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).

LHON was attributed to the variant m.11778A > G in ND5 occurring with a heteroplasmy rate of 94% in skin fibroblasts. The patient presented initially with blurred vision at age 27 years. Spasms and dry eyes were diagnosed but rewetting drops were ineffective. Subsequently, the patient developed headache. Bilateral optic neuropathy was suspected but cerebral magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) investigations were normal. At age, 31 years control cerebral MRI revealed multiple, T2-hyperintens, spotty white matter lesions (WMLs) and visual acuity was markedly reduced. Lupus, NMO, and multiple sclerosis (MS) were suspected and mycophenolate mofetil was initiated.

The second shortcoming of the study is that cerebral MRI provided in Figure 1 of the article 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. It is also conceivable that the alleged primary immunological disease represents a secondary autoimmune response to a single or multiple mutated mitochondrial protein(s). Mutated proteins may trigger a secondary T-cell response, which, in turn, causes autoimmune disease. 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.

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

Address for correspondence:
Josef Finsterer, Postfach 20, Klinik Landstrasse, Messerli Institute, Vienna - 1180, Austria.

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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. 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).

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**Table 1: Arguments for NMO and arguments for MID**

<table>
<thead>
<tr>
<th>Arguments</th>
<th>NMO</th>
<th>MID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired vision</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Supratentorial WMLs</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Headache</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight loss</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Nausea</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Weakness</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Bladder spasms</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dizziness</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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

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**ETHICAL APPROVAL**

The research has been given ethical approval.

**REFERENCES**
