Received: 16 February 2023 | Revised: 25 May 2023 | Accepted: 23 June 2023

DOI: 10.1111/nmo.14643

ORIGINAL ARTICLE

Neurogastroenterology & Motility NGM WILEY

Distinctive gastrointestinal motor dysfunction in patients with MNGIE

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Funding information
Instituto de Salud Carlos III; Ministerio de Ciencia e Innovación

Abstract

Background: Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare mitochondrial disease caused by mutations in *TYMP*, encoding thymidine phosphorylase. Clinically it is characterized by severe gastrointestinal dysmotility associated with cachexia and a demyelinating sensorimotor polyneuropathy. Even though digestive manifestations are progressive and invariably lead to death, the features of gastrointestinal motor dysfunction have not been systematically evaluated. The objective of this study was to describe gastrointestinal motor dysfunction in MNGIE using state-of-the art techniques and to evaluate the relationship between motor abnormalities and symptoms.

Methods: Prospective study evaluating gastrointestinal motor function and digestive symptoms in all patients with MNGIE attended at a national referral center in Spain between January 2018 and July 2022.

Key Results: In this period, five patients diagnosed of MNGIE (age range 16–46 years, four men) were evaluated. Esophageal motility by high-resolution manometry was abnormal in four patients (two hypoperistalsis, two aperistalsis). Gastric emptying by scintigraphy was mildly delayed in four and indicative of gastroparesis in one. In all patients, small bowel high-resolution manometry exhibited a common, distinctive dysmotility pattern, characterized by repetitive bursts of spasmodic contractions, without traces of normal fasting and postprandial motility patterns. Interestingly, objective motor dysfunctions were detected in the absence of severe digestive symptoms.

Conclusions and Inferences: MNGIE patients exhibit a characteristic motor dysfunction, particularly of the small bowel, even in patients with mild digestive symptoms and in the absence of morphological signs of intestinal failure. Since symptoms are not predictive of objective findings, early investigation is indicated.

KEYWORDS
intestinal manometry, intestinal pseudo-obstruction, MNGIE, small bowel motility

1 | INTRODUCTION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an ultra-rare mitochondrial disease caused by mutations in *TYMP*, the gene encoding the enzyme thymidine phosphorylase. The genetic defect is associated with systemic accumulation of the nucleosides thymidine and deoxyuridine that progressively impair mitochondrial function, primarily affecting neurological and digestive tissues.[1,2] Although there are no specific studies on MNGIE prevalence, ours and other data suggest that it is below one case per million.[3]

Clinically MNGIE is characterized by a combination of gastrointestinal and neurological manifestations, including severe gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoplegia, leukoencephalopathy and sensorimotor neuropathy.[4] Gastrointestinal dysmotility symptoms are the most frequent first manifestation of the disease, and include early satiety, nausea, dysphagia, postprandial emesis, abdominal pain, abdominal distention, and diarrhea.[5] The disease is relentlessly progressive, and the cause of death is primarily related to digestive motor dysfunction, leading to chronic intestinal pseudo-obstruction, spontaneous intestinal perforation, pneumonia due to bronchoaspiration of digestive refluxate or other infections in a malnourished patient.[5]

Digestive manifestations have been related to intestinal microangiopathy and neuromuscular abnormalities, which arise during the evolution of the disease.[6,7] However, the specific motor dysfunctions that produce the symptoms, that is, the underlying mechanisms, remain uncertain, because so far, no systematic studies on gastrointestinal motility evaluation in MNGIE have been published. The aims of this study were to identify the upper GI motor dysfunction in MNGIE patients, and to determine their relation to the clinical manifestations. Since the life-threatening consequences of the disease involve the whole gastrointestinal tract, all patients underwent state-of-the-art evaluation of the esophagus, stomach and small bowel.

