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

Report of 3 cases and review of the literature

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SUMMARY

We report 3 new cases of Mitochondrial-Neuro-Gastro-Intestinal Encephalomyopathy (MNGIE) (or Pseudo-Obstruction-Leukoencephalopathy-Intestinal-Pseudo-obstruction 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 (55%); (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 cells 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

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Nous décrivons 3 nouveaux cas de Mitochondrial-Neuro-Gastro-Intestinal Encephalomyopathy (ou Pseudo-Obstruction-Leukoencephalopathy-Intestinal-Pseudo-obstruction Syndrome), une affection rare entrainant 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 leucoencephalopathie (96 % des cas), d’une polyneuropathie (96 %), d’une ophthalmoplegie (91 %), et d’une surdité (55 %) ; b) une POIC, avec présence de diverticules de l’intestin grêle (53 %) ; c) une cytopathie mitochondriale, présente chez 36 des 37 malades chez lesquels elle a été recherchée (dont 2 de nos 3 cas), et une mutation du gène de la thymidine phosphorylase, présente dans les 37 cas où elle a été recherchée (dont 2 de nos 3 cas). L’étiologie 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.
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, 166 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 of the neurological symptoms of 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-jejunostomy 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. The superficial peroneal nerve showed segmentary demyelination and tomacular 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, 155 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 μg 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

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**Fig. 1** – Gut muscularis propria from Case 1 with increased number of mitochondria demonstrating mitochondrial cytopathy (Electron micrograph, original magnification x 5200).

**Augmentation du nombre des mitochon- dries dans la musculuse du grêle du malade 1 : aspect de cytopathie mitochondriale (microscopie électronique, grossissement 5200).**

**Fig. 2** – Higher magnification of Figure 1 in another cell showing abnormally-shaped mitochondria demonstrating mitochondrial cytopathy (Electron micrograph, original magnification x 8900).

**Mitochon- dries de formes anormales à un grossissement supérieur de la figure 1 : aspect de cytopathie mitochondriale (microscopie électronique, grossissement 8900).**
diverticules au niveau de l’ileum. Le test de pepsine s’est normalisé. L’endoscopie digestive n’a pas révélé d’autre anomalie. L’électromyogramme s’est normalisé. Le malade est resté stable avec une gastro-entérite chronique et une neuropathie polyradiculaire. Une rétrospective de 50 cm de l’intestin grêle a permis de voir des diverticules géants au bord mésentérique (cas 3).

**Case 3**

Un homme bulgare noir de 22 ans a été hospitalisé pour une diarrhée chronique, des vomissements et une douleur abdominale qui se sont reproduits depuis 15 ans. Il n’avait pas été opéré. Le patient avait reçu de l’EHA pour un épisode aigu de peritonite. L’intestin grêle a été montré normal sur les examens anatomiques. L’examen échographique de la rate et du foie a montré une augmentation de la taille. Le patient avait une attaque de rate à 20 ans. Aucune autre anomalie n’a été trouvée. Elle a développé des diarrhées persistantes et une dysphagie. Cliniquement, l’examen a révélé une cachexie (43 kg, 183 cm), du flou musculaire, des troubles oculaires externes et des hypoesthésies en bas du corps. Les fonctions cognitives étaient préservées.

À l’admission, les données biologiques étaient normales. Le taux d’EHA était de 4,5 mg/L (N: 7-13). L’œdème a persisté et la dysphagie a développé. Cliniquement, l’examen a révélé une cachexie (43 kg, 183 cm), du flou musculaire, des troubles oculaires externes et des hypoesthésies en bas du corps. Les fonctions cognitives étaient préservées.

**Literature review**

Les cas ont été identifiés en utilisant MEDLINE et les bibliographies de revues pertinentes. MNGIE ou POLIP syndrome a été défini comme (a) toute signe ou symptomatologie de la dysmotilité digestive chronique, et (b) au moins l’un des deux événements suivants : diarrhée sévère, vomissements et douleur abdominale qui se sont reproduits depuis 15 ans. Il n’avait pas été opéré. Le patient avait reçu de l’EHA pour un épisode aigu de peritonite. L’intestin grêle a été montré normal sur les examens anatomiques. L’examen échographique de la rate et du foie a montré une augmentation de la taille. Le patient avait une attaque de rate à 20 ans. Aucune autre anomalie n’a été trouvée. Elle a développé des diarrhées persistantes et une dysphagie. Cliniquement, l’examen a révélé une cachexie (43 kg, 183 cm), du flou musculaire, des troubles oculaires externes et des hypoesthésies en bas du corps. Les fonctions cognitives étaient préservées.

