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-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 (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 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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(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 (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’étiole 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 pathogenie 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, 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 (loccopheral 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-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. A 2.40 m small bowel specimen showed macroscopically alternated 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 thickeened, 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 detoid muscle biopsy showed one ragged red fiber (RFF), a few cytochrome oxidase (COX) negative fibers and moderate lipid storage in type 2 fibers with no mitochondrial modifications. Ultrastructural study of the rectus abdominals 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 detoid 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).
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. Electrophysiological 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 occurred 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 electrophysiological studies showed 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). Small bowel X-ray showed major gastroparesis, ptosis, polyneuropathy, leukoencephalopathy assessed by pathologic examination, and jejunal diverticulae at the mesenteric border (case 3).

**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 were 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 1.

**Literature review**

Cases were identified by searching MEDLINE and the bibliographies of relevant articles and reviews. MNGIE or POLIP syndrome was defined as (a) any sign or symptom of chronic gut dysmotility, and (b) at least 2 of the following conditions: progressive external ophthalmoplegia, ptosis, polyneuropathy, leukoencephalopathy assessed by pathology or imaging, or familial history, and (c) no other known cause of CIPO (such as: systemic sclerosis, amyloidosis, familial visceral myopathy, neoplastic diseases, etc...). All reports were carefully reviewed to avoid redundant cases. Seventy-two cases of MNGIE were 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 1.

**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]. Heteroplasmia, defined as the coexistence of variable proportions of normal and mutant mitochondria in each individual cell of different tissues is.

**Fig. 3** – Duodeno-jejunal manometry showing high-amplitude propagated contractions (case 2).

Contractions propagées de forte amplitude sur une manométrie duodéno-jéjunale chez le malade 2.
characteristic of mitochondrial diseases. This explains the pheno-
typic 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 phos-
phorylase 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
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.
Noteworthy, the third case was without evident pseudo-obstruc-
tion but with malabsorptive diarrhea associated with giant diver-
ticulae, 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 bacte-
rial 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 sec-
ondary to severe gut dysmotility rather than the cause, as
already suggested [40]; they may be responsible for life-threat-
ening complications such as perforation or abscesses as
observed in our case 2.

The mechanism of idiopathic CIFO is classically either vis-
ceral 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 neuro-
pathic 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 manom-
etry and myopathic-like changes in jejunal manometry of one
patient [26]. In our cases, manometric results were also discord-
ant: 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>
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<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>37</td>
<td>3</td>
</tr>
<tr>
<td>CIFOa</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>
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</table>
| Small bowel diverti-
cula                  | 7/24        | 17/24         | 3/3   | 27/51 (53%)  |
| Polyneuropathy       | 34/34       | 29/32         | 3/3   | 66/69 (96%)  |
| PEOb & ptosis        | 35/35       | 31/37         | 3/3   | 68/75 (91%)  |
| Hearing loss         | 14/31       | 17/26         | 2/3   | 33/60 (55%)  |
| Leuko-encephalopathy | 27/27       | 19/21         | 3/3   | 49/51 (96%)  |
| Hyperlactacidemia    | 12/19       | 8/10          | 2/3   | 19/24 (79%)  |
| Increased CSFb       | 8/9         | 11/15         | NDd  | 19/24 (79%)  |
| Mitochondrial disease| 21/21       | 13/14         | 2/2   | 36/37 (97%)  |
| Thymidine phosphoryl-
ase gene mutation     | 33/33       | 2/2           | 2/2   | 37/37 (100%) |

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

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 neuropathies 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 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 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 strategies to reduce thymidine load 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) 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 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.

ACKNOWLEDGEMENTS — The authors thank Doctors N Abdelli, A Dancourt, P Hautefeuille, P Marteau, C Mattuchansky, JC Rambaud, JM Reimund, G Said, K Vahedi, JM Vissy, for their clinical expertise; C Lacroix, A Lavergne, A Lambes, S Love, S Nicolov, P Rustin for their pathological expertise; A Slama for dosage of thymidine phosphorylase; P Bernard, A Chaulet, and MC Rouche for their expert technical reports and especially A. Gaiochon-Mantel for identification of novel thymidine phosphorylase gene mutations.

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