Leber's Hereditary Optic Neuropathy Associated With Schizophrenia

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Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease characterized by bilateral visual loss of central vision, generally affecting young men.[1] Three main mutations of mitochondrial DNA (mtDNA) involved in complex I of the oxidative phosphorylation system have been reported, encompassing over 90% of patients[2]: G3460A (genetic subunit *ND1*), G11778A (*ND4*), and T14484C (*ND6*). Mitochondrial oxidative phosphorylation is the major pathway producing adenosine triphosphatase (ATP), which supplies more than 95% of the total energy requirements in cells. Additional neurologic abnormalities have been described in these patients, including dementia, parkinsonism, multiple sclerosis–like illness, and polyneuropathy.[3–5] Although implication of mtDNA mutation has also been suggested in schizophrenia,[6,7] no case of genetically proven LHON associated with this condition has yet been reported. We describe here clinical and neuroimaging findings of a patient with G3460A mutation displaying both LHON and schizophrenia.

Case report. Mr A, a 24-year-old man, was addressed for refractory psychotic symptoms of disorganized schizophrenia according to *DSM-IV-TR* criteria and the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Clinician Version (SCID-CV). He had his first episode 4 years ago and had been hospitalized 6 times because of exacerbations of his chronic psychotic symptoms. A personal history of substance abuse, including nicotine, cannabis, benzodiazepine, cocaine, and methadone, was reported during this period. According to the interrogatory of the patient, the substance abuse did not precede the onset of psychotic symptoms. Moreover, the psychotic symptoms have persisted during periods of abstinence.

Mr A was treated with aripiprazole (15 mg/d) and risperidone (2 mg/d) but without clinical improvement. The negative symptoms were predominant, with blunted affect, avolition, apathy, lack of spontaneity, and flow of conversation. In particular, Mr A spent nearly all his time at home, lying in bed or in a chair watching television. He felt isolated, losing contact with friends and interacting minimally with his family. He produced very little speech and needed to be repeatedly prompted during the interview. These negative symptoms were associated with disorganized behavior characterized by sudden fluctuations from despondency to inappropriate and bizarre laughter and disorganized speech characterized by frequent derailment or incoherence such as loose associations and neologisms (Positive and Negative Syndrome Scale scores: Positive = 24, Negative = 36, General Psychopathology = 42).

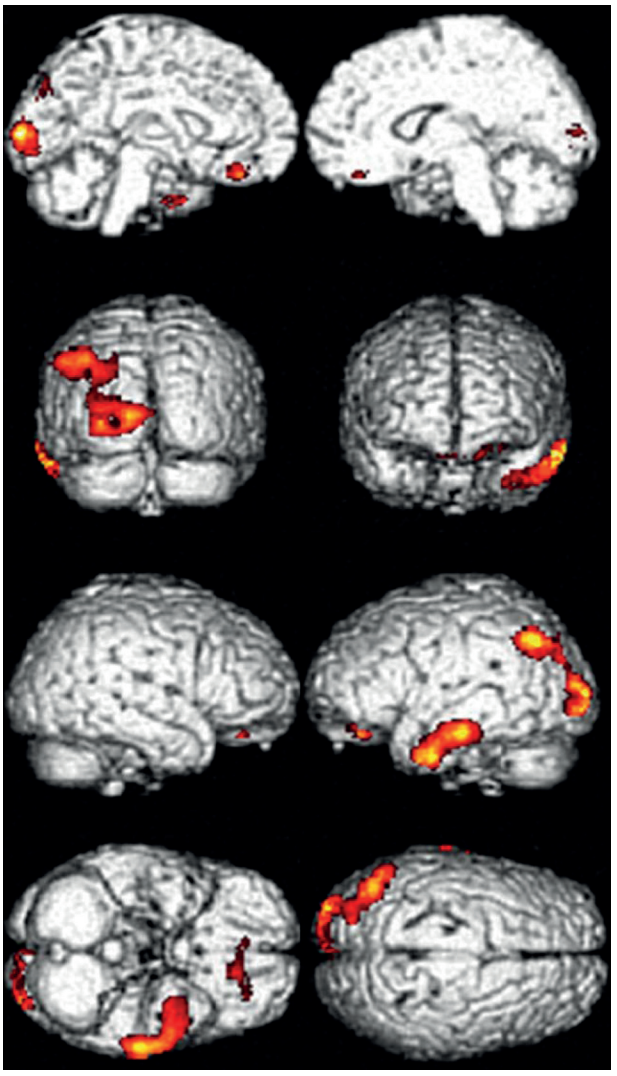
Mr A also reported a progressive bilateral visual loss associated with headaches and burning pains in his legs that appeared approximately 4 years ago but after the onset of psychotic symptoms. Family history revealed that 1 maternal uncle, 1 maternal cousin, and his brother have similar patterns of visual loss, without psychiatric disorders. Physical examination was normal except for the ophthalmologic examination, which showed a visual acuity for both eyes measured at 1/10, centrocecal scotoma, and dyschromatopsia. Retina angiofluorescein showed signs of pale optic discs bilaterally, without swelling or hemorrhages. The results concerning blood, thyroid, and toxicologic tests and gonadotropins or cortisol levels were within normal range. DNA analysis from peripheral leukocytes was performed, and homoplasmic G3460A mutation was thereby detected, confirming the diagnosis of LHON.

