



ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

ARCHIVIO ISTITUZIONALE DELLA RICERCA

Alma Mater Studiorum Università di Bologna Archivio istituzionale della ricerca

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): Position paper on diagnosis, prognosis, and treatment by the MNGIE International Network

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Hirano M., Carelli V., De Giorgio R., Pironi L., Accarino A., Cenacchi G., et al. (2021). Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): Position paper on diagnosis, prognosis, and treatment by the MNGIE International Network. *JOURNAL OF INHERITED METABOLIC DISEASE*, 44(2), 376-387 [10.1002/jimd.12300].

Availability:

This version is available at: <https://hdl.handle.net/11585/785099> since: 2020-12-21

Published:

DOI: <http://doi.org/10.1002/jimd.12300>

Terms of use:

Some rights reserved. The terms and conditions for the reuse of this version of the manuscript are specified in the publishing policy. For all terms of use and more information see the publisher's website.

This item was downloaded from IRIS Università di Bologna (<https://cris.unibo.it/>).
When citing, please refer to the published version.

(Article begins on next page)

1 **Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE):**

2 **Position Paper on Diagnosis, Prognosis and Treatment by the MNGIE**

3 **International Network**

4 Running Title: Position Paper on MNGIE

5 *Michio Hirano¹, Valerio Carelli^{2,3}, Roberto De Giorgio⁴, Loris Pironi⁵, Anna Accarino⁶,*
6 *Giovanna Cenacchi², Roberto D'Alessandro³, Massimiliano Filosto⁷, Ramon Mart⁸,*
7 *Francesco Nonino³, Antonio Daniele Pinna⁹, Elisa Baldin³, Bridget Elizabeth Bax¹⁰, Alessio*
8 *Bolletta¹¹, Riccardo Bolletta¹¹, Elisa Boschetti¹², Matteo Cescon¹³, Roberto D'Angelo¹⁴,*
9 *Maria Teresa Dotti¹⁵, Carla Giordano¹⁶, Laura Ludovica Gramegna^{2,3}, Michelle Levene¹⁰,*
10 *Raffaele Lodi^{2,3}, Hanna Mandel¹⁷, Maria Cristina Morelli¹⁸, Olimpia Musumeci¹⁹, Alessia*
11 *Pugliese¹⁹, Mauro Scarpelli²⁰, Antonio Siniscalchi²¹, Antonella Spinazzola²², Galit Tal²³,*
12 *Javier Torres-Torronteras⁸, Luca Vignatelli³, Irina Zaidman²⁴, Heinz Zoller²⁵, Rita Rinaldi¹⁴,*
13 *Massimo Zeviani²⁶*

14

15 **Affiliations:**

16 ¹Department of Neurology, Columbia University Irving Medical Center, New York, New
17 York, USA

18 ²Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy

19 ³IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy

20 ⁴Department of Morphology, Surgery and Experimental Medicine, University of Ferrara,
21 Ferrara, Italy

22 ⁵Clinical Nutrition and Metabolism Unit and Center for Chronic Intestinal Failure,
23 Department of Digestive System, St. Orsola-Malpighi Hospital, University of Bologna,
24 Bologna, Italy

