Digestive smooth muscle mitochondrial myopathy in patients with mitochondrial-neuro-gastro-intestinal encephalomyopathy (MNGIE)

Report of 3 cases and review of the literature

Hugues BLONDON (1), Marc POLIVKA (2), Francisca JOLY (1), Bernard FLOURIE (1), Jacqueline MIKOL (2), Bernard MESSING (1)

(1) Service d’Hépato-gastroentérologie et d’Assistance Nutritive, (2) Service d’Anatomopathologie, Hôpital Lariboisière, 75475 Paris Cedex 10.

SUMMARY

We report 3 new cases of Mitochondrial-Neuro-Gastro-Intestinal Encephalomyopathy (MNGIE) (or Pseudo-Obstruction-Leukoencephalopathy-Intestinal-Pseudoobstruction Syndrome [POLIP]), a rare disease that associates chronic intestinal pseudo-obstruction (CIPO) and neurological symptoms. A review of the 72 reported cases together with these 3 cases revealed that this condition was associated with (a) a specific cluster of neurological symptoms including leukoencephalopathy (96%), polyneuropathy (96%), ophthalmoplegia (91%) and hearing loss (53%); (b) a CIPO syndrome with the presence of small bowel diverticulae (53%); and (c) mitochondrial cytopathy in 36 of the 37 tested patients (2 of our 3 cases), and thymidine phosphorylase gene mutations in all the 37 tested patients (2 of our cases). The etiology of POLIP/MNGIE syndrome appears therefore to be due to a mitochondrial cytopathy secondary to thymidine phosphorylase gene mutation(s). In 3 cases, including 2 of our 3 patients, mitochondrial abnormalities were evidenced at the ultrastructural level in digestive smooth muscle demonstrating that the pathogenesis of gastrointestinal involvement was directly related to mitochondrial alterations in digestive smooth muscle cells.

RéSUMÉ

Démonstration d’une myopathie mitochondriale viscérale chez les malades atteints de MNGIE. Revue de la littérature à propos de 3 cas

Hugues BLONDON, Marc POLIVKA, Francisca JOLY, Bernard FLOURIE, Jacqueline MIKOL, Bernard MESSING

(Gastroenterol Clin Biol 2005;29:773-778)

Nous décrivons 3 nouveaux cas de Mitochondrial-Neuro-Gastro-Intestinal Encephalomyopathy (ou Pseudo-Obstruction-Leukoencephalopathy-Intestinal-Pseudoobstruction Syndrome), une affection rare entraînant une pseudo-obstruction intestinale chronique (POIC) et des symptômes neurologiques. Notre revue qui comprend les 72 cas de la littérature et ces trois cas montre que cette affection est caractérisée par a) un tableau neurologique spécifique comprenant l’association d’une leucoencéphalopathie (96 % des cas), d’une polyneuropathie (96 %), d’une ophthalmoplegie (91 %), et d’une surdité (53 %) ; b) une POIC, avec présence de diverticules de l’intestin grêle (53 %) ; c) une cytopathie mitochondriale, présente chez 36 des 37 malades et qui a été recherchée (donc 2 de nos 3 cas), et une mutation du gène de la thymidine phosphorylase, présente dans les 37 cas où elle a été recherchée (donc 2 de nos 3 cas). L’etiologie du MNGIE/POLIP syndrome est donc une cytopathie mitochondriale secondaire à une mutation du gène de la thymidine phosphorylase.

Dans 3 cas, dont 2 de nos malades, des anomalies mitochondriales ont été mises en évidence par microscopie électronique au niveau du muscle lisse de la paroi digestive démontrant le rôle direct des anomalies mitochondriales dans la pathogénie de ce syndrome au niveau digestif.

