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MyoNeuroGastroIntestinal Encephalopathy: natural history and means for early diagnosis

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Abbreviations: BMI: body mass index; MNGIE: MyoNeuroGastroIntestinal Encephalopathy; TP: thymidine phosphorylase;

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Author contributions

Giovanni Corazza: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript

Cécile Pagan: acquisition of data; analysis and interpretation of data; critical revision of the manuscript

Gaëlle Hardy: acquisition of data; analysis and interpretation of data; critical revision of the manuscript

Gérard Besson: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; material support

Anne Lombès: study concept and design; acquisition of data; analysis and interpretation of data; critical revision of the manuscript; obtained funding; study supervision.

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Introduction

MyoNeuroGastroIntestinal Encephalopathy (MNGIE) is a rare multisystem mitochondrial disease, which predominantly presents with chronic intestinal signs (diarrhea, gastroparesis, recurrent vomiting, abdominal pain and bloating, pseudo-obstruction episodes) with associated neurological involvement (leukoencephalopathy, ophthalmoparesis, deafness, and demyelinating sensory motor peripheral neuropathy)^{1,2}. Defective thymidine phosphorylase (TP), resulting from mutations in the *TYMP* gene, causes MNGIE via massive accumulation of thymidine and deoxyuridine that progressively alters mitochondrial DNA replication³.

Several treatments have targeted this toxic accumulation. Hemodialysis, peritoneal dialysis, or platelet infusion resulted in only transient efficacy³. More lasting positive outcomes resulted from partial enzymatic restoration via TP encapsulated in erythrocytes⁴, liver transplantation⁵ or hematopoietic stem cells transplantation⁶. The latter had a very high mortality rate, with 15/24 patients dying early during the procedure, most probably in relation to the cachexia constantly associated with MNGIE progression. In surviving patients, completely normalized thymidine/deoxyuridine levels accompanied long-term stabilization of the patients' clinical status. However, an absence of significant clinical recovery implied irreversibility of the intestinal and peripheral nerve damage. Early diagnosis of MNGIE, before severe tissue damage and cachexia, is therefore mandatory for treatment efficacy.

The sole previous report of a large cohort of MNGIE patients essentially described the clinical spectrum without addressing disease progression². To address the barriers associated with diagnosis of MNGIE, we analyzed the natural history of all French MNGIE patients.

Methods

Every French patient with a diagnosis of MNGIE according to the criteria of 2004⁷ was included in this retrospective study. Two French laboratories provide TP assay for diagnosis; they recruited patients from 1999 to January 2018. There was no *a priori* exclusion criteria.

The same investigator (GC) collected all clinical data by contacting the referring physician, the patient's general practitioner, and additional physicians when needed.

Collected data included gender, current age, family history (siblings and consanguinity), age at first specialized consultation in relation to MNGIE and at each follow-up, chief complaint at consultation, signs or symptoms and the age at their onset, physical examination, relevant laboratory data, electrophysiologic studies, and age at death when relevant. When available, Child Health Record booklets allowed establishing the patient's childhood growth curves.

Results

Twenty-eight patients had MNGIE diagnosed by the presence of a profound defect of TP activity and/or *TYMP* gene biallelic mutations (Supplemental Table 1). Insufficient information could be recovered for four patients who were already deceased; they were excluded from further analysis, resulting in a cohort of 24 patients from 21 independent families.

The main patient characteristics were remarkably similar to those in the previously reported MNGIE cohort ² (Supplemental Table 2). The French cohort was therefore representative of MNGIE, justifying its use to establish the natural history of the disease.

As shown in the Figure, comparison of the Kaplan-Meier survival curve (A) with that of the probability to remain undiagnosed (B) shows that diagnosis preceded death by only a few years, and that gastrointestinal complaints had an earlier onset than neurological signs, ophthalmoparesis, or deafness (C). The patients' median body mass index (BMI) at the first specialized medical consultation (at an average 25 years of age) was 14.5, confirming the early onset of gastrointestinal signs. BMI appeared as a sensitive early marker based on the Child Health Record booklet, available for 10 patients. It was close to the third centile before 10 years of age for 6/9 patients while weight curves showed progressively blunted growth and

height curves remained within the normal range, in accordance with the normal height observed for all adult MNGIE patients (Supplemental Figure).

