Gastrointestinal tract symptoms in Maternally Inherited Diabetes and Deafness (MIDD)

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SUMMARY

Objective: To evaluate the prevalence and clinical consequences of gastro-intestinal manifestations in Maternally Inherited Diabetes and Deafness syndrome (MIDD).

Methods: We report the case of fatal intestinal pseudo-obstruction in a patient with severe MIDD. Using a standardized questionnaire, we evaluate the frequency of gastrointestinal tract (GIT) symptoms in 10 patients with MIDD (8 A3243G and 2 T14709C mutations of mitochondrial DNA). The reference population consisted of 50 patients with type 1 diabetes matched for disease duration. In 4 patients with digestive manifestations endoscopic examination of upper and lower GIT was performed allowing multiple biopsies for ultrastructural and molecular analysis.

Results: GIT symptoms were frequently reported in MIDD specially in patients bearing the mt 3243 mutation. The manifestations i.e. constipation, diarrhea or both, were more frequent in this subgroup than in type 1 diabetic population (88% vs 28%, p < 0.05). Ileus is a rare and severe complication with a frequent fatal issue. Ultrastructural analysis of the mucosa from oesophagus, stomach, duodenum, colon and rectum showed mild modifications such as accumulation of normal mitochondria and lipid droplets. Heteroplasmy levels were determined in 4 patients harboring the 3243 mutation. In three patients the percentage of mutated DNA increased from upper to lower GIT.

Conclusions: Gastrointestinal symptoms are frequent in MIDD secondary to 3243 mutation. They might explain the lower body weight observed in these patients in comparison to reference diabetic populations. They can also lead to a severe complication namely the intestinal pseudo-obstruction.

Key-words: Diabetes mellitus • Mitochondriopathy • MIDD • GIT.

RESUME

Manifestations digestives des diabetes et surdités de transmission matrilinéaire (MIDD)

Objectifs : Evaluer la prévalence et les conséquences cliniques des manifestations digestives des diabètes et surdités de transmission matrilinéaire (MIDD).

Méthodes : Nous rapportons le cas d’une pseudo-obstruction intestinale fatale chez un patient souffrant d’une forme sévère de MIDD. En utilisant un questionnaire standardisé, nous avons ensuite apprécié la fréquence des symptômes digestifs chez 10 patients souffrant de MIDD (8 avec la mutation A3243G et 2 avec la mutation T14709C sur l’ADN mitochondrial). La population contrôle consistait en 50 patients avec un diabète de type 1, appariés pour la durée d’évolution du diabète. Chez six patients symptomatiques, un examen endoscopique de l’appareil digestif par voie haute et basse a été effectué et a permis la réalisation de biopsies multiples pour une étude ultra structurale et moléculaire.

Résultats : Des symptômes digestifs sont fréquents au cours du MIDD particulièrement chez les patients avec la mutation 3243. Ces manifestations, constipation, diarrhée ou alternance des deux, sont plus fréquentes que dans le diabète de type 1 (88 % vs 28 % p < 0.05). L’iléus est une complication rare et sévère avec une issue souvent fatale. L’analyse ultra structurale de la muqueuse de l’ösophaghe, de l’estomac, du duodénum, du côlon et du rectum montrait des anomalies minimes telles qu’une augmentation du nombre de mitochondries et la présence de gouttelettes lipidiques. Le niveau d’hétéroplasmie a été déterminé chez 4 patients avec la mutation 3243. Chez 3 d’entre eux le pourcentage d’ADN mitochondrial muté augmentait de la partie proximale jusqu’à la partie distale du tractus digestif.

Conclusions : Les symptômes digestifs sont fréquents au cours des MIDD dus à la mutation 3243. Ils pourraient expliquer le poids souvent diminué de ces patients par rapport à leurs homologues souffrant d’un diabète de type 1. Ils peuvent aussi conduire à une sévère complication, en l’occurrence la pseudo-obstruction intestinale.

Mots-clés : Diabète sucré • Mitochondriopathie • Diabète mitochondrial • Tractus digestif.

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Mitochondrial diabetes, also called MIDD for Maternal Inherited Diabetes and Deafness, is a monogenic form of diabetes mellitus [1]. Several molecular anomalies of mitochondrial DNA (mtDNA) have been related to this disease, but the A to G transition at nucleotide 3243 in the mitochondrial tRNA⁰⁰<sub>Leu</sub> (UUR) gene is the main cause of MIDD. This point mutation is also observed in another syndrome called MELAS (Mitochondrial myopathy, Encephalopathy, Lactic acidosis and Stroke-like episodes) [2]. Usually the diagnosis is based on the association of maternal transmission and extrapancreatic manifestations. Molecular analysis allows the identification of the responsible mtDNA mutation in blood or other tissues. In MIDD, extrapancreatic associations are mainly represented by specific symptoms involving muscle, myocardium, retina, cochlea and central nervous system [3].

