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BRIEF COMMUNICATION

ITA-MNGIE: an Italian regional and national survey for mitochondrial neuro-gastro-intestinal encephalomyopathy

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Abstract Mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE) is a rare and unavoidably fatal disease due to mutations in thymidine phosphorylase (TP). Clinically it is characterized by gastrointestinal dysfunction, malnutrition/cachexia and neurological manifestations. MNGIE diagnosis remains a challenge mainly because of the complexity and rarity of the disease. Thus, our purposes were to promote a better knowledge of the disease in Emilia-Romagna region (ERR) by creating an accurate and dedicated network; to establish the minimal prevalence of MNGIE in Italy starting from ERR. Blood TP activity level was used as screening test to direct candidates to complete diagnostic work-up. During the study period of 1 year, only 10/71 units of ERR recruited 14 candidates. Their screening did not show TP activity changes. An Italian patient not resident in ERR was actually proved to have MNGIE. At the end of study in Italy there were nine cases of MNGIE; thus, the Italian prevalence of the disease is ~0.15/1,000,000 as a gross estimation. Our study confirms that MNGIE diagnosis is a difficult process which reflects the rarity of the disease and, as a result, a low level of awareness among specialists and physicians. Having available novel therapeutic options (e.g., allogenic hematopoietic stem cell transplantation and, more recently, liver transplantation) and an easy screening test, an early diagnosis should be sought before tissue damage occurs irreversibly.

Keywords Mitochondrial neuro-gastro-intestinal encephalomyopathy · Prevalence · Allogenic hematopoietic stem cell transplantation · Orthotopic liver transplantation

Introduction

Mitochondrial neuro-gastro-intestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease due to mutations in nuclear *TYMP* gene, leading to a marked reduction/absence of the encoded thymidine phosphorylase (TP) enzyme. As a result, nucleosides [thymidine (dThd) and deoxyuridine (dUrd)] accumulate and exert a toxic effect with subsequent mitochondrial DNA damage [1]. The clinical picture is mainly characterized by gastrointestinal (GI) dysfunction with frequent intestinal sub-occlusive episodes, malnutrition, cachexia and neurological involvement including ptosis and ophthalmoparesis, peripheral neuropathy, myopathy, leukoencephalopathy [2]. The outcome of the syndrome is fatal and death occurs usually before the age of 40 years, although mild/atypical phenotypes have been reported [3]. There are no established therapeutic options for patients with MNGIE. Currently, the most effective treatment is the allogenic hematopoietic stem cell transplantation (AHSCT), which

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restores persistently TP activity and reduces circulating toxic levels of dThd and dUrd. However, the clinical impact of AHSCT is hampered by a high mortality rate and the need of a highly compatible donor [4].

MNGIE diagnosis remains a clinical challenge often misunderstood or confused with completely different conditions, e.g., anorexia nervosa and inflammatory bowel disease (IBD). Apart from its clinical complexity, MNGIE is often unrecognized mainly because is an extremely rare disorder. In Europe, the prevalence of this mitochondrial disorder has been estimated to be ~1/1,000,000 people (http://www.orphanet.it, May 2014), but no previous formal study on its prevalence has been ever performed. Thus, our goals were to promote a better knowledge of the disease in the Emilia-Romagna region (ERR), a region of Northern Italy, by creating an accurate and dedicated network and using TP enzymatic activity as diagnostic marker [5]. Furthermore, we aimed at establishing the minimal prevalence of MNGIE in Italy, starting from ERR.

Materials and methods

We performed a formal two-phase study in the ERR and a non-formal study based on case searching throughout Italy.

ERR study

From 1/11/2013 to 31/10/2014 we contacted all units of neurology ($n = 18$, 138 neurologists), gastroenterology ($n = 20$, 105 gastroenterologists), pediatric neurology ($n = 19$, 69 pediatric neurologists) and eating behavior disorders (EBS)/psychiatry ($n = 14$, 52 psychiatrics) of the ERR (4,457,115 inhabitants as of 31/12/2014) to record any possible case of MNGIE according to the following including criteria: presence of severe gastrointestinal dysfunction (chronic symptoms affecting patient's quality of life to impair a normal life and/or inducing absenteeism from work) or malnutrition/weight loss or suspected anorexia nervosa; with/without of neurological signs (e.g., sensory-motor peripheral neuropathy, deafness, ptosis/ophtalmoparesis) (Table 1). A summary of MNGIE symptoms was sent to physicians followed by a personal phone/mail reminder every 2 months. A blood sample (10 mL in EDTA) was obtained from each candidate samples were used to isolate the buffy coat in order to measure lymphocyte TP activity quantified by the rate of conversion of dThd to thymine. Patients with TP activity levels <252 nmol/h mg [5] completed the diagnostic work-up, i.e. EMG, brain MRI, muscle biopsy, and *TYMP* sequences analysis to confirm MNGIE diagnosis. The study was approved by the ethic committees of all participating centers of the ERR and all patients gave their informed consent to the inclusion.