Key points

- Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare mitochondrial disease characterized by severe digestive symptoms and malnutrition.
- Until now, intestinal motility had not been systematically evaluated in MNGIE.
- Using a novel high-resolution intestinal manometry technique, we have shown that MNGIE patients exhibit a distinctive small bowel dysmotility pattern, characterized by spasmodic contractions of the intestine.

2 | MATERIALS AND METHODS

2.1 | Study design

Prospective study evaluating gastrointestinal motor function in all patients diagnosed with MNGIE attended at the Vall d'Hebron University Hospital between January 2018 and July 2022. The diagnosis of MNGIE was established by assessment of the thymidine phosphorylase activity in buffy coat and the levels of thymidine and deoxyuridine in plasma. When thymidine phosphorylase dysfunction was detected, the pathogenic mutation was investigated by sequencing TYMP in patient's DNA.

The study protocol was approved by the Ethics Committee of the University Hospital Vall d'Hebron (PR(AG)56/2018; May 4, 2018) and all participants gave their written informed consent. The study protocol was registered with ClinicalTrials.gov (NCT05658822).

2.2 | Outcome measures

2.2.1 | Clinical history

Medical charts were reviewed and data on medical history, physical examination, digestive imaging tests (abdominal CT scans and endoscopic studies) and specific neurological evaluation (focused physical exam, brain imaging by magnetic resonance, electromyography and nerve conduction studies) were recorded.

2.2.2 | Digestive symptom questionnaire

At study entry, all participants completed a symptom questionnaire which evaluated: (a) the intensity of digestive symptoms (abdominal pain/discomfort, abdominal distension, early satiation, nausea, vomiting, heartburn, belching, dysphagia) in the previous 3 months on separate scales as absent (scored 0), mild (scored 1), moderate (scored 2), severe (scored 3) or invalidating (scored 4); (b) bowel movement frequency; and (c) fecal consistency by the Bristol form scale 1 (separate hard lumps) to 7 (liquid stools).

2.2.3 | High-resolution esophageal manometry

Esophageal motility was evaluated using a solid-state high-resolution manometry assembly with 36 circumferential sensors spaced at 1-cm intervals (ManoScan™; Medtronic). The manometric catheter was introduced transnasally and positioned to record from the hypopharynx to the stomach with at least three intragastric sensors. The catheter was then fixed in place by taping it to the nose. The following protocol was used: (1) in supine position: (a) three deep inspirations, to corroborate correct catheter position, followed by a 60 s basal recording; (b) 10 consecutive 5 mL water swallows at 30 s intervals, followed by multiple rapid swallow (MRS) maneuvers (five consecutive 2 mL swallows, separated by 2–3 s intervals); (2) in the sitting position: rapid drinking challenge (drinking 200 mL of water as fast as possible using a straw).

2.2.4 | Scintigraphic gastric emptying test

The gastric-emptying rate of the solid component of a meal was measured by scintigraphy. The meal (435 Kcal) consisted of a ham omelet (50 g egg and 20 g sliced ham cooked with 5 g oil), toast (20 g white bread) with 5 g butter and 12 g marmalade, and 200 mL fruit juice. The solid component of the meal was labeled by mixing one mCi99mTc-sulfur colloid with the beaten egg before being cooked to a firm consistency. Abdominal scans in the postprandial period were obtained with the patient standing in front of the gamma-camera. In each scan, the gastric outline was identified as region of interest and the activity of the isotope in the stomach was measured. The total activity of the isotope (100%) was calculated in the first determination immediately after patients completed their meal, by adding the activity detected within the gastric region to that already emptied from the stomach and detected outside the gastric region. Based on the values in our laboratory on proportion of meal residues remaining in the stomach at 4 h, gastric emptying was defined as normal (≤10% retention) or delayed, graded as mild (11%–20% retention), moderate (21%–35% retention) or severe, that is, gastroparesis (≥36% retention).

