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Mitochondrial neurogastrointestinal encephalopathy in an Indian family with possible manifesting carriers of heterozygous *TYMP* mutation

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ABSTRACT

Background: Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a distinctive autosomal recessive disorder with mitochondrial alterations due to mutations *TYMP* gene encoding thymidine phosphorylase.
Materials and methods: Study of clinical and biochemical characteristics of a family with MNGIE.
Results: Index case was a 32 year old man presenting with recurrent vomiting, early satiety and progressive weight loss. He had ptosis, restricted eye movements, generalized muscle wasting, and absent tendon reflexes. Lactate levels were elevated in venous blood and CSF lactate. MRI brain showed diffuse leucoencephalopathy. Barium swallow showed near total obstruction at mid portion of vertical limb of duodenum with ileus. Esophageal manometry suggested myopathy. Muscle biopsy revealed moderate numbers of ragged blue and ragged red fibers as well as cytochrome *c* oxidase deficient fibers. An elder brother had similar symptoms and expired after a surgical procedure and a 28 year old brother has similar illness. The father had asymptomatic bilateral ptosis with mild ophthalmoparesis. The paternal grandfather and paternal aunt also had bilateral ptosis. Clinical diagnosis of MNGIE was confirmed in the two living brothers by demonstrating severe defects of thymidine phosphorylase activity in buffy coat, elevated thymidine and deoxyuridine in plasma, and a homozygous *TYMP* c.893 G>A mutation.
Conclusions: This family with biochemically and genetically confirmed mitochondrial neurogastrointestinal encephalopathy syndrome uncharacteristically included heterozygous *TYMP* mutation carriers manifesting extra-ocular weakness. It is important to identify MNGIE patients early because therapeutic options are emerging.

1. Introduction

Mitochondrial diseases due to defects of intergenomic communication are caused by primary nuclear gene defects which cause pathogenic secondary alterations of mitochondrial DNA (mtDNA). Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is characterized by extraocular muscle weakness, gastrointestinal dysmotility, cachexia, peripheral neuropathy, leukoencephalopathy and mitochondrial DNA abnormalities [1–5]. MNGIE is caused by mutations in the *TYMP* gene encoding thymidine phosphorylase (TP) resulting in a severe or total abolition of TP activity [6]. In this report we present the clinical, biochemical, histopathological, and genetic features of a family with MNGIE.

2. Case report

Three brothers, with non-consanguineous parents, were affected with classical MNGIE syndrome. (Fig. 1) The proband was a 32-year-old man who presented with one year history of recurrent vomiting, early satiety and weight loss. After consuming small quantities of food he felt bloated and abdominal discomfort, and belched. The symptoms progressively worsened for 6 months and he was repeatedly admitted to a hospital for recurrent severe vomiting due to intestinal pseudo-obstruction. He lost 18 kg over one year. In retrospect, he recalled being thin and short and having bilateral ptosis with restricted ocular movements since early childhood No symptoms of cognitive dysfunction, hearing loss, peripheral neuropathy, or muscle weakness. Examination revealed an extremely slender constitution; height was 152 cm and weight was 32 kg (Fig. 2A). General physical examination was notable for scaphoid abdomen with prominent bowel sounds. Neurological examination revealed normal intellectual functions, vision, and fundi, but he had bilateral partial ptosis with gross restriction of eye movements in all directions (Fig. 2B), and mild bifacial weakness. Although muscles were generally thin and mildly

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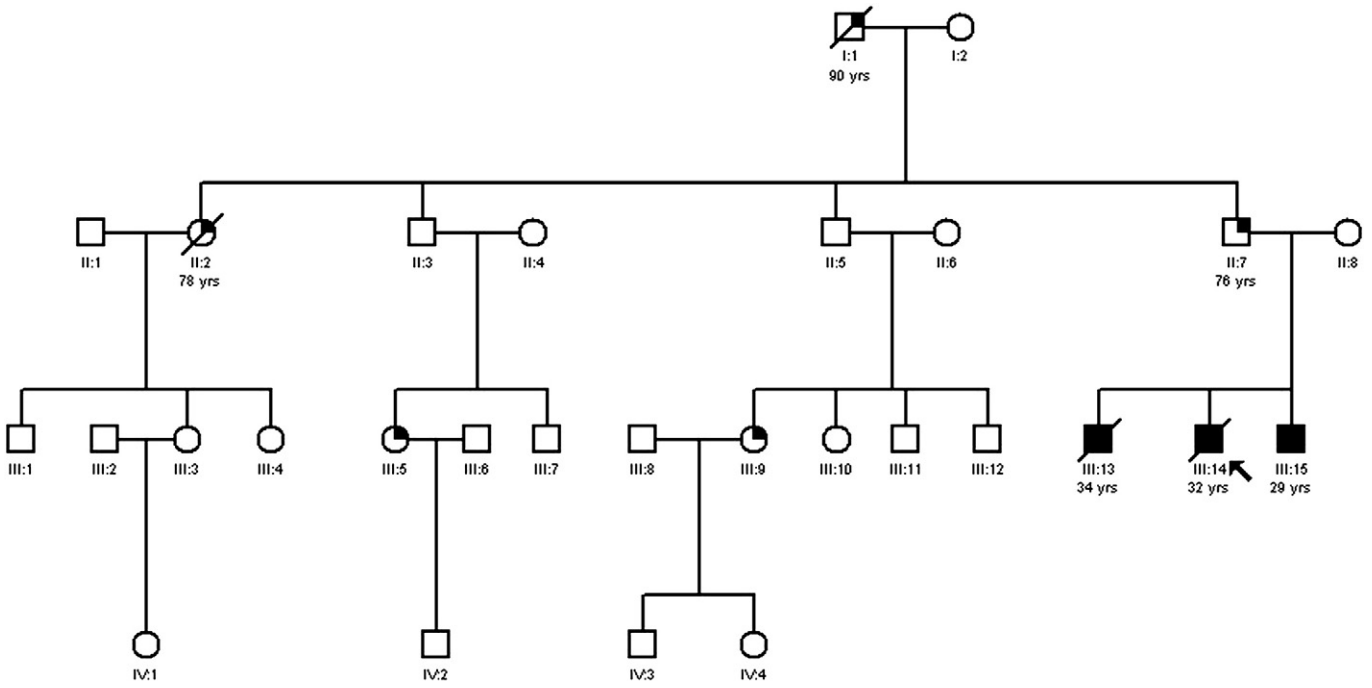