Except for two patients with siblings previously diagnosed as MNGIE, all MNGIE patients had several alternative diagnoses made, leading to a median delay of 6 years (range 0-23) between their first specialized medical consultation and the definitive diagnosis. The most frequent was anorexia nervosa, a diagnosis assigned to 41% of all patients, and 58% of women. The next most common was chronic inflammatory gastrointestinal disease, including Crohn's disease (in 33%), coeliac disease (22%), and esophagitis and/or gastritis (17%), which led to unnecessary diagnostic procedures, including esophagogastroduodenoscopy (14 patients), intestinal biopsies (16 patients), and CT scans (8 patients). Similarly, the occurrence of neurological signs led to diagnoses of Charcot-Marie-Tooth disease (42%), metabolic disorder (42%), or acute or chronic polyradiculoneuritis (29%). Electroneuromyography showing demyelinating neuropathy (19/21 patients) and/or brain imaging showing diffuse leukoencephalopathy (20/21 patients) were then major triggers for MNGIE diagnosis.

Discussion

Partial enzymatic restoration completely cures toxic accumulation causing MNGIE. However, early diagnosis, prior to the development of cachexia and irreversible tissue damage, is mandatory to ensure clinical benefit. With a goal of improving early diagnosis of MNGIE, we analyzed the natural history of all French MNGIE patients. Despite its retrospective nature, we believe that the overview of the MNGIE diagnostic process is accurate because we obtained 92 % for the information being sought.

Consistent with the initial signs being gastro-intestinal, the first specialized medical consultation was in Gastroenterology (63%) or Pediatrics (21%) but rarely in Neurology (13%). These signs lacked specificity and led to numerous differential diagnoses, all more frequent than MNGIE and several without specific diagnostic criteria, explaining their

recurrent discussion. Neurologists made the diagnosis more often than gastroenterologists (56% *versus* 24%) because signs in addition to intestinal troubles were major triggers for diagnosis. However, the delayed appearance of neurologic features means that cachexia often was already significant.

When suspected, the diagnosis of MNGIE is relatively easy because of the highly sensitive biochemical alterations. The TP assay is highly specific and easy to perform. Urinary organic acids chromatography showing peaks of thymine and uracile is suggestive. Molecular testing of *TYMP* gene is useful to confirm the diagnosis.

In conclusion, chronic intestinal troubles with a severe impact on BMI should prompt the clinician to consider TP deficiency and to order specific biochemical analyses. Although numerous negative results may be expected, the cost will be moderate and highly compensated for by the benefit for the rare MNGIE patients who, without early treatment, inexorably evolve towards severe cachexia, intestinal neuromyopathy and generalized polyneuropathy.

Figure legends

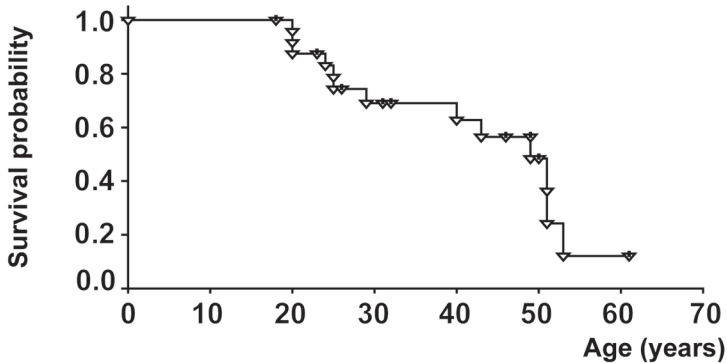
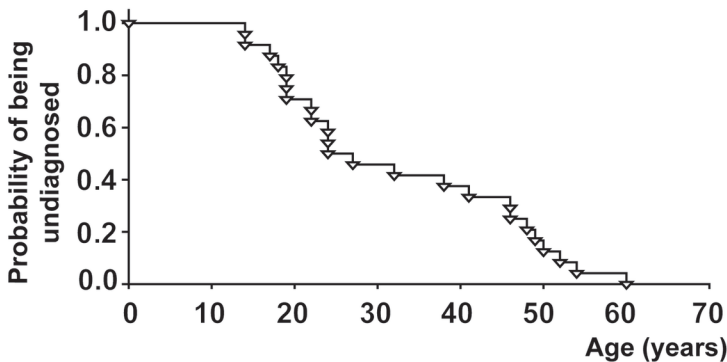
Kaplan-Meier curve of survival (**A**) and diagnosis (**B**); Natural history of MNGIE (**C**); Gastro=gastrointestinal symptoms (recurrent vomiting, chronic diarrhea, abdominal pain and bloating); Neuro=neurological symptoms (limb paresthesia, pain, sensory deficit or weakness); OPH = Ocular symptoms (ptosis and/or external ophthalmoplegia).

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