1 ⁶Digestive System Research Unit, University Hospital Vall d'Hebron; Centro de
2 Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD);
3 Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Spain
4 ⁷Center for Neuromuscular Diseases, Unit of Neurology, Azienda Socio Sanitaria Territoriale
5 degli Spedali Civili and University of Brescia, Brescia, Italy
6 ⁸Vall d'Hebron Research Institute, Autonomous University of Barcelona; Centro de
7 Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Barcelona, Spain
8 ⁹University of Bologna, St. Orsola-Malpighi Hospital, Bologna, Italy
9 ¹⁰Institute of Molecular and Clinical Sciences, St George's University of London, London,
10 United Kingdom
11 ¹¹Mitochondrial Patients, Mitocon ONLUS, Rome, Italy
12 ¹²Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
13 ¹³General Surgery and Transplant Unit, Department of Medical and Surgical Sciences,
14 University of Bologna, Bologna, Italy
15 ¹⁴IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Interaziendale Metropolitana
16 (NeuroMet), - Neurologia AOU S.Orsola-Malpighi, Bologna, Italy
17 ¹⁵Neurological and Metabolic Diseases Clinic, Siena Hospital, Department of Medicine,
18 Surgery and Neuroscience, University of Siena, Siena, Italy
19 ¹⁶Department of Radiological, Oncological and Pathological Sciences, Sapienza, University
20 of Rome, Umberto I Policlinic, Rome, Italy
21 ¹⁷Institute of Human Genetics and Inherited Metabolic Disorders, Galilee Medical Center,
22 Nahariya, Israel
23 ¹⁸Department for Care of Organ Failures and Transplants, Internal Medicine for the
24 Treatment of Severe Organ Failures, St. Orsola-Malpighi Hospital, Bologna, Italy
25 ¹⁹Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

1 ²⁰Neurology Unit, Department of Neuroscience, Azienda Ospedaliero Universitaria Integrata
2 Verona, Verona, Italy

3 ²¹Anaesthesiology Intensive Care and Transplantation Unit, St. Orsola-Malpighi Hospital,
4 Bologna, Italy

5 ²²Department of Clinical Movement Neurosciences, Royal Free Campus, University College
6 of London, Queen Square Institute of Neurology, London, United Kingdom

7 ²³Metabolic Unit, Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa,
8 Israel

9 ²⁴Department of Bone Marrow Transplantation, Hadassah University Medical Center,
10 Jerusalem, Israel

11 ²⁵Department of Internal Medicine I, Medical University of Innsbruck, Innsbruck, Austria

12 ²⁶Department of Neurosciences, Veneto Institute of Molecular Medicine, University of
13 Padova, Padova, Italy

14

15 **Word count:** 3251

16 **Number of Tables:** n= 3 **and Number of Figures:** n= 2

17 **Colour Figures:** none

18

19 **Corresponding Author:**

20 Rita Rinaldi, M.D.

21 IRCCS Istituto delle Scienze Neurologiche di Bologna, UOC Interaziendale Metropolitana
22 (NeuroMet), - Neurologia AOU S.Orsola-Malpighi, Via Albertoni 15, 40138, Bologna, Italy.

23 Phone: +390512142641 or +390512142652

24 Fax: +390512142640

25 E-mail: rita.rinaldi@aosp.bo.it

26

1 **SUMMARY**

2 Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) is a rare autosomal
3 recessive disease caused by *TYMP* mutations and thymidine phosphorylase (TP) deficiency.
4 Thymidine and deoxyuridine accumulate impairing the mitochondrial DNA maintenance and
5 integrity. Clinically, patients show severe and progressive gastrointestinal and neurological
6 manifestations. The onset typically occurs in the second decade of life and mean age at death
7 is 37 years. Signs and symptoms of MNGIE are heterogeneous and confirmatory diagnostic
8 tests are not routinely performed by most laboratories, accounting for common misdiagnosis.
9 Factors predictive of progression and appropriate tests for monitoring are still undefined.
10 Several treatment options showed promising results in restoring the biochemical imbalance of
11 MNGIE. The lack of controlled studies with appropriate follow-up accounts for the limited
12 evidence informing diagnostic and therapeutic choices. The International Consensus
13 Conference (ICC) on MNGIE, held in Bologna, Italy, on March 30th-31st, 2019, aimed at an
14 evidence-based consensus on diagnosis, prognosis and treatment of MNGIE among experts,
15 patients, caregivers and other stakeholders involved in caring the condition. The conference
16 was conducted according to the National Institute of Health Consensus Conference
17 methodology. A consensus development panel formulated a set of statements and proposed a
18 research agenda. Specifically, the ICC produced recommendations on: (1) diagnostic
19 pathway; (2) prognosis and the main predictors of disease progression; (3) efficacy and safety
20 of treatments; and (4) research priorities on diagnosis, prognosis and treatment. The Bologna
21 ICC on diagnosis, management and treatment of MNGIE provided evidence-based guidance
22 for clinicians incorporating patients' values and preferences.