We would like to draw the attention of specialists in Diabetology to gastrointestinal tract involvement in this disease and more specifically to warn them about a severe digestive complication that is intestinal pseudo-obstruction.

Here, we report the occurrence of a fatal intestinal pseudo-obstruction in a patient with a severe MIDD syndrome. We have also assessed the frequency of digestive symptoms in 10 patients with characterized MIDD and a reference group of 50 matched patients with type 1 diabetes. Finally, serial biopsies have been performed along the gastrointestinal tract in 4 patients with MIDD and digestive symptoms allowing ultrastructural and molecular analysis.

Case report

A 64 year old diabetic patient known as bearing the mt DNA mutation at the 3243 position was referred for progressive malaise, weight loss and digestive symptoms as alternation of severe constipation and profuse diarrhea. The diagnosis of mitochondriopathy had been made at the age of 40 years on worsening of previous myopathy with proximal weakness and bilateral neurosensory hearing impairment associated with possible matrilinear transmission of diabetes and hearing impairment in the pedigree. Diabetes was diagnosed at 50 years and needed insulin treatment 8 years later. In addition, a cardiac conduction defect occurred at 50 years leading to implantation of a pace-maker, a cerebellar syndrome with ophthalmoplegia appeared at 60 years and finally severe cardiomyopathy with only 25% of ventricular ejection fraction was diagnosed at 62 years. Macular pattern dystrophy of retina and peripheral neuropathy were also present. Treatment by L-Carnitine (2 g/day) and CoEnzyme Q10 (150 mg/day) was introduced 7 months before admission.

At admission, his complaints were nausea, abdominal pain, and profound anorexia. The abdomen was bloated. X ray examination showed a diffuse dilatation of intestinal loops. Endoscopic examinations and tomodensitometry did not show any obstacle. Plasma lactate level was found massively increased (range: 3.78-10.82 mmol/l, normal range: 1-1.8 mmol/l). Finally the context and the absence of obvious cause of obstruction lead to the conclusion of a functional intestinal occlusion secondary to mitochondriopathy.

The patient was subsequently fed by parenteral route and insulin was administered IV. Digestive aspiration was not necessary. An attempt of stimulation of gastrointestinal peristalsism was performed using drugs as cisaprid or pyridostigmine. The transit was partially restored but relapses of intestinal paralyse occurred during the following days. Finally, 40 days after admission, the patient died from a septic shock due to a septicemia secondary to either contamination of infusion system or bacterial translocation from digestive tract.

Frequency of gastrointestinal complaints in MIDD

In order to evaluate the true frequency of gastrointestinal symptoms in MIDD we submitted the other patients suffering of mitochondrial diabetes and followed in our departement to a standardized questionnaire. The MIDD group was composed of 8 non related patients with a point mutation at nt 3243 and 2 related diabetic subjects with a point mutation at nt 14709. As digestive complaints are rather common in diabetes specially after a long duration of the disease in patients developing vegetative neuropathy, we submitted also 50 type 1 diabetic patients attending the outpatient clinic and matched for the disease duration to the same questionnaire.

The results are presented on the Table 1. In MIDD group, constipation and diarrhea were only observed in MIDD secondary to 3243 mutation. The frequency of these symptoms in this subgroup was significantly higher than in type 1 diabetic patient population (88% of constipation or diarrhea or both in MIDD vs. 28% in type 1 diabetes, p ≤ 0.05). The frequency of such complaints observed in our MIDD subgroup is also higher than that published in large community based series of either type 1 or type 2 diabetes [4, 5]. The large frequency of the GIT manifestations in MIDD patients prevented of detecting any relation with the clinical presentation, except in the patient with pseudo-obstruction who had a very severe form of the disease.

Six MIDD patients positive for the 3243 mutation, with very unpleasant gastrointestinal symptoms were submitted to oesogastrodudenal and colorectal endoscopic examinations. The findings of these investigations were unspecific colitis in 2, atrophy of mucosa of stomach or duodenum in 2, diverticulosis of duodenum in 1, diverticulosis of colon in 1 and colorectal cancer in 1. These findings suggest that digestive symptoms in these patients might be heterogeneous in their mechanisms.

Concerning the MIDD syndrome associated with a T14709C point mutation in the tRNA<sub>Glu</sub> gene [6], the
sample size is too small to conclude that gastrointestinal manifestation cannot occur in this subgroup. But it is known that the phenotype of this mutation is rather different from the classical MIDD. For instance, we never observed macular pattern dystrophy [6] which is very frequent in MIDD, at least in French population [3].

