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Case report

A novel *TYMP* mutation in a French Canadian patient with mitochondrial neurogastrointestinal encephalomyopathy

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ABSTRACT

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disorder characterized by gastrointestinal, extraocular muscle, peripheral nerve, and cerebral white matter involvement. Mutations in the nuclear gene TYMP encoding for thymidine phosphorylase (TP) cause loss of TP activity, systemic accumulation of its substrates in plasma and tissues, as well as alterations in mitochondrial DNA including deletions, depletion, and somatic point mutations. To date, more than 30 mutations have been reported in diverse ethnic populations. We present herein the clinical, neuroimaging, neuromuscular, and molecular findings of the first French Canadian patient with MNGIE caused by a novel homozygous invariant splicing site (IVS5 +1 G>A) mutation of the *TYMP* gene.

1. Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive multisystem disorder characterized by severe gastrointestinal (GI) dysmotility leading to cachexia, ptosis, external ophthalmoplegia, peripheral neuropathy, and leukoencephalopathy [1,2]. GI symptoms are among the most debilitating features and include early satiety, borborygmi, vomiting, diarrhea, constipation, abdominal cramps, and episodic pseudo-obstruction. Because onset is typically in the late teens, a differential diagnosis of anorexia nervosa is often considered. Most patients die before age 40 and although its prevalence is unknown, less than 75 cases have been reported to date.

MNGIE is due to mutations in the nuclear gene (endothelial cell growth factor 1 or TYMP) encoding thymidine phosphorylase (TP) [3]. TYMP mutations cause loss of TP activity, accumulation of thymidine and deoxyuridine in plasma and tissues, as well as secondary alterations in mitochondrial DNA (mtDNA) including deletions, depletion, and somatic point mutations [4,5]. MNGIE is thus understood as a defect of intergenomic communication between nuclear and mitochondrial genomes [6]. To date, more than 30 mutations have been reported in diverse ethnic populations. We report here the first French Canadian patient with MNGIE caused by a novel homozygous invariant splicing site (IVS5 +1 G>A) mutation of the *TYMP* gene.

2. Case report

A 20-year-old French Canadian woman was admitted for abdominal pain, recurrent episodes of vomiting and diarrhea, significant weight loss (6.8–9.1 kg over 4–6 months), and severe fatigue. She had been described as cachectic since she was 16 years old, weighing between 32 and 34 kg for most of her young adult life. At the time of her hospitalization, she reported eating three meals a day and having snacks at night. Despite this, her body mass index was 14.1 kg/m^2. She denied fear of gaining weight, self-induced vomiting or misuse of laxatives. Initial GI investigation including routine laboratory tests, abdominal CT scan and ultrasound, upper GI contrast radiography, esophagogastroduodenoscopy, parasites, and duodenal biopsy, was normal. She was evaluated by a neurologist and neuro-ophthalmologist who noted bilateral ophthalmoplegia and tonic pupils with light-near dissociation, and

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therefore recommended brain imaging. CT scan was normal but T2-weighted/proton density MRI revealed bilateral subcortical white matter hyperintensities in the frontal and temporal regions, as well as in the external capsules. Retrospectively, she presented several features of MNGIE, yet was diagnosed with anorexia nervosa and discharged home with follow up visits with a specialized eating disorders team.

Three years later, during Fall 2007, she was hospitalized on the internal medicine ward of our academic center and treated for a right lobar pneumonia. She had lost 4.5 additional kg (she now weighed 27.2 kg), and again denied anorexic behaviours. Throughout her hospitalization she gained a maximum of 1.4 kg despite multiple strategies including nutritional supplements, cognitive-behavioural therapy, and filmed parenteral feeding. Three months into her hospitalization, she began to show signs of encephalopathy which culminated into cardio-pulmonary resuscitation in the context of an asystole likely secondary to hypoxemia (pulmonary aspiration). Because she also showed moderate abdominal distension, hypotension and severe electrolyte imbalances, an exploratory laparotomy was conducted to exclude intra-abdominal pathology. The latter revealed severe small bowel hypomotility and atonia. Repeat abdominal CT scan documented small bowel dilation and thickening. She was then admitted to the Intensive Care Unit and slowly recovered to a point where she showed some eye contact and obeyed simple commands. She continued to report abdominal pain. Over the following days, her level of consciousness was fluctuating and, in light of her CT scan following cardio-pulmonary resuscitation which showed bilateral parieto-occipital hypodensities, the neurology service was consulted again. Neurological examination revealed a young cachectic patient with clear signs of encephalopathy. Brainstem reflexes were intact. At times she could maintain some visual contact and reacted to visual menace. She showed motor responses to pain and could move all four limbs. All tendon reflexes were absent.

Laboratory studies showed elevated arterial lactate (3.3–4.4 mmol/L; normal 0.5–2.2 mmol/L) that reached 7.0 mmol/L when enteral and parenteral feedings were given concomitantly. The latter elevation is likely as a result of thymidine containing parenteral supplements. A lumbar puncture revealed elevated CSF lactate (7.1; normal <2.8 mmol/L) and proteins (0.80; normal 0.15–0.40 g/L). Arterial blood gas indicated a refractory metabolic acidosis with elevated anion gap. There was marked hypoalbuminemia (13; normal 35–50 g/L) and a chronic inflammatory anemia. Creatine kinase level was normal.