DIOPATHIC CHRONIC INTESTINAL PSEUDO-OBSTRUCTION (CIPO) is characterized by ineffective intestinal peristalsis which results from a disorder of unknown etiology of the intestinal smooth muscle (myopathy) or of the enteric nervous system (neuropathy) that can be recognized by full thickness small bowel biopsies and specific pathological studies [1]. Association of extradigestive muscular and/or neurological involvement with idiopathic CIPO had been reported and suggests a common pathogenesis [2-33]. The association of idiopathic CIPO and arreflexia and dysautonomia with a specific picture of intranuclear neuronal inclusions is a rare but well characterized entity [28-30]. The association of idiopathic CIPO with one or more of the following conditions: polyneuropathy, external progressive ophthalmoplegia and ptosis, leukoencephalopathy, which appears to be more frequently reported [2-27, 31-33] and has been independently described as either a POLIP syndrome (Polyneuropathy-Ophthalmoplegia-Leukoencephalopathy-Intestinal-Pseudo-obstruction syndrome) [11] or a MNGIE (initially for Myo-Neuro-Gastro-Intestinal-Encephalopathy, currently for Mitochondrial-Neuro-Gastro-Intestinal-Encephalomyopathy) [9]. This syndrome, often familial, affects predominantly young adults, is slowly progressive and potentially lethal. It is now recognized to be secondary to mitochondrial diseases [8-10, 13-20, 21-26, 31-33]. Mitochondrial diseases [34-36] are multisystemic disorders expressed mainly in skeletal muscles or central nervous system due to mitochondrial enzyme defects. Diagnosis is based upon functional mitochondrial abnormalities such as lactic acidosis, mitochondrial enzyme defect assessed by biochemical studies, and/or histopathological morphologic mitochondrial abnormalities such as classical "ragged red fiber" in muscle, and specific mitochondrial changes at ultrastructural level. Causes are mtDNA mutations or deletions [15-18, 21, 31], or nuclear DNA mutations inducing defects of intergeneric communication or expression of mitochondrial.

Two of the reported cases were partly presented at the 5th meeting on Neuromuscular Disease, Strasbourg, France 1993: poster 376 [27].
Mitochondrial genome [31]. Recently, in MNGIE, mutations mapped to locus 22q13.32qter of the gene of thymidine phosphorylase have been described [26, 33]. However, the pathogenesis of the CIPO in MNGIE is not well understood, and pathological studies of the gut remain to be fully described.

The aim of the present study is to report 3 new cases of MNGIE with a review of all the published cases with special emphasis on clinical manifestations and in pathological study of the digestive muscle in order to highlight the digestive features and pathogenesis of this syndrome.

Case reports

Case 1

A 26 year-old Caucasian French woman was hospitalized for denutrition. She had a history of chronic diarrhea, vomiting, bloating and abdominal cramping since infancy. At 23 years of age, laparotomy revealed mesenteric abscesses due to jejuno-ileal diverticular perforations. Clinical examination indicated cachexia (39 kg, 1.66 cm), diffuse muscle wasting, abdominal distention, bilateral external ophthalmoplegia, ptosis, gait ataxia, and lower limb hypoesthesia. Deep tendon reflexes were absent in the lower limbs and diminished in the upper limbs. Cognitive functions were preserved. Parenteral nutrition, oral vitamin E (tocopherol 2 g per day) and coenzyme Q10 (200 mg per day) were instituted. While on home parenteral nutrition, there was no improvement in neurological symptoms, and the patient developed insulin-dependent diabetes mellitus. Cisapride and oral erythromycin were ineffective in improving digestive symptoms. Following cardiac failure due to bacterial translocation, a partial enterectomy with an end-jejunosotomy was performed. The patient died of cachexia 2 months later. Consent for necropsy was not given.

At admission, routine laboratory data were normal. Vitamin E level was 3 mg/L (N: 7-13). Small bowel X-ray studies showed segmental small bowel dilation and multiple small ileal diverticulae. Esophageal manometric study revealed the absence of peristalsis. Cerebral magnetic resonance imaging (MRI) showed leukoencephalopathy with fronto-temporal periventricular white matter abnormalities. Electrophysiologic studies showed sensorimotor polyneuropathy of the upper and lower limbs. A 2.40 m small bowel specimen showed macroscopically altered stenosis and dilatations up to 7 cm wide and diverticulae. Routine histological examination on paraffin sections showed normal mucosa and submucosa. The inner layer of the muscularis propria was focally thickened, while the outer layer showed segmentary lesions of atrophy and fibrosis with vacuolization of smooth muscle cells. The myenteric plexus was within the normal range on light microscopy and after immunolabelling with S-100 protein and neurofilaments. Electron microscopy (EM) was performed on Epon ultra-thin sections stained with uranyl acetate and lead citrate. Myocytes of the muscularis propria harbored large numbers of abnormally large mitochondria associated with rarefaction of myofilaments and lipid accumulation (Figures 1 and 2). EM of the detroit muscle biopsy showed one ragged red fiber (RRF), a few cytochrome oxydase (COX) negative fibers and moderate lipid storage in type 2 fibers with no mitochondrial modifications. Ultrastructural study of the rectus abdominis showed mitochondria that were abnormal in shape and number. The peroneus brevis showed only neurogenic atrophy. The superficial peroneal nerve showed segmentary demyelination and axonal neuropathy on teased fibers. Tomacular neuropathy was also demonstrated in her father. Serum lactate was 2.63 mmol/L (N: 0.63-2.44). Spectrophotometric study of the deltoid muscle showed low activity of NADH-cytochrome c-reductase. Southern blot analysis of mitochondrial DNA of lymphocytes was normal. Studies were unsuccessful using paraffin-embedded gut specimens. A double mutation in the thymidine phosphorylase gene was found (E286K/E289A).