Fig. 1. Pedigree diagram of the family. Solid Symbols: Affected with classical MNGIE. Semisolid symbols: individuals manifesting only bilateral ptosis. Case II.7 examined. Has only ptosis. Case III.4 and Case III.8. Reported to have ptosis. Not examined.

hypotonic limb strength was normal. Sensory examination was normal. Tendon reflexes were absent. Over the next two years, the gastrointestinal manifestations progressed with recurrent episodes of pseudo-obstruction culminating in a fatal bout of pseudo-obstruction one and a-half years after presentation.

Electromyography revealed features of myopathy and nerve conduction studies showed demyelinating sensorimotor neuropathy. Barium swallow and barium meal studies performed during an episode of intestinal pseudo-obstruction showed normal esophageal emptying, gastric dilatation and delayed emptying, dilatation of the duodenal cap and segment up to the level of papilla, but near total pseudo-obstruction at mid portion of vertical limb of duodenum. The remainder of the small bowel loops were normal. Endoscopy revealed normal esophagus, fluid residue in the stomach, enlarged duodenal bulb, grossly dilated and tortuous second segment of the duodenum with effaced folds and residue. Esophageal manometry showed decreased lower esophageal sphincter pressure, low amplitude esophageal contractions suggestive of myopathy. Lactate levels were

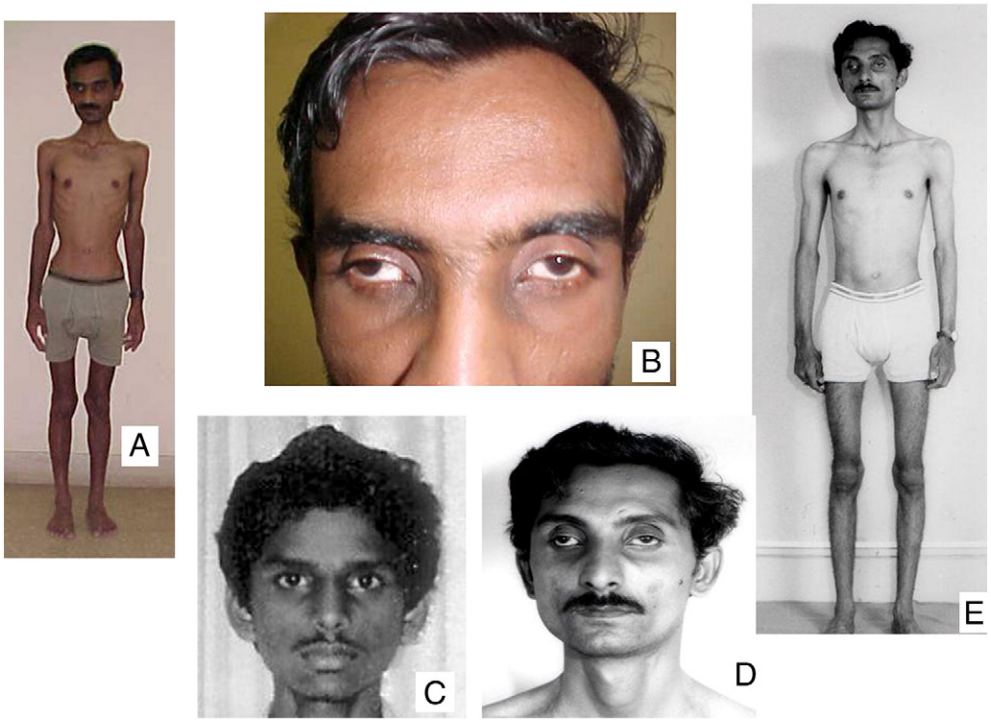

Fig. 2. A–E. 2A,B. Proband with typical slender habitus, ptosis and ophthalmoparesis 2C. Proband's elder sibling had no ocular symptoms 2D,E. Proband's younger brother with slender habitus, ptosis, and ophthalmoparesis.