2.2.5 | High-resolution intestinal manometry

Small bowel motility was evaluated by a high-resolution intestinal manometry system, as previously described.[8,9] Briefly, after an overnight fast, a customized 35-channel water-perfused manometry catheter designed to measure jejunal motility (Mui Scientific) was orally introduced into the jejunum under fluoroscopic guidance. The first two perfusion side-holes (recording sites) were located 58 and 48 cm from the tip of the catheter to register antral and duodenal contractions; the following 33 side-holes, starting at 37 cm from the tip, were separated by 1 cm (4–37 cm from the tip) to measure jejunal contractile activity. Radio-opaque markers were located before the first and third most proximal side-holes to facilitate fluoroscopic localization. The catheter was connected to a low-compliance manometric system (Solar GI HRM manometry system, MMS-Laborie), and each channel was perfused with distilled water (315 mL/h). First, small bowel motility recordings were obtained for 3 h during fasting; after this period, a liquid meal (Ensure HN; Abbott) was continuously perfused at 1 kcal/mL into the jejunum (via a dedicated infusion tube attached to the manometric catheter) to induce a fed state, and small bowel motility was recorded for two additional hours.

Manometric tracings were evaluated following dysmotility criteria previously established by conventional intestinal manometry.[10,11] High-resolution intestinal manometry patterns from MNGIE patients were also compared to a set of normal values in our laboratory from a cohort of healthy subjects obtained during fasting conditions ($n = 18$) and during infusion of nutrients into the duodenum ($n = 16$).[8,9] Computerized analysis was used obtain a global motility index, measuring the number of contractions >10 mmHg every 1 min.

2.3 | Statistical analysis

Statistical analysis was performed with SPSS Statistics for Windows (V22.0, IBM). Normality of data distribution was evaluated by the Shapiro–Wilk test. Mean or median values (for parameters with normal and non-normal distribution, respectively) were calculated for each individual, and grand means (±SE) for the group of patients. The Wilcoxon signed rank test was used to compare paired data within groups. Differences were considered significant at a $p < 0.05$.

3 | RESULTS

3.1 | Clinical features

3.1.1 | Demographics and past medical history

Five patients with MNGIE were included in the study. Demographics of patients at study entry are summarized in Table 1. The diagnosis of MNGIE had been reached during familiar screening in two patients (sibling with MNGIE) and de-novo in three patients.

The two patients who were diagnosed during familiar screening (patient 1 at 30 years, and patient 5 at 29 years) were asymptomatic at the time of genetic testing, and their digestive manifestations started 4 and 17 years after the diagnosis, respectively (at 34 and 46 years of age), prompting gastrointestinal motility evaluation.[12] Of note, both patient's siblings had died from complications of intestinal pseudo-obstruction due to MNGIE.

The other three patients, without familial history of MNGIE, had all initially been misdiagnosed of neurological (patient 3 with Charcot-Marie-Tooth disease and patient 4 Kearns-Sayre syndrome) or digestive (patient 2 with superior mesenteric artery syndrome) disorders. In these three patients, the diagnosis of MNGIE was suspected due to the combination neurological and digestive manifestations and was finally established by biochemical and genetic testing 2–8 years after the onset of the first symptoms.

3.1.2 | General clinical evaluation

Clinical features of patients are shown in Table 1. Four patients were cachectic (BMI < 18.5 kg/m^2) and one had a normal BMI (20.3 kg/m^2). All patients had an abdominal CT scan that evidenced a normal appearance of the digestive tract with no dilated loops of small intestine or signs suggestive of intestinal pseudo-obstruction. Upper endoscopy, performed in four patients, did not detect esophageal, gastric or duodenal abnormalities.