Case 2

A 30 year-old Kabyle woman was hospitalized for denutrition, chronic diarrhea, and recurrent episodes of vomiting, bloating, and abdominal cramping. She had had a history of chronic diarrhea alternated with constipation and abdominal pain since the age of 17. At 24 years of age a laparotomy was performed but no obvious cause of mechanical obstruction was found. Clinical examination revealed severe cachexia (28 kg, 1.55 cm), diffuse muscle wasting, abdominal distention, bilateral external ophthalmoplegia, gait ataxia, and lower limb hypoesthesia. Deep tendon reflexes were present. Cognitive functions were preserved. Parenteral nutrition was instituted. Oral vitamin E supplementation did not improve neurological symptoms. A cholecystectomy was performed for acute biliary pancreatitis. During the 5 year follow-up of the patient, CIPO progressively worsened but neurological symptoms remained stable. The patient was maintained on exclusive home parenteral nutrition with total enteral intolerance despite repeated attempts of bacterial overgrowth treatment associated with sequential prokinetic drugs such as cisapride, low dose intravenous erythromycin or octreotide (25 to 50 mg twice a day). She developed insulin-dependent diabetes and chronic pancreatitis.

At admission, routine laboratory data were normal. Vitamin E level was 5.6 mg/L (N: 7-13). Small bowel X-ray disclosed multiple small
diverticulae in the jejunum and ileum. Breath-test disclosed bacterial overgrowth. Esophageal manometric study was normal. Manometric study of the first 50 cm of small bowel showed normal motor migrating complexes, but high-amplitude propagated contractions (figure 3). Brain MRI showed periventricular bifrontal leukoencephalopathy. Electrophysiologic studies showed sensorimotor polyneuropathy. Audiogram disclosed hearing loss. EM revealed a large number of abnormally shaped mitochondria in gallbladder smooth muscle. The peroneus brevis showed neurogenic atrophy, and slight lipid accumulation in type 2 fibers without RRF and COX negative fibers. Mitochondria were within the normal range at ultrastructural examination. Superficial peroneal nerve biopsy segmentary demyelination on teased fibers. Serum lactate was 2.43 mmol/L (N: 0.63-2.44). Spectrophotometric study of the rectus abdominis showed low activity of succinate-C-reductase. Thymidine phosphorylase lymphocyte activity was nil and a homozygous mutation (GLU 289 ALA) in the thymidine phosphorylase gene (exon 7) was found.

Case 3

A 22 year-old Caucasian Bulgarian man was hospitalized for chronic diarrhea, vomiting, and abdominal pain that had recurred since the age of 15. Diarrhea had not improved after a gluten-free diet. The patient had undergone laparotomy for acute peritonitis secondary to a jejunal diverticular perforation at 20 years of age. No other abnormality was found. Thereafter, diarrhea persisted and dysphagia developed. Clinical examination revealed cachexia (43 kg, 183 cm), diffuse muscle wasting, moderate external ophthalmoplegia, and lower limb hypoesthesia. Deep tendon reflexes were absent in the lower limbs. Cognitive functions were preserved.

At admission routine laboratory data were normal. Vitamin E level was 4.5 mg/L (N: 7-13). Small bowel X-ray showed major gastroparesis and jejunal diverticulae at the mesenteric border (figure 4). Esophageal manometric study showed retropropagated or non-propagated swallowing and spontaneous activity. Brain MRI disclosed periventricular leukoencephalopathy, and peripheral polyneuropathy. A full-thickness biopsy of small bowel stained by hematoxylin and eosin in Bulgaria was reviewed. There was no villous atrophy, and no inflammatory infiltrate in the serosa and the muscularis propria. The external muscularis propria showed focal fibrosis and atrophy. A skeletal muscular biopsy was normal on usual stains. Serum lactate was 3.65 mmol/L (N: 0.63-2.44). Because this patient was lost to follow-up, biochemical investigations for mitochondrial disease were not performed.

