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CASE REPORT

TUFM variants lead to white matter abnormalities mimicking multiple sclerosis

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Abstract

Background and purpose: Defects in the mitochondrial respiratory chain (MRC) can lead to combined MRC dysfunctions (COXPDs) with heterogenous genotypes and clinical features. We report a patient carrying heterozygous variants in the *TUFM* gene who presented with clinical features compatible with COXPD4 and radiological findings mimicking multiple sclerosis (MS).

Methods: A 37-year-old French Canadian woman was investigated for recent onset of gait and balance problems. Her previous medical history included recurrent episodes of hyperventilation associated with lactic acidosis during infections, asymptomatic Wolff–Parkinson–White syndrome, and nonprogressive sensorineural deafness.

Results: Neurological examinations revealed fine bilateral nystagmus, facial weakness, hypertonia, hyperreflexia, dysdiadochokinesia, dysmetria, and ataxic gait. Brain magnetic resonance imaging (MRI) showed multifocal white matter abnormalities in cerebral white matter as well as cerebellar hemispheres, brainstem, and middle cerebellar peduncles, some of which mimicked MS. Analysis of native-state oxidative phosphorylation showed a combined decrease in CI/CII, CIV/CII, and CVI/CII. Exome sequencing detected two heterozygous *TUFM* gene variants. Little clinical progression was noted over a 5-year follow-up. Brain MRI remained unchanged.

Conclusions: Our report broadens the phenotypic and radiological spectrum of *TUFM*-related disorders by adding milder, later onset forms to the previously known early onset, severe presentations. The presence of multifocal white matter abnormalities can be misinterpreted as due to acquired demyelinating diseases, and thus *TUFM*-related disorders should be added to the list of mitochondrial MS mimickers.

KEYWORDS
mitochondrial diseases, multiple sclerosis, *TUFM*, white matter abnormalities

INTRODUCTION

Defects in translation and assembly of mitochondrial respiratory chain (MRC) subunits lead to mitochondrial disorders with heterogenous genotypes, broad clinical spectrum, and diverse imaging features, some of which may resemble those of multiple sclerosis (MS) [1]. Variants in the *TUFM* gene, encoding the mitochondrial elongation factor Tu (EF-Tu), have been associated with combined MRC dysfunctions type 4 (COXPD4) causing early onset severe encephalopathy, brain malformations, and diffuse white matter disease [2, 3]. We report an adult patient

carrying heterozygous *TUFM* variants who presented with clinical features compatible with COXPD4 and imaging findings mimicking MS.

CASE DESCRIPTION

A 37-year-old French Canadian woman who presented with recurrent hyperventilation and associated lactic acidosis was referred for possible mitochondrial disorder. The family history was negative for mitochondrial or metabolic diseases and consanguinity. The patient was born after an uncomplicated pregnancy. She presented short stature, failure to thrive, low weight, and learning disabilities during childhood. Her past medical history included an episode of metabolic acidosis in the context of gastroenteritis at the age of 8 years (bicarbonate 8 mmol/L; lactate levels not available), recurrent episodes of hyperventilation during infections, asymptomatic Wolff–Parkinson–White syndrome, nonprogressive sensorineural deafness, hypothyroidism, and ovarian failure due to gonadal dysgenesis. Following in vitro fertilization with donor ovum, she became pregnant. She was first seen in medical genetics at the age of 36 years for marked hyperventilation and dyspnea during labor. Investigations revealed respiratory alkalosis (pH 7.53, bicarbonate 12.8 mmol/L, pCO_2 = 15.2) and hyperlactic acidemia (3–4 mmol/L, normal = 0.5–2.2). The episode resolved with supportive therapy, and genetic investigations were performed.

The patient reported progressive balance problems starting at the age of 36 years. Neurological assessment revealed fine bilateral gaze-evoked nystagmus in the lateral gaze, absent in primary gaze. She also had slight symmetric facial weakness, in both the upper and lower face, associated with mild myopathic facies. She presented very mild upper limb hypertonia and hyperreflexia with asymmetry R > L, end-of-action tremor, dysdiadochokinesia, and dysmetria. At that time, the Scale for Assessing and Rating of Ataxia (SARA) was not performed. The muscular strength was normal, as was the sensory examination; there were no Hoffman or Babinski signs. Walking was broad-based; tandem walking was possible but with some missteps.