23

24 **SYNOPSIS**

1 This is the first International Consensus Conference (ICC) aimed at an evidence-based
2 consensus on diagnosis, prognosis and treatment among experts, patients, caregivers and
3 other stakeholders involved in MNGIE. The ICC provided recommendations on diagnostic
4 pathway, prognosis and the main predictors of disease progression, efficacy and safety of
5 treatments, and, finally, identified priorities on cogent research topics on MNGIE.

6

7 **ABBREVIATION LIST**

8 CAPD: continuous ambulatory peritoneal dialysis; CDP: consensus development panel;
9 CPEO: chronic progressive external ophthalmoplegia; dThd: thymidine; dUrd: deoxyuridine;
10 EE-TP: erythrocyte encapsulated TP; EWGs: expert workgroups; GI: gastrointestinal; HD:
11 hemodialysis; HSCT: hematopoietic stem cell transplantation; ICC: International Consensus
12 Conference; MNGIE: Mitochondrial Neurogastrointestinal Encephalomyopathy; mtDNA:
13 mitochondrial DNA; OLT: orthotopic liver transplantation; PEG: percutaneous endoscopic
14 gastrostomy; QoL: quality of life SC: scientific committee; SIBO: small intestinal bacterial
15 overgrowth; TC: technical committee; TP: thymidine phosphorylase.

16

17 **ACKNOWLEDGEMENTS**

18 [The authors thank Rosanna Foderà for her translation support to patients with MNGIE during](#)
19 [the conference and Giulia Amore, Umberto Pensato and Vincenzo Mastrangelo for their help](#)
20 [in the organization of the conference.](#)

21

22

23

24

25

Formatted: Tab stops: 1.88 cm, Left

1 **COMPLIANCE WITH ETHICS GUIDELINES**

2 **CONFLICT OF INTEREST**

3 Valerio Carelli is a consultant for Santhera Pharmaceuticals, GenSight and Stealth
4 BioTherapeutics and has received research support from Santhera Pharmaceuticals and
5 Stealth BioTherapeutics.

6 Bridget Elizabeth Bax has received a travel grant and licence fee payment from Orphan
7 technologies and honorariums from Recordati Rare Diseases Fondation d'entreprise and the
8 European Science Foundation.

9 Michio Hirano received research support from Entrada Therapeutics.

10 Giovanna Cenacchi, Rita Rinaldi, Heinz Zoller, Francesco Nonino, Luca Vignatelli, Roberto
11 D'Alessandro, Massimiliano Filosto, Maria Teresa Dotti, Hanna Mandel, Laura Ludovica
12 Gramegna, Olimpia Musumeci, Matteo Cescon, Roberto D'Angelo, Alessia Pugliese,
13 Antonella Spinazzola, Elisa Boschetti, Javier Torres-Torronteras, Irina Zaidman, Antonio
14 Siniscalchi, Roberto De Giorgio, Maria Cristina Morelli, Carla Giordano, Elisa Baldin, Loris
15 Pironi, Ramon Martí, Galit Tal, Michelle Levene, Anna Accarino, Raffaele Lodi, Alessio
16 Bolletta, Riccardo Bolletta, Massimo Zeviani, Antonio Daniele Pinna and Mauro Scarpelli
17 declare that they have no conflict of interest.

18
19 **AUTHORS' CONTRIBUTION**

20 V.C., R.D.G, L.P., R.R., E. Ba., F.N, L.V. participated to the planning, conducting and
21 reporting of the project; R.B, A.B M.H, R.M., A.P., R.DA., E. Bo. participated to the
22 planning and conduction of the project.

23 B.E.B. contributed to the conduction and reporting of the project.

24 L.L.G., M.S., A.S., G.T., C.G., O.M., M.C.M., M. C., M.T.D., M. L., H.M., A. S., J. T-T, I.
25 Z., H.Z. contributed to the conduction of the project.

