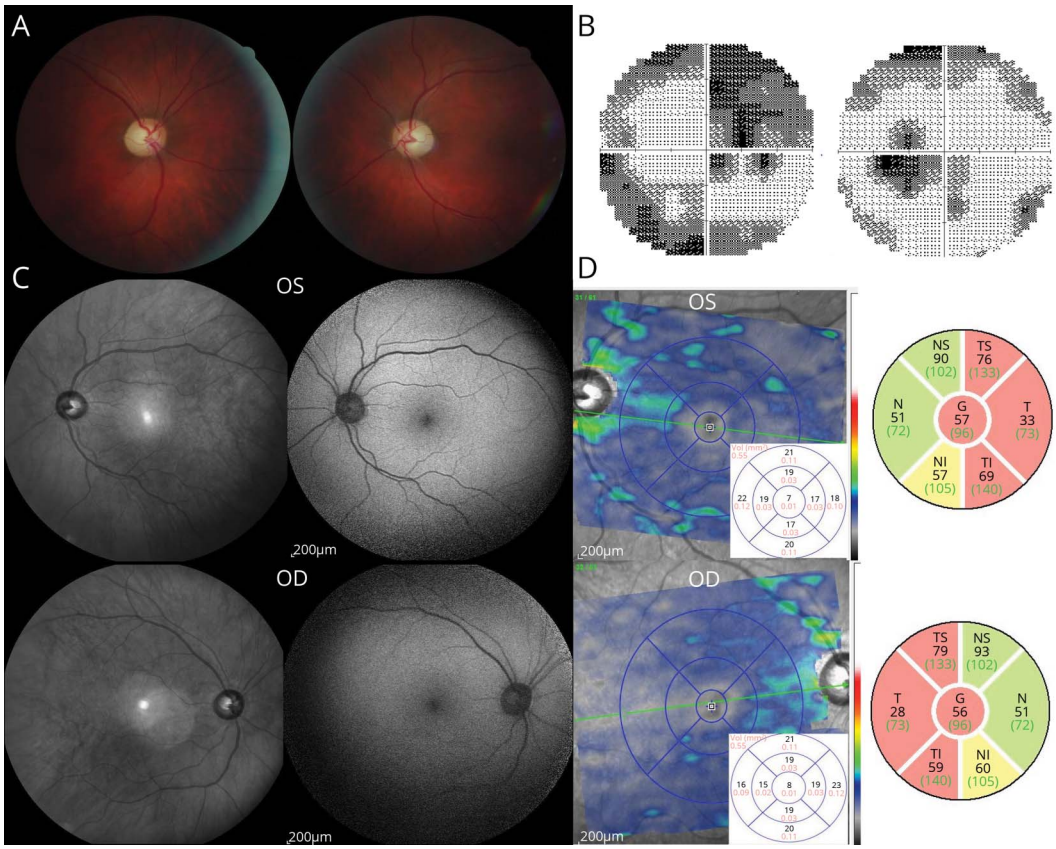
Figure Neuro-ophthalmologic evaluations



Fundus color image showing bilateral optic disc pallor and excavation, with main involvement of the temporal sectors (A). Humphrey automatic visual field analysis 30-2 revealing a superotemporal defect in the OD and centrocecal scotoma in the OS (B). No retinal abnormalities were detected at IR and autofluorescence (C, OS upper row, OD lower row), whereas OCT showed a diffused macular ganglion cell layer thinning and a RNFL atrophy of the temporal sectors (D, OS upper row, OD lower row). IR = infrared retinoscopy; OCT = optical coherence tomography; OD = oculus dexter; OS = oculus sinister; RNFL = retinal nerve fiber layer.

may be associated with arrhythmias and mitochondriopathies with cardiac involvement, we performed ECG, echocardiogram, and 24-hour ECG monitoring, resulted all normal. Frequency of headache episodes responded partially to riboflavin 200 mg twice a day.[3] Clinical evaluation and ophthalmologic assessments, performed 1 year later, were substantially stable.

Here, we describe the mitochondrial A13084T mutation in the *ND5* gene, still not reported in other families, in association with a LHON-like presentation and migraine, in addition to the previously described LS/MELAS phenotype.[1] *ND5* is a mtDNA gene encoding for the nicotinamide adenine dinucleotide dehydrogenase 5, part of the complex I of the respiratory chain in mitochondria, which mutations have been so far associated with MELAS, LHON, Leigh syndrome (LS), and overlap syndromes (MELAS/LS, MELAS/LHON/LS, MELAS/Chronic Progressive External Ophthalmoplegia, MELAS/Myoclonic Epilepsy with Ragged-Red Fibers).[4,5]

LHON, usually affecting young men, is typically characterized by bilateral and painless loss of vision, with centrocecal scotoma, prominent temporal optic nerve atrophy, and selective degeneration of retinal ganglion cells,[2] as occurred in our patient. However, our patient did not complain of acute or subacute visual loss. In the literature, heteroplasmy has been reported in 10%–15% of LHON cases with levels above 70%,[6] which are higher compared with those found in our patient. We speculate that lower heteroplasmy levels and female sex may be responsible for the milder presentation of visual loss in our patient, although further observation is needed to confirm this theory.

Despite being a common disorder in the population, a higher prevalence of migraine has been reported in several mitochondrial disorders, probably because of impaired oxidative metabolism in the CNS.[7]

In conclusion, our findings expand the spectrum of phenotypes arising from the A13084T mutation. We support the role of *ND5* as a candidate gene for LHON or LHON-like presentations. Moreover, we suggest periodic evaluations in paucisymptomatic or asymptomatic carriers to detect subclinical signs of optic atrophy.

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Disclosure

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Eleonora Mauri, MD	IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Conceptualized and wrote the manuscript; performed the neurologic evaluations of the patient; and collected clinical history and other assessments
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Francesca Magri, MD	IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Reviewed the manuscript
Dario Ronchi, MD, PhD	IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Performed mtDNA studies
Valeria Minorini, MD	IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Performed orthoptic evaluations
Claudia Mainetti, MD	IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Performed orthoptic evaluations
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Irene Faravelli, MD	IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Italy	Reviewed the manuscript and participated in neurologic evaluations
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Nereo Bresolin, MD	IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy	Reviewed the manuscript
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Giacomo Comi, MD	IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Italy	Contributed for intellectual content and reviewed the manuscript

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