3.1.3 | Neurological evaluation

A neurological evaluation, including a focused physical exam, brain imaging by magnetic resonance, electromyography and nerve

TABLE 1 Demographic and clinical characteristics of patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender (M/F); Age (y)	M; 34	M; 16	M; 41	M; 31	F; 46
Body mass index (kg/m^2)	20.3	10.8	15.4	14.7	14.7
TYMP mutations[a]	c.1340_1361del22 p.(Leu447Profs*?) Homozygote	c.866A>C p.(Glu289Ala) Homozygote	c.1112T>C p.(Leu371Pro) Homozygote	c.518T>G p.Met173Arg Homozygote	c.131G>A p.(Arg44Gln) Homozygote
Nucleoside plasma levels, dThd–dUrd (μM)[b]	9.8–12.7	7.6–10.2	8.6–15.3	6.3–9.0	4.7–10.7
Gastrointestinal symptoms[c]					
Heartburn	1	2	2	3	1
Regurgitation	0	1	1	3	2
Belching	0	0	1	4	0
Dysphagia	1	2	0	2	0
Early satiety	0	1	0	4	0
Postprandial fullness	1	2	0	4	0
Nausea/vomiting	0	2	1	4	0
Abdominal pain	1	2	2	4	1
Abdominal distension	2	2	2	4	2
Bowel habit	Normal	Normal	Normal	Diarrhea[d]	Normal
Gastrointestinal motility studies					
Esophageal HRM	Normal	Absent contractility	Ineffective motility	Ineffective motility	Absent contractility
Gastric emptying test, % retention at 4 h[e]	14%	13%	21%	50%	11%
Small bowel HRM[f]; bursts/5 h	9	26	19	50	69

Abbreviations: dThd, thymidine; dUrd, deoxyuridine; F, Female; HRM, High-resolution manometry; M, Male.

[a]Numbered according to the reference sequence: NM_001953.5 (NP_001944.1).

[b]At the time of diagnosis. Normal values; below 0.05 μM.

[c]Measured by 0–4 scales (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = incapacitating).

[d]>3 bowel movements/day, Bristol score 6–7.

[e]Measured by scintigraphy (≤10% normal; 11%–35% mild/moderate delay; ≥36% severe delay).

[f]All fulfilled established criteria of dysmotility.

conduction studies, was systematically performed, and detected clinical signs of neurological involvement in all patients. Neurological exam evidenced some degree of ophthalmoparesis in all patients, and ptosis in three (patient 3, patient 4 and patient 5). Sensorineural hearing loss was evidenced in two (patient 3 and patient 5). All patients showed signs suggestive of length-dependent sensorimotor peripheral neuropathy with muscle weakness, amyotrophy, hypoesthesia, loss of vibration sensation and abnormal two-point discrimination in the distal extremities. Three patients had pes cavus with hammertoes (patient 3, patient 4 and patient 5). Electrodiagnostic examinations detected neuromuscular abnormalities in all patients, with different degrees (from moderate to severe) of demyelinating bilateral sensorimotor polyneuropathy and signs of autonomic dysfunction (absent sympathetic skin response). All patients exhibited symmetric leukoencephalopathy in brain magnetic resonance imaging study.

3.2 | Digestive symptom questionnaire

At study entry, all five patients reported gastrointestinal symptoms, but the presence and intensity of specific symptoms varied (Table 1). Four patients had mild to moderate symptoms; all exhibited some degree of abdominal pain and distension. One patient had severe, incapacitating symptoms, with marked early satiety, postprandial fullness and vomiting. To note, BMI in this patient was not different to patients with minor symptomatic expression.

3.3 | Esophageal motility assessment

Abnormal esophageal motor function was detected in four of the five patients, who showed impaired esophageal peristalsis, either hypoperistalsis (i.e., ineffective esophageal motility, $n = 2$) or complete aperistalsis (i.e., absent contractility, $n = 2$). None of the patients had evidence of motor dysfunction of the upper or lower esophageal sphincters.

3.4 | Gastric motility assessment

Gastric emptying was severely delayed in one patient (50% meal retention at 4 h) fulfilling criteria of gastroparesis, and mildly delayed in four patients (11%, 13%, 14% and 21% retention at 4 h, respectively).