1 **ETHICS**

2 This article does not contain any studies with human or animal subjects performed by any of
3 the authors. No ethical approval was required.

4

5 **STUDY FUNDING**

6 Azienda Ospedaliero-Universitaria di Bologna Policlinico St. Orsola-Malpighi and IRCCS,
7 Istituto delle Scienze Neurologiche di Bologna (Bologna, Italy).

8

9 **SEARCH TERMS**

10 Mitochondrial Neurogastrointestinal Encephalomyopathy; MNGIE; enzyme replacement;
11 mitochondrial disease; *TYMP*; thymidine phosphorylase, consensus conference.

12

13

1 **1 INTRODUCTION**

2 Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE) is an autosomal
3 recessive disease caused by mutations in the thymidine phosphorylase gene (*TYMP*)(Pacitti et
4 al 2018). *TYMP* encodes for thymidine phosphorylase (TP), which catabolizes thymidine
5 (dThd) and deoxyuridine (dUrd) into their respective bases. *TYMP* mutations markedly
6 reduce/abolish TP activity leading to accumulation of dThd and dUrd and mitochondrial
7 DNA (mtDNA) defects.

8 MNGIE is an ultra-rare condition, characterized by severe gastrointestinal (GI) and
9 neurological symptoms(D'Angelo et al 2016) that is often misdiagnosed. Although the
10 disease is progressive and fatal, natural history is still uncharacterized(Nishino et al 2000;
11 Garone et al 2011; Corazza et al 2019). Various experimental therapeutic approaches aimed
12 to the temporary enzyme replacement, e.g. erythrocyte encapsulated TP (EE-TP) infusions
13 (Pacitti et al 2018), or permanent restoration of TP activity through hematopoietic stem cell
14 transplantation (HSCT) (Halter et al 2015) and orthotopic liver transplantation (OLT) (De
15 Giorgio et al 2016). Since the severity of GI symptoms influences treatment success, timing of
16 HSCT and OLT is crucial (Halter et al 2015; De Giorgio et al 2016). Possible future options
17 include gene therapy, which has shown pre-clinical efficacy (Torres-Torronteras et al 2014;
18 Cabrera-Pérez et al 2015; Torres-Torronteras et al 2016; Torres-Torronteras et al 2018;
19 Yadak et al 2018; Cabrera-Pérez et al 2019).

20 An International Consensus Conference (ICC) was held to produce an unbiased, evidence-
21 based assessment on MNGIE, leading to a consensus and guidance on the following areas: (I)
22 diagnostic pathway; (II) prognosis and main predictors of disease progression; (III) efficacy
23 and safety of treatments.

24

25 **2 METHOD**

1 **2.1 Panel/experts selection**

2 The Bologna MNGIE ICC was organized and promoted by the Azienda Ospedaliero-
3 Universitaria di Bologna, Policlinico S.Orsola-Malpighi, and the IRCCS Istituto delle
4 Scienze Neurologiche di Bologna, Italy, according to the NIH Consensus Development
5 Program methodology(Nair et al 2011) and the Methodological Handbook of the Italian
6 National Guideline System(Candiani et al 2009). The members of the technical committee
7 (TC) and scientific committee (SC), the expert workgroups (EWGs) and the consensus
8 development panel (CDP) were invited based on their expertise in the field, ensuring the
9 participation of all the clinical and non-clinical stakeholders (including patients) and a broad
10 involvement of healthcare professionals from all the clinical aspects of MNGIE. Researchers
11 were identified based on a review of the main authors in the field. The official language of
12 the conference was English supported by a professional translator. A declaration of interest
13 form was signed by every participant. Of the 36 stakeholders invited to the ICC, four
14 declined and five accepted but did not participate. One member attended via teleconference.