Cytogenetic analysis revealed normal comparative genomic hybridization and karyotype. Sequencing of mtDNA uncovered no known deleterious variants. Brain magnetic resonance imaging (MRI) showed multifocal white matter lesions located in the subcortical and juxtacortical white matter of both cerebral hemispheres as well as in the cerebellar hemispheres, brainstem, and middle cerebellar peduncles (Figure 1). Some lesions were oval-shaped and perpendicular to the ventricular walls. No callosal lesions were identified.

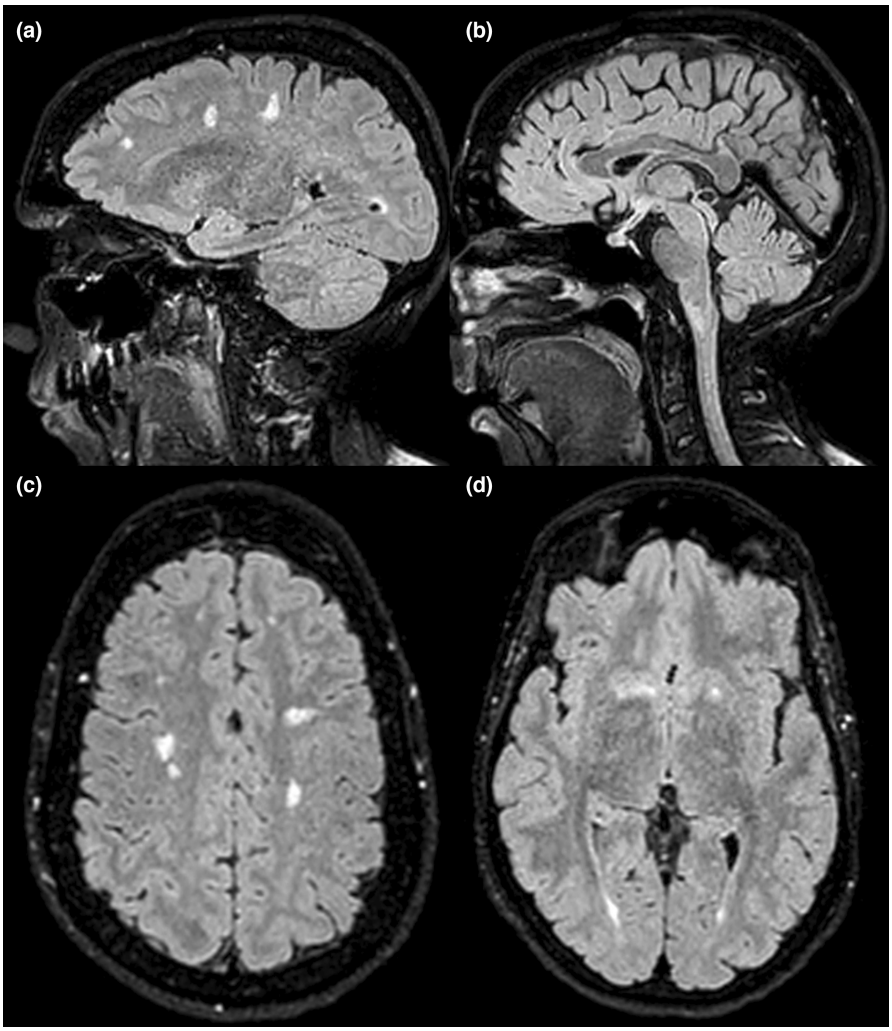

FIGURE 1 Brain magnetic resonance images of the *TUFM*-mutated subject. Sagittal (a, b) and axial (c, d) fluid-attenuated inversion recovery T2-weighted images showing multiple, oval-shaped hyperintense lesions localized in the subcortical and juxtacortical white matter (a, c), bilateral at the level of the caudate nuclei (d) and paramedian medulla (b). No vermian, cerebellar, or brainstem atrophy is noted (a, d).