**Ultrastructural and molecular analysis**

In the group submitted to digestive endoscopy, serial biopsies (oesophagus, stomach, duodenum, colon and rectum) were performed in 4 patients. The samples were prepared for ultrastructural examination under electronic microscopy from one hand and for quantification of heteroplasmy from the other hand.

GIT samples were treated for conventional transmission electron microscopy. Specimens were fixed in 2.5% glutaraldehyde in 0.1 M phosphate buffered saline, post fixed with 1% osmic acid and embedded in araldite. Ultrathin sections were double stained with uranyl acetate and lead citrate. Ultrastructural analysis was performed with a Jeol 100 C electron microscope. The ultrastructural aspects of mucosa in various parts of GIT from one patient are represented on the Figure 1. It can be conclude from this analyses that in some area an accumulation of mitochondria can be observed but these organelles don’t exhibit obvious structural abnormality. Lipids droplets were also found suggesting a possible anomaly in fatty acid handling and/or lipolytic pathway in the mitochondria. In conclusion, no gross anomaly was observed thorough the gastrointestinal tract but it is worthy to note that very few smooth muscle cells could be observed as the biopsy were too superficial for safety reasons. Unfortunately, no tissue from the patient with the intestinal pseudo-occlusion was available for this study.

We determined the relative proportions of mutant and wild-type mtDNA in biopsies as previously described [6]. Despite the absence of major ultrastructural changes, the molecular analysis confirmed the presence of mutated mtDNA in rather large amount all along the GI tract in these patients. Heteroplasmy results in various tissues is represented on the Figure 2. In three patients out of 4 there was a gradient in heteroplasmy from oesophagus to rectum with higher percentage of mutated mtDNA observed in the last part of GI tract.

**Discussion**

Gastrointestinal tract functional impairment in mitochondrial disease has been mainly related to a specific entity named MNGIE (Mitochondrial NeuroGastroIntestinal Encephalomyopathy) [reviewed in 7]. This disease which combines various digestive complaints, pseudo-obstruction, diverticulosis, cachexia from one hand with neuromuscular symptoms (ophthalmoplegia, neuropathy, leucoencephalopathy) from the other, has an autosomic recessive transmission. The mitochondrial anomalies i.e. multiple deletions with mtDNA depletion, are secondary to a nuclear mutation located in the thymidine phosphorylase gene.

In MELAS, intestinal pseudo-obstruction has been also described in few patients. Thirteen cases have been reported as yet, 10 without diabetes [8-15] and 3 with diabetes (the present observation included) [16, 17]. The observations of the two patients with MELAS and diabetes are very similar to this case report. It is worthy to note that the prognosis in that series is poor as more than 50% of the cases (7/13) lead to the death of the patient. In most of these reports, high plasma levels of lactate were observed during GIT obstruction, suggesting that either the severity of MELAS or hyperlactacidemia itself is involved. Hyperlactacidemia could also

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**Table I**  
Clinical characteristics and prevalence of GIT symptoms in various populations of mitochondrial diabetes or more common forms of type 1 and type 2 diabetes in the present study and in community-based series published in the literature.

<table>
<thead>
<tr>
<th></th>
<th>MIDD 3243</th>
<th>MIDD 14709</th>
<th>TD1 Marseille</th>
<th>TD1 Maleki (5)</th>
<th>TD2 Maleki (5)</th>
<th>TD2 Bytzer (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>number</td>
<td>8</td>
<td>2</td>
<td>50</td>
<td>138</td>
<td>217</td>
<td>423</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>4/4</td>
<td>2/0</td>
<td>23/27</td>
<td>59/79</td>
<td>117/110</td>
<td>229/174</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.6 ± 12.6</td>
<td>45-54</td>
<td>42.5 ± 9.9</td>
<td>40 (18-72)</td>
<td>61 (29-76)</td>
<td>59.5 ± 15.1</td>
</tr>
<tr>
<td>Diabetes duration (yr)</td>
<td>12.8 ± 10</td>
<td>1-22</td>
<td>15 ± 11</td>
<td>23 (5-50)</td>
<td>11 (0.8-41)</td>
<td>49.4% &gt; 5yr</td>
</tr>
<tr>
<td>Insulin treatment (%)</td>
<td>60</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>10.6</td>
</tr>
<tr>
<td>Constipation (%)</td>
<td>6 (75%)</td>
<td>0</td>
<td>7 (14%)</td>
<td>37 (27%)</td>
<td>37 (17.1%)</td>
<td>66 (15.6%)</td>
</tr>
<tr>
<td>Diarrhea (%)</td>
<td>4 (37%)</td>
<td>0</td>
<td>12 (24%)</td>
<td>1 (0.7%)</td>
<td>10 (4.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea or Vomiting (%)</td>
<td>2 (12%)</td>
<td>0</td>
<td>2 (1%)</td>
<td>15 (10.6%)</td>
<td>12 (5.5%)</td>
<td>30 (7.1%)</td>
</tr>
<tr>
<td>Abdominal pain (%)</td>
<td>2 (12%)</td>
<td>0</td>
<td>10 (20%)</td>
<td>NA</td>
<td>NA</td>
<td>57 (13.5%)</td>
</tr>
</tbody>
</table>

