LETTER TO EDITOR

Leber's Hereditary Optic Neuropathy Plus Can Imitate Neuromyelitis Optica

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We read with interest the excellent article by Uittenbogaard *et al*. about a 34-year-old female with the double trouble Leber's hereditary optic neuropathy (LHON) and neuromyelitis optica (NMO).[1] LHON was attributed to the variant m.11778A > G in ND5 occurring with a heteroplasmy rate of 94% in skin fibroblasts.[1] The patient presented initially with blurred vision at age 27 years.[1] Spasms and dry eyes were diagnosed but rewetting drops were ineffective.[1] Subsequently, the patient developed headache. Bilateral optic neuropathy was suspected but cerebral magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) investigations were normal.[1] At age, 31 years control cerebral MRI revealed multiple, T2-hyperintens, spotty white matter lesions (WMLs) and visual acuity was markedly reduced.[1] Lupus, NMO, and multiple sclerosis (MS) were suspected and mycophenolate mofetil was initiated.[1] Control MRI "confirmed" NMO and plasmapheresis was started.[1] Nonetheless, she subsequently developed weight loss, nausea, weakness, dizziness, urinary retention, and bladder spasms requiring self-catheterization [Table 1].[1] The authors concluded that the m.11778A > G variant can manifest as LHON-MS overlap. The study has a number of shortcomings.

The first shortcoming of the study is the diagnosis NMO.[1] Criteria for diagnosing NMO include (a) visual impairment, (b) supratentorial WMLs, (c) eccentric T2 hyperintensities on spinal MRI extending >2 segments of the spinal cord, which occur most frequently if the thoracic myelon, (d) elevated titers of antibodies directed against aquaporin-4 immunoglobulin-G, (e) increased cell count in the CSF, and f) positive oligoclonal bands.[2] The patient presented by Uittenbogaard *et al*. did not meet these diagnostic criteria. He fulfilled criterion a and b but not the other criteria. In addition, the patient responded only minimally to glucocorticoids, mycophenolate mofetil, and plasmapheresis.[1]

The second shortcoming of the study is that cerebral MRI provided in Figure 1 of the article[1] is not compatible with NMO. The presented MRI reveals non-specific, non-enhancing T2-hyperintensities in the deep white matter without a corresponding hyperintensity on diffusion-weighted imaging. Since WMLs are most frequently due to micro- or macroangiopathy, it would be interesting to know if the patient had a history of arterial hypertension, diabetes mellitus, smoking, hyperlipidemia, or alcohol abuse. WMLs shown in Figure 1 could be simply due to the presence of one or several of the classical cardiovascular risk factors.

The third shortcoming is that the authors did not consider involvement of the cellular immune system in LHON. From other mitochondrial disorders (MIDs), it is known that the cellular immune system may be primarily affected by the mitochondrial metabolic defect.[3] It is also conceivable that the alleged primary immunological disease represents a secondary autoimmune response to a single or multiple mutated mitochondrial protein(s).[4] Mutated proteins may trigger a secondary T-cell response, which, in turn, causes autoimmune disease.[4] Why not all patients with LHON respond with a secondary immune reaction remains elusive but it can be speculated that heteroplasmy rates in immune cells are randomly heterogeneous. Anyhow, several patients with double trouble LHON and MS have been reported.[5-8]

A fourth shortcoming is that the index patient was not prospectively investigated for multisystem disease.

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Table 1: Arguments for NMO and arguments for MID

Arguments	NMO	MID
Impaired vision	Yes	Yes
Supratentorial WMLs	Yes	Yes
Headache	No	Yes
Weight loss	No	Yes
Nausea	No	Yes
Weakness	Yes	Yes
Urinary retention	Yes	Yes
Bladder spasms	Yes	Yes
Dizziness	No	Yes

MID: Mitochondrial disorder, NMO: Neuromyelitis optica, WMLs: White matter lesions

It is well appreciated that LHON is frequently not a single-organ disease but a multiorgan problem affecting the brain, retinal ganglion cells, inner ears, endocrine organs, heart, kidneys, hematological system, arteries, and peripheral nerves.[5] Knowing involvement of other organs, particularly the heart, is crucial as it may determine the outcome of these patients.

Overall, NMO or MS-like features on cerebral imaging in LHON represent rather involvement of immune cells or a secondary immune reaction to mutated mitochondrial proteins than a primary immunological disorder. Not to confuse readers the terms LHON-MS or LHON/NMO should be avoided. Nonetheless, MID patients are occasionally misdiagnosed as MS/NMO due to unawareness of the mitochondrial background and commercial rather than medical interests determining medical reasoning.

AUTHORS' CONTRIBUTIONS

All authors contributed equally (JF: Design, literature search, discussion, and first draft, FS+CS: Literature search, discussion, and critical comments).

ETHICAL APPROVAL

The research has been given ethical approval.

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