Table 1 Inclusion criteria/clinical features of 14 "ERR patients" screened for MNGIE: 14 subjects (7 M + 7 F), mean age 40.8 ± 11.5 years (range 22–55), mean BMI 18.1 ± 3.1 kg/m^2 (range 16–24)

	n (%)
Gastrointestinal (1 or more)[a]	
Malnutrition	
Weight loss	14 (100 %)
Cachexia	3 (21 %)
Severe gastrointestinal dysfunction	
Early satiety	13 (93 %)
Postprandial distension	12 (86 %)
Abdominal cramps	11 (79 %)
Abdominal borborygmi	10 (71 %)
Sub-occlusive episodes	9 (64 %)
Nausea	8 (57 %)
Gut surgery	7 (50 %)
Vomiting	5 (36 %)
Suspected anorexia nervosa	0 (0 %)
Neurological[b]	
Neuropathy	7 (50 %)
Opthalmopharesis	5 (36 %)
Ptosis	2 (14 %)
Deafness	2 (14 %)

[a] Mandatory

[b] Optional

Search for MNGIE cases in Italy

Italian "extra-ERR" resident patients fulfilling the inclusion criteria and examined in the aforementioned units were tested. Moreover, we contacted all genetic centers in Italy enquiring about MNGIE cases still alive as of 30/11/2014.

Results

Among the 71 units involved, only 5 neurology, 4 gastroenterology, and 1 pediatric neurology centers recruited candidates for TP activity screening. No candidates were identified by EBS/psychiatry units. A total of 30 patients were tested, i.e. 19, 8, and 3, referred by neurologists, gastroenterologists, and pediatric neurologists, respectively.

ERR study

During the study period, 14 ERR resident cases of suspected MNGIE were included (Table 1). All patients had TP activity levels within normal range (332–1580 nmol/h mg; normal value >252).

Extra-ERR study

Sixteen extra-ERR resident patients were tested and one of these with low TP activity level (4 nmol/h mg) was eventually confirmed to have MNGIE by genetic test. Notably, this patient was misdiagnosed as an IBD and managed for 3 years with immunosuppressive agents.

As of 30/11/2014 there were nine established cases of MNGIE recorded in Genetic Centers in Italy, a Country with 59,464,644 inhabitants (2011 census). Thus, the Italian prevalence of MNGIE is ~0.15/1,000,000 as a gross estimation.

Discussion

Despite an accurate and dedicated network, based on individual periodical contacts with different specialists, we could not identify any case of MNGIE in the ERR, a finding reflecting the rarity of such condition and, possibly, the difficulty to diagnose it. Therefore we cannot rule out the possibility that some patients with MNGIE has not been conveniently recognized in the ERR network despite our efforts. In this line, the number of patients screened was considerably lower than expected on the basis of the anorexia nervosa prevalence (0.3 and 0.03 % for females and males, respectively, aged 15–24, accounting for 606 estimated patients in the ERR) [6], a known misdiagnosis of MNGIE. The reason why no candidates were screened from the EBS/psychiatric units of ERR remains unknown and may reflect a lower level of awareness of these specialists about MNGIE. This is a crucial issue since the misdiagnosis of patients with MNGIE may lead to a significant delay of possible currently available therapeutic solutions, i.e. AHSCT [4] or, more recently, liver transplantation [7, 8] aimed to restore permanently TP. The extra-ERR MNGIE patient, identified during this study, was successfully treated for the first time with liver transplantation. His clinical conditions and biochemical data are satisfactory at 8 months of follow-up [8].

Our survey further indicates that MNGIE is an extremely rare disease with a prevalence in Italy of ~0.15/1,000,000, lower than that indicated by Orphanet, probably due to overestimation by assessing published cases rather than through case finding, or alternatively, we have underestimated MNGIE.

In conclusion, having available novel therapeutic options (AHSCT or liver transplantation) and the possibility to rely to a relatively easy screening test (TP activity assay), specialists and physicians in general should recognize conveniently patients with MNGIE in order to achieve an early diagnosis and treat patients before tissue damage occurs irreversibly.

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Compliance with ethical standards

The study was approved by the Ethic Committees of all participating centers of the ERR (protocol#31/2013/O/Tess)
All patients gave their informed consent to the inclusion.

Conflict of interest The authors declare that they have no conflict of interest.

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