Discussion

We report three new cases of idiopathic CIPO with neurological symptoms defining complete MNGIE syndrome according to the definition of Hirano et al. [21]. Two of our patients had mitochondrial cytopathy, and 2 had a mutation of the thymidine phosphorylase gene. Seventy-two other cases of MNGIE have been identified [2-26, 31-33], including 35 previously reported patients collected by Nishino et al. [33]. Comparison of the main clinical, morphological, biochemical and genetic features of the 72 cases with our cases is presented in table I.

MNGIE syndrome appears to be related to mitochondrial cytopathy, because evidence of mitochondrial dysfunction was found in 36 of the 37 investigated cases [8-10, 13-26, 31-33], including two of our three cases. Moreover, a mitochondrial disease was certain although not evidenced in two cases with thymidine phosphorylase gene mutation [26], and suspected in two other cases on biochemical grounds (12, case 3), or in 16 affected siblings of patients [14, 19, 33]. Heteroplasmy, defined as the coexistence of variable proportions of normal and mutant mitochondria in each individual cell of different tissues is

Familial cases are frequent in MNGIE (76%), especially in families with consanguinity, and are consistent with autosomal recessive transmission.

Digestive features of MNGIE consisted of manifestations of digestive dysmotility, beginning during childhood or in young adults with progressive evolution without remission. Symptoms of varying severity included mainly dysphagia, gastroparesis, chronic or recurrent acute pseudo-obstruction (which may be responsible for multiple laparotomies), and chronic diarrhea (table I). Severe denutrition was almost constant during the course of the disease and was an indication for home parenteral treatment. This aim of the latter treatment is to decrease bacterial overgrowth that can lead, in case of severe obstruction, to bacterial translocation. A rare complication of such a finding was an acute cardiac insufficiency that led in case 1 to urgent bowel resection. Large diverticula of the small intestine at the mesenteric border were indeed reported in 53% of cases, but this frequency is probably underestimated because most patients investigated by neurologists did not have small bowel imaging. Presence of multiple large small bowel diverticulae at the mesenteric border is suggestive of the diagnosis. Diverticulae were likely to be secondary to severe gut dysmotility rather than the cause, as already suggested [40]; they may be responsible for life-threatening complications such as perforation or abscesses as observed in our case 2.

The mechanism of idiopathic CIPO is classically either visceral myopathy or neuropathy [1]. To distinguish between a myogenic or neurogenic mechanism, manometric studies may be helpful, but the gold standard remains pathological study of full-thickness bowel biopsies. This important pathogenic issue has been rarely assessed in patients with MNGIE. Results of the few manometric studies reported in the literature were conflicting [3, 10, 14, 26, 32]. Esophageal manometry showed neuropathic changes in 2 patients [10, 14]; jejunal manometry in one patient [26] and in 4 asymptomatic relatives of patients with MNGIE also showed abnormalities consistent with neuropathy [3]. In contrast, Mueller et al. found normal esophageal manometry and myopathic-like changes in jejunal manometry of one patient [32]. In our cases, manometric results were also discordant: esophageal manometry was consistent with myopathy in case 1, with neuropathy in case 3, and was normal in case 2. Jejunal manometry was rather consistent with neuropathy than myopathy in case 2. Among the 72 reported cases of MNGIE (or POLIP) full-thickness small bowel biopsies were available in only 10 patients [3, 4, 9, 11, 12, 16-20, 25]. A myopathy was found in most of them [3, 4, 7, 9, 12, 16-20], but also a neuropathy in two cases [11] or a mixed myo-neuropathy in one case [25].

### Table I. – Main features of 75 patients with MNGIE or POLIP syndrome.

<table>
<thead>
<tr>
<th>Case reported in [33]</th>
<th>Other cases*</th>
<th>Personal cases</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>CIPO(b)</td>
<td>11/17</td>
<td>35/37</td>
<td>2/3</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>27/29</td>
<td>25/37</td>
<td>3/3</td>
</tr>
<tr>
<td>Denutrition</td>
<td>35/35</td>
<td>33/37</td>
<td>3/3</td>
</tr>
<tr>
<td>Small bowel diverticula</td>
<td>7/24</td>
<td>17/24</td>
<td>3/3</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>34/34</td>
<td>29/32</td>
<td>3/3</td>
</tr>
<tr>
<td>PEO(h) &amp; ptosis</td>
<td>35/35</td>
<td>31/37</td>
<td>3/3</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>14/31</td>
<td>17/26</td>
<td>2/3</td>
</tr>
<tr>
<td>Leuko-encephalopathy</td>
<td>27/27</td>
<td>19/21</td>
<td>3/3</td>
</tr>
<tr>
<td>Hyperlactacidemia</td>
<td>12/19</td>
<td>8/10</td>
<td>2/3</td>
</tr>
<tr>
<td>Increased CSF protein</td>
<td>8/9</td>
<td>11/15</td>
<td>ND(i)</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>21/21</td>
<td>13/14</td>
<td>2/2</td>
</tr>
<tr>
<td>Thymidine phosphorylase gene mutation</td>
<td>33/33</td>
<td>2/2</td>
<td>2/2</td>
</tr>
</tbody>
</table>