3.5 | Small bowel motility assessment

All patients, exhibited a similar pattern of intestinal dysmotility, characterized by the absence normal fasting and postprandial patterns, failure of intestinal nutrient infusion to induce changes in motor activity, and the appearance of bursts of contractions (7 ± 2 bursts per hour, 2–14 range; 30 ± 3 s duration; Table 1). Small bowel motor activity was similar during fasting and during nutrient infusion both, in terms of global motility index (2.1 ± 1.3 and vs. 2.1 ± 0.2 contractions/min, respectively) and number of bursts (6.9 ± 1.9 vs. 7.0 ± 2.5 bursts per hour, respectively) (Figure 1). These abnormalities fulfilled the conventional criteria of neuropathic-type intestinal dysmotility.[10,11]

High-resolution manometry allowed a more precise characterization and provided a visual picture of the motor dysfunction in MNGIE patients, depicting the bursts as spasms of long segments of the small bowel. Each burst consisted of 4 ± 1 spastic contractions at a regular rate (every 4–5 s). Individual contractions developed simultaneously over a length of small bowel that varied between 24 ± 6 cm. Some contractions exhibited some degree of antegrade (31%) or retrograde (8%) propagation (Figures 1 and 2). Large part of burst activity (77%) extended beyond the distal recording sites, so it cannot be ascertained whether the spasms affected the whole small bowel or only part of it. Each individual contraction lasted 5 s, but 74 ± 13% of the bursts contained one prolonged contraction (defined as >8 s), seemingly a fusion of 2–3 consecutive contractions with 9.6 ± 1.7 s mean duration, reaching a very high contraction peak (153 ± 32 mmHg vs. 74 ± 34 mmHg in the rest; $p = 0.001$).

3.6 | Relationship between digestive symptoms and motor dysfunctions

The correlation between subjective symptoms and objective motility findings was inconsistent (Table 1). For instance, heartburn and regurgitation tended to correlate with esophageal dysfunction; however, some degree of dysphagia was present in the patient with normal esophageal motility, but not in two patients with impaired peristalsis (ineffective and absent peristalsis, respectively). Gastroparesis (50% gastric retention 4 h after meal ingestion) was associated with severe symptoms. However, the rest of the patients exhibited a repertoire of only mild to moderate symptoms, despite the presence of objective intestinal dysmotility. To note, among this relatively small population, the two sides of the clinical severity spectrum were represented. At one end, patient 1, with normal body weight, minimal symptoms and less signs of gastrointestinal dysmotility. Interestingly, this patient had been evaluated at our center 2 years before and, at that time, he had no digestive symptoms and both intestinal manometry and gastric scintigraphy were normal. At the other end of the spectrum, patient 4 represents a more advanced stage of digestive disease with prominent symptoms and severe gastrointestinal dysmotility including florid small bowel manometric dysfunction.

4 | DISCUSSION

Our study shows that patients with MNGIE exhibit objective gastrointestinal dysmotility, even in the absence of severe digestive