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**Discussion**

Nous rapportons trois nouveaux cas de diarrhée chronique, vomissements et douleur abdominale qui se sont reproduits depuis 15 ans. Il n’avait pas été opéré. Le patient avait reçu de l’EHA pour un épisode aigu de peritonite. L’intestin grêle a été montré normal sur les examens anatomiques. L’examen échographique de la rate et du foie a montré une augmentation de la taille. Le patient avait une attaque de rate à 20 ans. Aucune autre anomalie n’a été trouvée. Elle a développé des diarrhées persistantes et une dysphagie. Cliniquement, l’examen a révélé une cachexie (43 kg, 183 cm), du flou musculaire, des troubles oculaires externes et des hypoesthésies en bas du corps. Les fonctions cognitives étaient préservées.

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 [2-26, 31-33]. Comparison of the main clinical, morphological, biochemical and genetic features of the 72 cases with our cases is presented in table 1.
Table I. – Main features of 75 patients with MNGIE or POLIP syndrome.

<table>
<thead>
<tr>
<th></th>
<th>Case reported in [33]</th>
<th>Other cases*</th>
<th>Personal cases</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>37</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>CIP OA</td>
<td>11/17</td>
<td>35/37</td>
<td>2/3</td>
<td>48/67 (72%)</td>
</tr>
<tr>
<td>Chronic diarrhea</td>
<td>27/29</td>
<td>25/37</td>
<td>3/3</td>
<td>55/69 (80%)</td>
</tr>
<tr>
<td>Denutrition</td>
<td>35/35</td>
<td>33/37</td>
<td>3/3</td>
<td>71/75 (95%)</td>
</tr>
<tr>
<td>Small bowel diverticula</td>
<td>7/24</td>
<td>17/24</td>
<td>3/3</td>
<td>27/51 (53%)</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>34/34</td>
<td>29/32</td>
<td>3/3</td>
<td>66/69 (96%)</td>
</tr>
<tr>
<td>PEOb &amp; ptosis</td>
<td>35/35</td>
<td>31/37</td>
<td>3/3</td>
<td>68/75 (91%)</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>14/31</td>
<td>17/26</td>
<td>2/3</td>
<td>33/60 (55%)</td>
</tr>
<tr>
<td>Leuko-encephalopathy</td>
<td>27/27</td>
<td>19/21</td>
<td>3/3</td>
<td>49/51 (96%)</td>
</tr>
<tr>
<td>Hyperlactacidemia</td>
<td>12/19</td>
<td>8/10</td>
<td>2/3</td>
<td>19/24 (79%)</td>
</tr>
<tr>
<td>Increased CSF protein</td>
<td>8/9</td>
<td>11/15</td>
<td>NDd</td>
<td>19/24 (79%)</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>21/21</td>
<td>13/14</td>
<td>2/2</td>
<td>36/37 (97%)</td>
</tr>
<tr>
<td>Thymidine phosphorylase gene mutation</td>
<td>33/33</td>
<td>2/2</td>
<td>2/2</td>
<td>37/37 (100%)</td>
</tr>
</tbody>
</table>

* from references 2-26, 31 & 32 ; ° chronic intestinal pseudo-obstruction; ° progressive external ophthalmoplegia ;  
° cerebrospinal fluid ; ° not done

characteristic of mitochondrial diseases. This explains the phenotypic heterogeneity of the disease with clinical expression in each organ varying from undetectable to high. Recently Nishino et al. found a homozygous mutation in the gene of thymidine phosphorylase in patients with MNGIE [26, 33]. Severe reduction of the activity of this enzyme leads to increased plasma levels of thymidine which could alter mitochondrial replication and/or repair [38]. A double thymidine phosphorylase gene mutation was found in our 1st patient and a homozygous mutation in our case 2nd patient, the only patients in which this identification was performed [39].

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 nutrition. The latter treatment was only supportive and indicated in case of severe chronic pseudo-obstruction, resistant to usual prokinetic treatment, a finding observed in 2 of our 3 cases. Note-worthy, the third case was without evident pseudo-obstruction but with malabsorptive diarrhea associated with giant diverticulae, a fate that can be ameliorated with sequential antibiotic 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 CIFO 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].
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 neuropa-thies have been described in the “POLP-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 only 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 myo-genic, 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 seems if available to induce thymidine metabolism 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 alpha tocopherol (vitamin E which is a potent anti-oxydant) supplementa-tion 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 mito-chondrial dysfunction and reveal a latent mitochondrial disease or increase its symptomatic expression. To date, the basis of the management of severe CIP0 syndrome remains the classical association of prokinetic drugs and home parenteral nutrition. However, if parenteral treatment, in approved centers, restored nutrition rehabilitation without too many complications, the chronic pseudo-obstruction was completely resistant to any prokinetic drug in our 2 cases.

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REFERENCES


