ELSEVIER

Journal of the Neurological Sciences 228 (2005) 35–39

Journal of the Neurological Sciences

www.elsevier.com/locate/jns

A novel *thymidine phosphorylase* mutation in a Spanish MNGIE patient

Josep Gamez[a], Maria Carmen Lara[b], Fermin Mearin[c], Carlos Oliveras-Ley[d], Nuria Raguer[e], Montse Olive[f], Andres T. Leist[g], Antonia Perello[c], Monica Perona[c], Carlos Cervera[a], Antonio Luis Andreu[b], Ramon Martí[b], Michio Hirano[h,*]

[a]*Department of Neurology, Hospital Universitari Vall d' Hebron, Barcelona, Spain*
[b]*CIBBIM, Hospital Universitari Vall d' Hebron, Barcelona, Spain*
[c]*Department of Gastroenterology, Centro Medico Teknon, Barcelona, Spain*
[d]*Department of Neurology, Centro Medico Teknon, Barcelona, Spain*
[e]*Department of Neurophysiology, Hospital Universitari Vall d' Hebron, Barcelona, Spain*
[f]*Department of Neurophysiology, Centro Medico Teknon, Barcelona, Spain*
[g]*Department of Radiology, Centro Medico Teknon, Barcelona, Spain*
[h]*Department of Neurology, Columbia University College of Physicians and Surgeons, 630 West 168th St., P and S 4-443, New York, NY 10032, USA*

Received 4 June 2004; received in revised form 9 September 2004; accepted 10 September 2004
Available online 12 November 2004

Abstract

A 29-year-old Spanish man presented with chronic intestinal pseudo-obstruction, progressive external ophthalmoplegia, peripheral neuropathy, and diffuse leukoencephalopathy. This combination of clinical features is characteristic of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). Genetic analysis revealed a novel 18-base pair (bp) duplication (*5044–5061dup*) in exon 8 of the *thymidine phosphorylase* (TP) gene. The mutation is predicted to produce a 6 amino acid insertion in the alpha–beta-domain of the protein. This 18-bp insertion in the *thymidine phosphorylase* gene is the first duplication mutation identified in MNGIE.

Keywords: Mitochondrial encephalomyopathies; MNGIE; Thymidine phosphorylase; Mutation; Intergenomic communication defect; Duplication

1. Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive multisystem disorder, characterized by gastrointestinal, extraocular muscle, peripheral nerve, and cerebral white matter involvement [1–3]. Although the onset of symptoms is typically between the second and fifth decades of life, some individuals have presented in infancy with recurrent vomiting and difficulty gaining weight. Although the exact incidence and prevalence of the disease in the general population is unknown, disproportionately large numbers of patients have been identified in Mediterranean, Hispanic, Iranian–Jewish, and Ashkenazi–Jewish populations [3].

While neurological and gastrointestinal features are uniformly present in MNGIE patients, symptoms and signs of visceral neuropathy and myopathy are usually the most prominent and debilitating manifestations of the disease. Consequently, MNGIE patients complain of early satiety, borborygmi, vomiting, diarrhea, constipation, chronic abdominal pain, and episodic intestinal pseudo-obstruction. Gastrointestinal involvement leads to a severe weight loss in patients, who rapidly acquire a cachexic appearance, with signs of malnutrition including hypoproteinemia. The prognosis for MNGIE patients is related to the severity of gastrointestinal manifestations. The age at death has ranged between 18 and 58 years old, with a mean of 37 years old [3].

Mutations in the gene encoding thymidine phosphorylase (TP) have been identified as the cause of the disease [4]. TP

* Corresponding author. Tel.: +1 212 305 1048; fax: +1 212 305 3986.
E-mail address: mh29@columbia.edu (M. Hirano).

0022-510X/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.jns.2004.09.034

catalyses the reversible phosphorolysis of thymidine (dThd) to thymine and is an essential enzyme in maintaining homeostasis of cellular nucleotide pools [5]. As a consequence of the absence of TP, high levels of dThd and deoxyuridine (dUrd) are present in the plasma of patients [6,7]. It has been hypothesized that excess dThd and dUrd alter mitochondrial nucleoside/nucleotide pools, which, in turn, impair mitochondrial DNA replication and/or repair [4,6,7]. MNGIE thus belongs to the group of mitochondrial encephalomyopathies caused by defects in intergenomic communication [2,8–10].

