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TWO NEW GENE MUTATIONS FOR LATE ONSET MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOPATHY (MNGIE)

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Abstract

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a multisystem, autosomal recessive disorder characterized by ptosis, progressive external ophthalmoplegia, gastroparesis cachexia, peripheral neuropathy, and diffuse leukoencephalopathy. MNGIE is rare and the prevalence is unknown, however, to date there have been 76 mutations reported in the TYMP gene associated with MNGIE. We report two novel mutations that have not been previously described in a patient with clinical MNGIE syndrome.

Keywords

• Mitochondrial neurogastrointestinal encephalopathy (MNGIE) • Thymidine • Deoxyuridine • Nucleoside • TYMP gene • Human gene mutation database (HGMD)

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Introduction

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a multisystem, autosomal recessive disorder characterized by ptosis, progressive external ophthalmoplegia, gastroparesis, cachexia, peripheral neuropathy, and diffuse leukoencephalopathy [1]. It is caused by mutations in the *TYMP* gene encoding thymidine phosphorylase (TP) located on chromosome 22q13.33 [1,6]. This enzyme catalyzes the nucleosides thymidine and deoxyuridine to thymine and uridine respectively. It has been postulated that the accumulation of these nucleosides (thymidine and deoxyuridine) leads to mitochondrial DNA instability [2], hence the multisystem involvement. MNGIE is rare and the prevalence is unknown, however, to date there have been 76 mutations reported in the *TYMP* gene associated with MNGIE [3]. Our aim is to report two novel mutations that have not been previously described or reported in a patient with clinical MNGIE syndrome.

Case History

A 48-year-old Anglo-American male with an approximate 20 year history of ophthalmoparesis, hearing loss, and ptosis presented with 8 months history of gastroparesis, diarrhea, emesis, weight loss, cachexia, and polyneuropathy. Initial cancer work-up was negative. Magnetic resonance imaging (MRI) of brain showed moderate severity of periventricular and brainstem white matter disease without abnormal enhancement. Rectal biopsy was negative for amyloidosis. Given a working diagnosis chronic inflammatory demyelinating polyneuropathy (CIDP), the patient received two rounds of intravenous immunoglobulin (IVIG) without any improvement in symptoms. Patient was transferred to our facility. On examination he had bilateral ptosis, complete external opthalmoplegia without retinopathy, stocking-glove neuropathy with all sensory modalities involved, absent reflexes, muscle atrophy with severe generalized weakness Medical Research Council (MRC) Scale for Muscle Strength grade 3, and borborygmi. Repeat nerve conduction study showed a sensorimotor neuropathy that had mixed demyelinating and axonal features, possibly hereditary. Further work-up also included urine porphyria screen, heavy metal screen, paraneoplastic panel, human immunodeficiency virus (HIV), autoimmune markers, including antibodies against myelin-associated glycoprotein (MAG) and ganglioside GQ1b, angiotensin-converting enzyme (ACE), thyroid-stimulating hormone (TSH), creatine phosphokinase (CPK), cerebrospinal fluid (CSF) studies, duodenal biopsy for Whipple's disease; all of which were unremarkable. Video swallow was remarkable for severe dysphagia, which improved throughout the clinical course. Given the constellation of the above clinical symptoms, MNGIE was suspected. Gene testing revealed two heterozygous missense mutations on the *TYMP* gene. There was a G-T transition at location766 (c.766G>T) resulting in a valine to phenylalanine substitution (p.Val256Phe) and a T-G transition at location 1142 (c.1142T>G) resulting in a leucine to arginine substitution (p.leu381Arg). These variants have not been previously identified nor clinically correlated with MNGIE. To further confirm the diagnosis, studies were done on TP activity and thymidine levels but we had technical difficulties obtaining those levels.

Discussion

To date the Human Gene Mutation Database (HGMD) reported 76 mutations of the *TYMP* gene which is associated with MNGIE. There were 47 missense/nonsense mutations, 11 splicing, 11 small deletion, 6 small insertions and 1 small indels mutations [3]. Literature review revealed that these two newly found

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missense mutations in our patient have not been previously described or associated with any diseases. It is not known if one or both are responsible for the defective TP enzyme. Thus far no correlation has been made between the specific type of mutation and disease severity; but it has been postulated that heterozygotes have less severe and later disease onset than homozygotes [4]. Marti et al. [5] discovered that asymptomatic heterozygous mutation carriers had 26 to 35% residual *TYMP* activity, suggesting that only a minimal level of the enzyme activity is required to prevent disease. They also demonstrated that when TP activity is 10 to 15% of normal in late-onset MNGIE patients, the clinical phenotype is less severe [5] but Garone et al. [2] also showed that late onset disease can manifest as a rapidly progressive disease. In a cohort of 102 patients, Garone et al. [2] found that the average age of onset of MNGIE was 17.9 yrs (5mths-35yrs) and average age of death was 37yrs (15-54 yrs). Our patient had symptoms initially in his teenage years, but the gastrointestinal symptoms at age 48 years.

Survival and prognosis are generally related to the degree of gastrointestinal involvement, and not necessarily with the degree of TP deficiency [2]. Patients often die as a result of cachexia, peritonitis, intestinal rupture, or esophageal bleeding related to cirrhosis, or aspiration pneumonia [4]. We believe that besides the chronic ptosis and opthalmoplegia, our patient had late onset neuropathic symptoms affecting the limbs and severe gastrointestinal tract dysfunction. Though he slightly improved in terms of some weight gain, resolution of emesis, and decreased diarrhea, he had repeated admissions for recurrent bouts of aspiration pneumonia and *Clostridium difficile* colitis, which were successfully treated with antibiotics. Currently, there are no established treatments; however, there are reports of decrease thymidine levels treated with platelet transfusion [2,7] and peritoneal dialysis and clinical improvement with stem cell transplantation [2].

Conclusion

MNGIE is a multisystem disease due to defective TP activity, which may result from several types of mutations. It can be easily overlooked due to its variable clinical presentation. So, regardless of age of onset, individuals presenting with ptosis, opthalmoplegia, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and leukoencephalopathy should be screened for MNGIE with genetic testing, TP activity or elevations of thymidine and deoxyuridine levels. Since the affected enzyme is known, further work is needed in the various treatment methods including enzyme replacement therapy.

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