15

16 **2.2 The assignment, scoping and assessment stages**

17 The assignment, scoping and assessment stages occurred between January 2018 and March
18 2019. The ICC took place in Bologna on March 30th and 31st. During assignment, the SC
19 appointed a TC, a CDP and three EWGs (Appendix 1). The SC identified three MNGIE
20 topics (diagnosis, prognosis and treatment) and questions to be addressed by the EWGs
21 (scoping). Assessment of the evidence was carried out by the TC through a systematic
22 literature search with evidence mapping (Bragge et al 2011) according to the PRISMA
23 guidelines (Moher et al 2009) (Appendix 2). Studies of any design, in English language,
24 published in full on peer reviewed journals, reporting original data on diagnosis, prognosis,
25 and/or treatment of MNGIE on humans were searched on MEDLINE and the Cochrane

1 Central Register of Controlled Trials in January 2018 and 2019, and finally updated in May
2 2020. Retrieved studies were selected independently by LV, EB and RD. Disagreement was
3 resolved by discussion. Each study was graded according to four classes of methodological
4 quality (from Class I, highest quality to Class IV, lowest quality) according to the
5 Classification of Evidence Schemes of the Clinical Practice Guideline Process Manual of the
6 American Academy of Neurology (Appendix 3) (Gronseth et al 2011) and appraised by the
7 EWGs to draft answers to the questions posed by the SC. During the ICC the scientific
8 evidence and the answers to the questions were presented by the EWGs. The final statements
9 by the CDP were presented at the end of day 2 to the audience including stakeholders and
10 general public.

11

12 **3 RESULTS**

13 The literature search retrieved 1,305 citations after duplicate removal; 1,146 were excluded
14 because the covered topic was not of interest for our review (Appendix 2). Of the 159 full
15 text articles selected, 81 were excluded mostly because they were animal studies or studies
16 describing genetic mutations causing the clinical manifestations of MNGIE. The 78 selected
17 articles were submitted to the three working groups. Since 36 of them were out of scope
18 regarding the specific topics, 42 were used for the statements (4 of them were assigned to two
19 topics each). The CDP issued the following Position Statements on diagnosis, prognosis and
20 treatment of MNGIE. In Appendix 4 a summary of the scientific evidence and rationale for
21 the statements is presented.

22

23 **3.1 Position Statements on the Diagnosis of MNGIE**

24 The following statements are based on 7 Class III level studies (case series with controls)
25 (Spinazzola et al 2002; Nishigaki et al 2003; Marti et al 2004; Valentino et al 2007;

1 Mohamed et al 2014; Gramegna et al 2018; Kipper et al 2020), 7 Class IV level studies (two
2 case series and five case reports) (Millar et al 2004; Marti et al 2005; Giordano et al 2006;
3 Filosto et al 2011; Garone et al 2011; Scarpelli et al 2013; Corazza et al 2019) and expert
4 opinion.

5 **3.1.1 Clinical elements that can indicate MNGIE**

6 MNGIE can be suspected when one or more of the following clinical cardinal elements are
7 present:

- 8 • Symptoms and signs of otherwise unexplained GI dysmotility
- 9 • Thin constitution/cachexia, [even](#) with normal food behaviour and [nutritional](#) intake
- 10 • Neurological features such as ptosis and symptoms suggesting peripheral neuropathy
- 11 • A progressive course of the above with frequent misdiagnosis

12 The features of the full-blown MNGIE typically are:

- 13 • Symptoms onset: childhood, adolescence/young adulthood (typical), adulthood (late
14 onset, >40 years)
- 15 • GI symptoms/signs: sub-occlusive episodes, nausea, vomiting, early satiety,
16 borborygmi, severe abdominal pain, abdominal distension, dysphagia, constipation and
17 diarrhoea, acute peritonitis due to small bowel perforation
- 18 • Unexplained weight loss, thinness, cachexia, [even with normal food behaviour and](#)
19 [nutritional intake](#)
- 20 • Radiological GI signs: small bowel diverticulosis, GI dilation (e.g. gastric or intestinal
21 dilation)
- 22 • Neurological symptoms/signs: chronic progressive external ophthalmoplegia (CPEO),
23 ptosis, peripheral neuropathy, hearing loss
- 24 • Neuroradiological signs: leukoencephalopathy without other neuroradiological
25 abnormalities