(*: in this study constipation and diarrhea were pooled).
worsened by fasting and gastrointestinal pseudo-obstruction. In “pure” MIDD, the GIT involvement has been previously noted only in a diabetic patient characterized by an acceleration of the digestive motility and chronic diarrhea [18]. To our knowledge, another case of fatal ileus has been notified to the French register of MIDD which is composed of 54 diabetic patients bearing the nt 3243 mutation of mt DNA (P.J. Guillausseau, personal communication). One can deduce a minimal risk of severe intestinal pseudo-obstruction of 4% in the French MIDD population.

The treatment of these pseudo-obstruction should never be surgical as this intervention can increase lactic acidosis. Niacine and nicotinamide administered via gastrostomy in one patient were inefficient [16]. The use of IV CoEnzyme Q10, a cofactor of the respiratory chain of mitochondria, has been proposed [12]. But we should remember that, as in our observation, ileus can occur in patients already receiving such a chronic oral treatment [8].

Our study on a relatively short effective shows that minor digestive manifestations are frequent in MIDD when the patients are systematically questioned. The main symptoms are constipation, diarrhea or succession of both. In MELAS, the same figure is observed as chronic diarrhea has been described in 65 to 70% of cases [12]. These symptoms are not useful for the diagnosis as they are too common specially in diabetic patients who have multiple reasons for such inconveniences (vegetative neuropathy, metformine intolerance). However, they should not be neglected in MIDD patients as they can announce the risk of more severe complication as ileus. In addition, it is likely that GIT impairment may contribute to the lower body weight noted in the MIDD patients in comparison to matched diabetic populations in the French series [3].

In our study, the ultra structural analysis was poorly informative probably because the biopsies were too superficial. In the literature, most of the pathological descriptions were

Figure 1
Ultrastructural analysis of samples from various parts of GIT: oesophagus (A), stomach (B), duodenum (C), colon (D) and rectum (E). Only mild anomalies are observed, i.e. accumulation of structurally normal mitochondria and some lipid droplets.
made on tissues sampled during necropsy. The typical lesion is an accumulation of enlarged and structurally abnormal mitochondria in two sites: the smooth muscle cells in every muscle layer of intestine and vascular smooth muscle cells and endothelium. Diverging results were reported concerning ganglionic neurones. However, it seems that biopsy of rectum deep enough to include smooth muscle cells could be a suitable and safe investigation as shown by Kobayashi [19] and Kuroiwa [11]. The diversity of ultrastructural features suggests that GIT manifestations can depend from complexes phenomena’s including multiple factors as intrinsic myopathy, neuropathy, vascular reaction or lactic acidosis.

Finally, molecular study performed in biopsy samples shows that high levels of mutated mtDNA in gastrointestinal tract are associated with digestive symptoms. The heteroplasmy in GIT is more closed to that found in muscle than in blood. The same observation has been made by Kishimoto [18] in a MIDD patient with chronic diarrhea. The increasing gradient of heteroplasmy observed from upper to lower parts of digestive tract in 3 patients among 4 is amazing. It is likely that the various replication rate of these tissues is at least partly responsible of the discrepancies in heteroplasmy as shown already for blood cells [20].

Figure 2
Heteroplasmy levels (%) in four patients with the 3243 mutation. The amount of mutant DNA was determined along GIT from oesophagus to rectum, in muscle and blood cells. An increasing percentage of mutated mtDNA from the upper to the lower part of the GIT is clearly observed in the first 3 cases. (ND: not determined).
In conclusion, gastrointestinal manifestations are frequent in MIDD syndrome specially in patients bearing the nt 3243 mutation of the mtDNA. These symptoms are usually mild and some times found only with a directed questionnaire. However, intestinal pseudo-obstruction is a rare but severe complication of this digestive localization of mitochondrialopathy with a mortality rate around 50%.

References