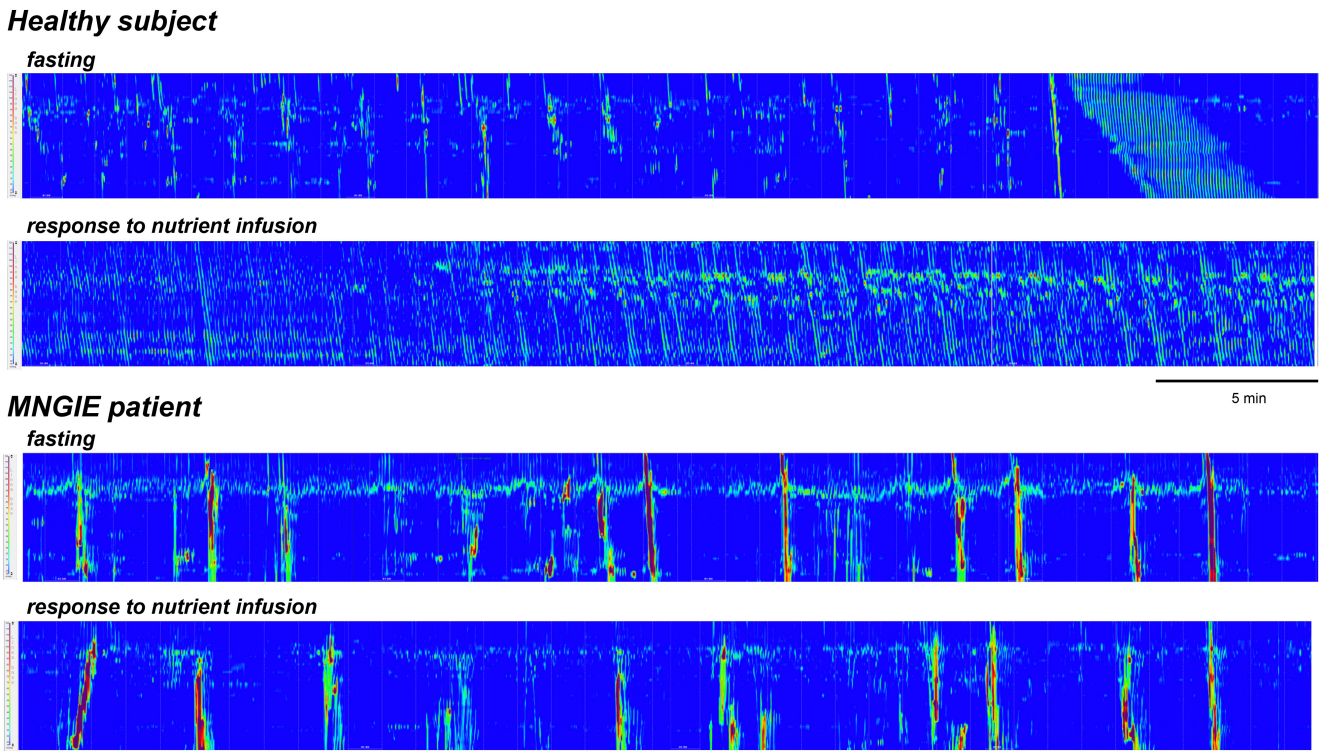

FIGURE 1 Examples of high-resolution manometry tracings in a healthy subject and a MNGIE patient. Note in the healthy subject characteristic segmental and propagated contractions and in MNGIE bursts of extended spastic contractions.