* from references 2-26, 31 & 32 ; \(b\) chronic intestinal pseudo-obstruction; \(h\) progressive external ophthalmoplegia ; \(c\) cerebrospinal fluid ; \(d\) not done

Principaux symptômes et résultats chez les 75 malades atteints de MNGIE (ou POLIP syndrome).

our three cases, pathological studies of surgical full-thickness digestive biopsies (small bowel or gallbladder) showed features of myopathy. In this disorder, the digestive picture is then mainly a myopathy but a neuropathy, or a myo-neuropathy is possible: indeed, a mixed myogenic and neurogenic involvement is a characteristic of mitochondrial diseases. All the visceral neuro-pathies have been described in the “POLIP-syndrome” reported by Simon et al. [11], and in these cases a mitochondrial cytopathy has not been searched for. However, it seems logical to conclude that they belong to the same clinical pathological entity than MNGIE because (a) the very specific clinical cluster was similar and (b) a visceral neuropathy has also been found in association with a myopathy in a case of MNGIE with proven mitochondrial disease [25].

Mitochondrial morphological abnormalities have been rarely documented in the gut: they were previously reported in the muscularis propria myocytes and ganglion cells of one case of MNGIE [25], in the muscularis propria myocytes of one case of a non-MNGIE mitochondrial cytopathy associated with CIP0 [20], and in the muscularis mucosae myocytes of two cases of a mitochondrial disease without significant digestive symptoms [41]. In our first two patients, underlying mitochondrial morphological abnormalities were clearly evidenced by EM of digestive myocytes of the small intestine (case 1) and of the gallbladder (case 2). These mitochondrial abnormalities are similar to those observed in skeletal muscle of patients affected by mitochondrial cytopathies. These findings explain, as in skeletal muscle, the dysfunction of digestive smooth muscle and therefore the clinical digestive patterns. Moreover, in some patients, digestive symptoms and signs are prominent and the involvement of skeletal muscle is lacking; in such cases, the pathological diagnosis of mitochondrial disease cannot be based on muscular biopsy, but on full-thickness intestinal biopsies if available.

In summary, visceral involvement in MNGIE may be myogenic, neurogenic, or both, even if myogenic involvement appeared to be more frequent. The visceral myo-neuropathy is directly related to mitochondrial dysfunction in the gut. Thus, systemic treatments which restore normal mitochondrial functions, or which more specifically lower thymidine plasma level, might be theoretically effective for improving digestive symptoms in MNGIE [36, 37]. Several drugs have been tried in mitochondrial diseases with more or less clinical efficiency like coenzyme Q10, vitamin K3, vitamin C or carnitine [36, 37], but data on their clinical efficiency in MNGIE are lacking: in addition hemodilution therapy does not seem to be effective [37]. In two of our patients treated with coenzyme Q10 neither digestive nor neurological improvements was noted. We suggest that alfa tocopherol (vitamin E which is a potent anti-oxydant) supplementation is important, because vitamin E deficiency is frequent in chronic digestive malabsorption, as observed in our patients. Such a severe and long-standing deficiency may worsen mitochondrial dysfunction and reveal a latent mitochondrial disease or increase its symptomatic expression. To date, the basis of the management of severe CIPO syndrome remains the classical association of prokinetic drugs and home parenteral nutrition. However, if parenteral treatment, in approved centers, restored nutritional rehabilitation without too many complications, the chronic pseudo-obstruction was completely resistant to any prokinetic drug in our 2 cases.

ACKNOWLEDGEMENTS — The authors thank Doctors N Abdelli, A Dancourt, P Hautefeuille, P Marteau, C Matushansky, JC Ramband, JM Reimdun, G Said, K Vahedi, JM Vissy, for their clinical expertise; C Lacroix, A Lavergne, A Lombes, S Love, S Nicolov; P Rustin for their pathological expertise; A Slaama for dosage of thymidine phosphorylase; F Bernard, A Chazalbert, and MC Roche for their expert technical reports and especially A. Gaicho-Chantel for identification of novel thymidine phosphorylase gene mutations.

REFERENCES