A brain magnetic resonance imaging confirmed a bilateral atrophy in optic nerve, without other brain abnormalities. The electroencephalogram showed slow wave activity in right parietal and occipital areas. A brain perfusion 99m Tc-ethyl cysteinate dimer single-photon emission computed tomography (SPECT) was also performed and findings compared to 15 healthy subjects (mean ± SD age = 29.5 ± 5.3 years) using version 5 of Statistical Parametric Mapping software (Wellcome Trust Centre for Neuroimaging, University College London, London, United Kingdom; $P < .001$, corrected for the volume).[8] Mr A exhibited significant ($P < .001$, corrected for the volume of the cluster) hypoperfusions: (1) within the left inferior and left middle temporal and fusiform gyrus; (2) within the left cuneus/precuneus, left inferior parietal lobule, left lingual gyrus, and left middle occipital gyrus; and (3) within the left inferior, left middle, and left medial frontal gyrus and bilateral orbital gyrus (Figure 1).

Mitochondrial disease represents a malfunction in the biochemical process of energy production resulting from disruption of either mtDNA or nuclear DNA.[9–11] In schizophrenia, studies provide evidence for abnormalities in mitochondrial structure and function.[12] Alterations of mitochondrial oxidative phosphorylation have been reported in several brain areas[13] and also in platelets.[14] Several studies have suggested that mutations of mtDNA are involved in psychiatric disorders[7,15,16] and in particular those of mitochondrial complex I subunits in schizophrenia.[16,17] The G3460A mutation found in our patient affects the ND1 subunit of respiratory chain complex I. Moreover, schizophrenia has been reported in patients with mitochondrial diseases such as mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes.[6] In our patient, the concomitant appearance of psychiatric and physical symptoms also suggests this association between schizophrenia and mitochondrial disease, LHON in this case. Finally, LHON is not restricted to the optic nerve and visual pathways, and abnormal mitochondrial energy metabolism has been identified in several brain areas.[18] Several studies have shown reduced levels of ATP in frontal and temporal areas of individuals with schizophrenia.[19,20] In our case, the SPECT showed hypoperfusions in the frontal and middle temporal regions, in accordance with previous imaging studies in schizophrenia.[21] The hypoperfusions in the inferior temporal gyrus, fusiform gyrus, and occipital regions are not usual in schizophrenia and may be linked to the impairment of the visual cerebral pathway of LHON.[18]

To conclude, psychiatrists should consider mitochondrial disease as possible diagnoses in their patients who present physical

Figure 1. Brain SPECT Hypoperfusions in the Patient, in Comparison to 15 Healthy Subjects ($P < .001$, corrected for the volume of the cluster)



Abbreviation: SPECT = single-photon emission computed tomography.

symptoms. In this line, therapeutic approaches strengthening mitochondrial function should be considered. Indeed, some antipsychotics, such as risperidone, inhibit the mitochondrial respiratory chain[22] and should be replaced. Smoking cessation treatment has also been proposed to reduce oxidative stress and mitochondrial damage.[23]

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Drug names: aripiprazole (Abilify), methadone (Methadose and others), risperidone (Risperdal and others).
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