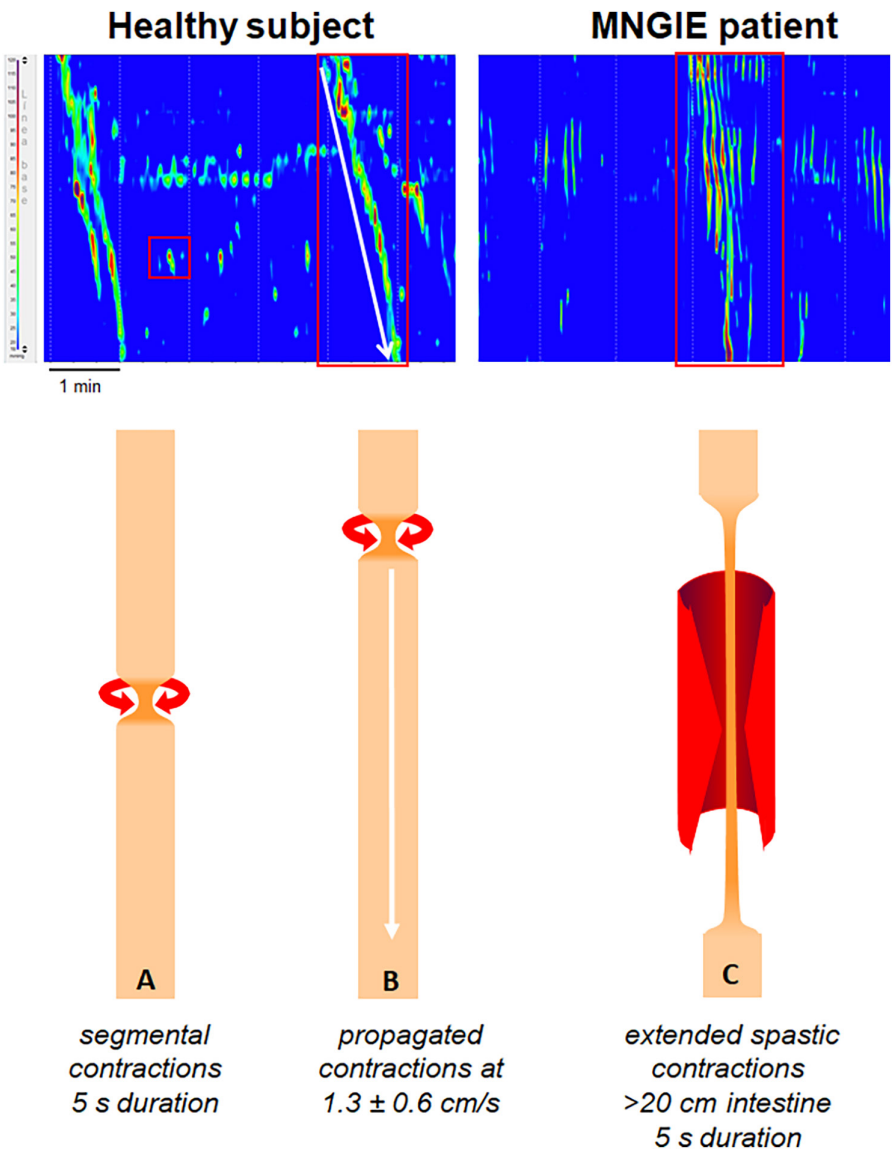

FIGURE 2 In normal conditions, the small bowel generates (A) segmental (non-propagated) and (B) propagated contractions; propagated activity predominates during fasting and non-propagated in the postprandial period. (C) MNGIE patients develop crisis of intestinal seizures (bursts of extended spastic contractions) with only traces of normal activity in between crisis.

symptoms or morphological consequences of digestive failure (gut distension, pooling of contents). Interestingly, small bowel manometry, performed with the newly developed high-resolution technique, was the most sensitive test, revealing a highly characteristic intestinal dysmotility in all patients included in the study.

These findings fit with the observation that patients with MNGIE may rapidly evolve from a paucisymptomatic state to severe intestinal dysfunction, leading to malnutrition and death.[13] Based on our data, it could be speculated that, the underlying dysmotility anticipates the intestinal failure typical of the advanced stages of the disease. As in other forms of intestinal motility disorders, conventional imaging studies (e.g., abdominal CT scanning and endoscopy) did not detect morphological abnormalities, and probably would only detect the pseudo-obstruction features (intestinal dilation and pooling of contents) in the pre-terminal stage.

All five MNGIE patients in our series exhibited a strikingly similar small intestinal dysmotility pattern, characterized by bursts of rhythmic, seizure-like, spasmodic contractions of a large intestinal extension, without trace of the normal fasting and postprandial activity patterns. This motor pattern has not been observed in other diseases involving neuro-myopathies of the small bowel, and hence it seems pathognomonic of MNGIE; however, given the rare condition of these disorders, we cannot ascertain whether other intestinal mitochondriopathies share these characteristics, and whether all patients with MNGIE, or at which stage, develop it. In fact, by the time of reviewing this paper, a sixth patient with MNGIE was evaluated at our center and the same distinctive manometric pattern was detected. Cachexia, a main feature of MNGIE, was present in four patients included in the study, suggesting this type of activity may hinder absorption of nutrients, even in the absence of pseudo-obstruction features, for example, pooling of contents and dilation.