There was no contrast enhancement or restricted diffusion. Spinal cord MRI was not performed. At 5-year follow-up, the patient showed little clinical progression of the ataxia, the SARA score was 10, and the brain MRI was unchanged since previously; specifically, no new white matter abnormalities were documented.

Analysis of native-state oxidative phosphorylation showed a combined decrease in CI/CII, CIV/CII, and CV/CII. Whole exome sequencing identified two heterozygous missense *TUFM* gene variants (NM_003321.5: c. 1075G>T; p.Val359Phe and c.374A>G; p.Tyr125Cys). c.1075G>T affects a consensus splice site. Both variants affect highly conserved residues and are present in the heterozygous state at very low frequencies in the gnomAD dataset (0.00001 and 0.000008, respectively). Both are classified as deleterious by MutationTaster2021 and probably damaging by PolyPhen-2; the CADD (Combined Annotation Dependent Depletion) scores are 33 and 30, respectively, and the REVEL (Rare Exome Variant Ensemble Learner) scores are 0.696 and 0.833, respectively. Both variants are American College of Medical Genetics and Genomics category 3 (uncertain significance). An additional variant of unknown significance was identified in *TUFM* (c.684+6C>T). The p.Val359Phe variant is of maternal origin; analysis from the father was not available. The clinical and biochemical data are compatible with a mitochondrial disorder caused by *TUFM* variants.

DISCUSSION

TUFM variants have been previously associated with COXPD4 characterized by early onset lactic acidosis and fatal encephalopathy associated with multisystem involvement. In young patients previously described, brain MRI features include cerebral atrophy, polymicrogyria, diffuse white matter abnormalities, and cystic lesions [3]. Our patient's clinical features are consistent with COXPD4 caused by *TUFM* variants, which was confirmed by genetic testing, even though the age at onset was older, and the clinical picture and disease course are considerably milder than the previously reported cases. Importantly, although white matter involvement is common [1], multifocal lesions like those documented in our subject have not been previously reported in patients with *TUFM* variants [2, 3]. This pattern of multifocal white matter abnormalities can be misinterpreted as due to acquired inflammatory demyelinating diseases such as MS [1]. However, in our patient, the absence of contrast enhancement and temporal dissemination over 5-year follow-up were not in favor of MS. Moreover, the bilateral basal ganglia and brainstem involvement was suggestive of mitochondrial disease, and multifocal white matter abnormalities have been well documented in other mitochondrial MS mimickers [1]. In addition to the MRI findings, some clinical features (i.e., nonprogressive sensorineural deafness, mild myopathic facies, lactic acidosis episodes) argued against an acquired demyelinating disorder. Although some MRI findings in our patient with *TUFM*-related disorder mimicked MS lesions, the MRI criteria for MS diagnosis were not fulfilled; nonetheless, it is important to remember that *TUFM* variants could coexist with MS. When in doubt between a diagnosis of MS and genetic MS mimics, additional testing is recommended, such as spinal cord MRI and cerebrospinal fluid examination, keeping in mind that oligoclonal bands have been occasionally documented in mitochondrial disorders [1, 4].

TUFM codes for EF-Tu, a highly conserved guanosine triphosphatase involved in MRC translation. Biochemically, defects of MRC complexes I, III, and IV have been detected in our patient, like previously reported results [5]. Studies have also demonstrated the role of complex I and IV dysfunction in axonal demyelination and MS pathogenesis [6].

The present report expands on the phenotypic spectrum of *TUFM*-related conditions by adding milder, later onset forms to the known fatal and early onset presentations. Our report highlights the overlap of radiological features between TUFM-related disorders and MS and emphasizes the necessity of integrating clinical, biochemical, genetic, and radiological evidence to differentiate these two conditions in adult patients.

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CONFLICT OF INTEREST STATEMENT

None of the authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This report is in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the ethics committee of the Montreal Neurological Institute. Full written informed consent was obtained from the patient.

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