Neurological investigation further included EEG, MRI, neurophysiologic studies, muscle biopsy, neuro-ophthalmologic examination, and molecular genetic testing. EEG showed bilateral intermittent delta activity. An MRI of the brain revealed bilateral leukoencephalopathy, edema and possible subacute ischemia in parieto-occipital regions, basal ganglia, and hippocampi (see Fig. 1). Electrophysiologic studies were consistent with a severe sensory and motor polyneuropathy showing mixed axonal and demyelinating features: left median and ulnar motor nerves showed diminished amplitudes (5.5 mV; 3.6 mV) and velocities (35 m/s; 28 m/s); Compound motor action potentials from the left peroneal and the left tibialis posterior nerves were absent; left median F wave was prolonged (41 ms); left median, ulnar and sural sensory potentials were absent. Needle electromyography of the left tibialis anterior muscle showed no fibrillations, but numerous polyphasic potentials indicative of chronic denervation. A biopsy of the right biceps showed significant reduction and variability in fiber diameter on standard hematoxyl and eosin stain. Angular fibers were also observed, hence suggesting neurogenic changes in addition to myopathic changes. Cytochrome *c* oxidase (COX) histochemical stain showed a few COX-negative fibers. No ragged-red fibers were seen with modified Gomori trichrome stain but ragged-blue fibers were observed with combined COX/SDH (succinate dehydrogenase) histochemical stain. Foci of type 2 fiber grouping were found on ATPase pH 4.6 staining. Finally, neuro-ophthalmologic reexamination again showed bilateral ophthalmoplegia, but this time revealed retinitis pigmentosa.

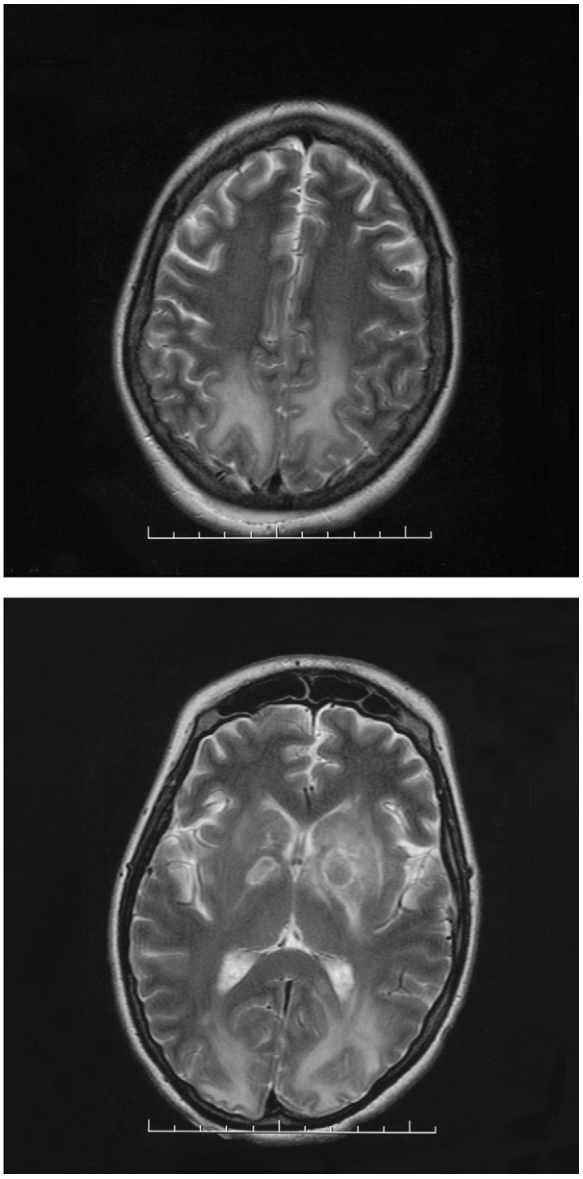

Fig. 1. T2-weighted MRI images showing (A) bilateral leukoencephalopathy, edema and subacute ischemia in parieto-occipital regions, and (B) bilateral subacute ischemic (and partially hemorrhagic) lesions in the basal ganglia (globus pallidus, caudate, putamen) and hippocampi (head). These findings likely represent the combined effects of diffuse leukoencephalopathy secondary to MNGIE and ischemic/hypoxic changes following cardio-pulmonary resuscitation.

It had been 4 years since she first consulted before molecular genetic studies and TP function were ordered. An MNGIE-TP sequencing test was performed and revealed a novel homozygous c.130 G to A transition in the first base pair of the intron following exon 5 (IVS5 +1 G>A) in the *TYMP* gene (see Fig. 2). This disrupted the GT splice donor site and is predicted to prevent the proper splicing of the exon and translation of the TP protein. The next GT in the sequence is 30 bp after the exon, thus at least 10 amino acids would be added to the protein, although a more likely scenario is that intron 5 is retained which would lead to a stop codon and premature truncation of the TP protein. Fol-