The specific pathogenic mechanisms of intestinal dysmotility in MNGIE have not been established, but histopathological studies have identified neuro-myopathic and mesenchymal abnormalities[14] A selective atrophy of the external longitudinal muscular layer of the small bowel, with a preserved internal circular layer has been reported in five MNGIE patients by laser capture microdissection

of post-mortem samples.[6] A recent study by Boschetti et al. identified marked vascular abnormalities in the intestinal submucosa associated to fibrotic degeneration of the longitudinal muscle layer and a drastic reduction in the number of myenteric neurons in full-thickness small bowel biopsies from five MNGIE patients, and proposed that the neuromyopathy had an ischemic–hypoxic origin.[7] Our study showed forceful manometric activity of the small bowel, suggesting that the atrophy of the muscular layer is not the main determinant of intestinal dysfunction in MNGIE, and that enteric denervation may be the predominant mechanism, at least at a stage prior to intestinal claudication and dilation. Other histopathological studies evidenced the absence of interstitial cells of Cajal in small bowel full thickness biopsies of four MNGIE patients.[15,16] Cajal cells form a mesenchymal syncytium that operates as a pacemaker and governs the rhythm and propagation of contractions along the small bowel. However, the role of Cajal cell depletion in intestinal motor disorders is still debated, since it is unclear whether it is a cause or consequence of severe dysmotility.[17] A single case report of a patient with MNGIE, evaluated by duodenal manometry, described a frequency of contractions above the normal pace, for which the authors coined the graphic term tachyduodenia.[18] Our patients exhibited a borderline increase in the frequency of contractions during the burst activity, which could be indicative of pacemaker dysfunction.

An obvious limitation of our study is the small number of patients included, but this is inherent to the ultra-rare condition of MNGIE; the cohort included in the study represents the totality of patients attended over a 5-year period in a national referral center. Therefore, the specificity of the dysmotility pattern detected, whether pathognomonic or not, remains to be established, when a larger cohort of patients becomes available for manometric studies. Furthermore, other pathophysiological aspects, such as colonic involvement and the clinical value of the different motility tests, remain to be addressed.

Two main findings of our study have clinical relevance. First, the present study shows that MNGIE patients exhibit objective gastrointestinal dysmotility, suggesting that early digestive involvement, and particularly small bowel dysmotility, has to be systematically considered (and investigated) in patients with MNGIE, regardless of the severity of digestive symptoms. Second, our study identified characteristic features in small bowel motility; since MNGIE patients are frequently misdiagnosed, the identification of this specific small bowel motility pattern in the evaluation of a patient referred to small bowel manometry, should trigger the suspicion of MNGIE, with indication for genetic testing. Not delaying the diagnosis of MNGIE is essential, given the recent advances in the treatment with autologous hematopoietic stem cell or liver transplantation, which have shown to halt the progression of the disease, and therefore indicated at early stages.[13]

AUTHOR CONTRIBUTIONS

Luis G. Alcalá-González: study management, data analysis and manuscript preparation. Anna Accarino: conduction of studies and data interpretation. Ramon Martí: collecting and interpreting data. Daniel Sánchez-Tejerina: collecting and interpreting data. Arnau Llauradó: collecting and interpreting data. Fernando Azpiroz: study design, data interpretation and manuscript preparation. Carolina Malagelada: study design, study management, data analysis and manuscript preparation.

ACKNOWLEDGMENTS

This work was supported by the Instituto de Salud Carlos III and co-financed by the European Union (FEDER/FSE) [PI17/01794]; Spanish Ministry of Science and Innovation (Dirección General de Investigación Científica y Técnica, PID2021-122295OB-I00); Ciberehd is funded by the Instituto de Salud Carlos III. LA was supported by scholarship from the Instituto de Salud Carlos III (CM20/00182).

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: Alcalá-González LG, Accarino A, Martí R, et al. Distinctive gastrointestinal motor dysfunction in patients with MNGIE. *Neurogastroenterology & Motility*. 2023;35:e14643. doi:10.1111/nmo.14643