Although fewer than 75 MNGIE patients have been reported, the molecular genetic basis of the disease is heterogeneous [3,11,12]. Thirty different mutations in the *TP* gene have been identified and no predominant mutation has been reported [3,11,12]. Most of the mutations are missense mutations. Deletions, insertions, and frameshift and splice-site mutations have also been reported. To date, and to the best of our knowledge, no duplications have been described [2–4,11–13].

In this study, we report on the clinical, biochemical, and genetic characteristics of a family with MNGIE and a novel microduplication mutation in the *TP* gene.

2. Patients and methods

2.1. Case report

The patient, a 29-year-old man (case III:5 in Fig. 1), was referred in May 2003 for evaluation of chronic intestinal pseudo-obstruction, associated with severe weight loss and hypoalbuminemia for 12 months.

In retrospect, he had suffered from postprandial abdominal pain, early satiety, borborygmi, nausea, recurrent vomiting, and poor weight gain since infancy. Despite being 1.78 m tall, he had never weighed more than 50 kg. His parents were not consanguineous. In August 1999, he developed mild symmetric distal limb weakness. Three months later, he noted paresthesias in the hands and feet. Electrophysiological studies suggested a demyelinating polyneuropathy. CSF showed normal proteins and no cells.

On admission in May 2003, he was markedly cachectic and weighed 44 kg. He had mild bilateral external ophthalmoparesis and enophthalmos, but no ptosis. Mild muscle weakness was present affecting the deltoids, biceps, and iliopsoas muscles (Medical Research Council scale 4+/5). Distal muscle strength was normal. Tendon reflexes were absent.

A radionuclide gastric emptying study 3 h after ingestion revealed gastroparesis with remnant material. Upper gastrointestinal series showed distended jejunum and ileum without obstruction. Esophagogastroduodenoscopy, ileoscopy, and colonoscopy were normal. Gastrointestinal manometry showed a neuropathic pattern affecting the distal half of the stomach and the duodenum. An increase in nonperistaltic duodenal motility was observed after the administration of octreotide. Abdominal CT showed no alterations. Rectal biopsy was normal.

T2-weighted brain magnetic resonance (MRI) showed a diffuse leukoencephalopathy affecting both cerebral hemispheres, the brain stem and the cerebellum, but sparing the corpus callosum and basal ganglia. Electrophysiological studies revealed a severe sensory motor demyelinating neuropathy, and a mild myogenic pattern in the proximal muscles in all four limbs. Electrocardiogram showed a sinus

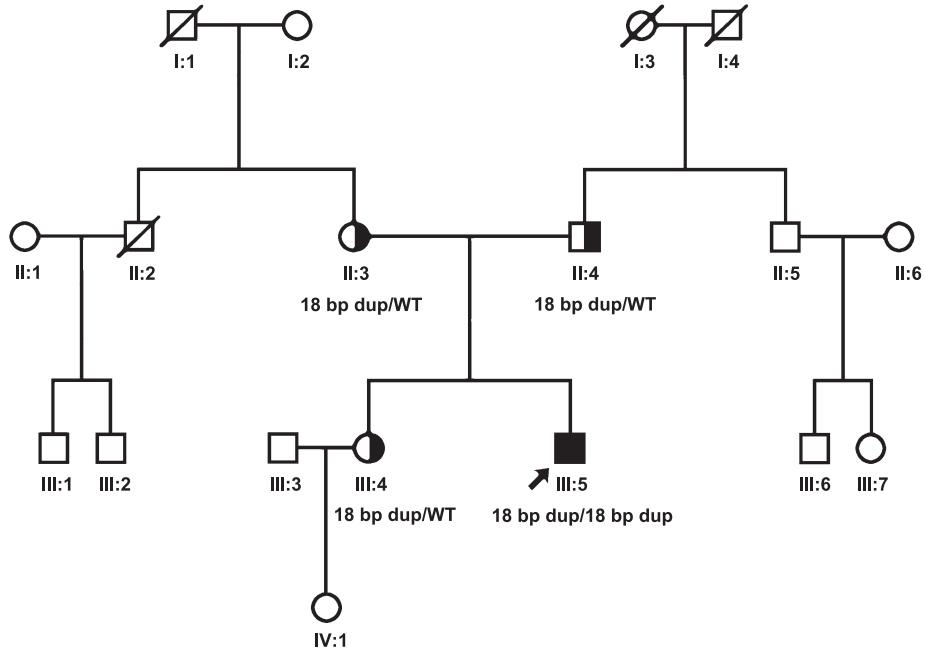

Fig. 1. Family Pedigree. The proband is indicated by an arrow. Genotypes are shown below the symbols. WT, wild-type. dup=*nts. 5044–5061dup*.