- 1 • Metabolic alterations: liver steatosis evolving in cirrhosis, pancreatitis, early onset
2 diabetes mellitus, increased triglyceride levels, elevated plasma lactate

3 MNGIE is most frequently misdiagnosed as:

- 4 • Anorexia nervosa
- 5 • GI diseases: Crohn's disease, coeliac disease, esophagitis and/or gastritis, irritable bowel
6 syndrome, superior mesenteric artery syndrome, Whipple's disease, chronic intestinal
7 pseudo-obstruction
- 8 • Neurological diseases: chronic inflammatory demyelinating polyneuropathy, Charcot-
9 Marie-Tooth disease, other mitochondrial diseases such as CPEO, Kearns-Sayre
10 syndrome

11 **3.1.2 Recommended diagnostic tests**

12 Cardinal diagnostic tests:

- 13 • Swallowing test, gastric emptying and GI manometry (when possible): altered GI
14 motility and transit
- 15 • Brain MRI: leukoencephalopathy without any other neuroradiological abnormalities
16 (almost universally present) (Table 1 and Fig. 2)
- 17 • Nerve conduction studies: peripheral neuropathy, predominantly demyelinating

18 Ancillary tests:

- 19 • Muscle biopsy: ragged-red and COX deficient fibers, deficiencies of respiratory chain
20 enzyme activities, ultrastructurally abnormal mitochondria, and mtDNA depletion,
21 multiple deletions, and somatic point mutations
- 22 • Mucosal GI histology of small bowel (to exclude other conditions), and gut full thickness
23 biopsy (when possible)

24 **3.1.3 Recommended metabolic and genetic tests**

1 Mandatory tests to confirm MNGIE diagnosis:

- 2 • *TYMP* sequencing: homozygous or compound heterozygous allelic pathogenic variants,
3 no further testing.
- 4 • If one variant of uncertain significance or a wild-type sequence is identified, the
5 following biochemical assessments should be performed:
 - 6 ○ TP activity: severely reduced or virtually absent in the buffy coat (below 8%
7 of the mean of reference TP values; laboratory cutoffs may differ depending
8 on sample processing and biochemical assay). If TP activity is only partially
9 reduced, then it is mandatory to measure plasma dThd and dUrd levels. The
10 diagnosis is excluded if TP activity is normal.
 - 11 ○ dThd and dUrd levels: increased in plasma (assessment of urine is unreliable)

12 Fig. 1 shows the recommended algorithm in persons with suspected MNGIE.

13

14 **3.2 Position Statements on the Prognosis of MNGIE**

15 The following statements are based on one Class II level study (retrospective cohort) (Garone
16 et al 2011), two Class III level study (retrospective cohorts) (Nishino et al 2000; Corazza et al
17 2019), 4 Class IV level studies (four case reports) (Ionasescu et al 1984; Carrozzo et al 1998;
18 Marti et al 2005; Massa et al 2009) and expert opinion.

19

20 **3.2.1 The natural history of MNGIE**

- 21 • Mean age at onset: 17.9 years (5 months - 43 years).
- 22 • GI symptoms (57% at onset; 100% at diagnosis); onset/diagnosis: diarrhea, abdominal
23 pain, borborygmi, vomiting, pseudo-obstruction (32% - 65%), weight loss/cachexia
24 (100%); evolution: diverticulosis/diverticulitis (67%), hepatopathy (22%).

- 1 • Neurological symptoms / signs (43% at onset; 100% at diagnosis);
2 onset/diagnosis/evolution: ocular signs (ptosis, ophthalmoparesis) (74-100%),
3 polyneuropathy (92-100%), hearing loss (39-45%), leucoencephalopathy (\pm 100%);
4 cognitive impairment (20%).
- 5 • Symptoms are cumulative and progressive.
- 6 • Mean age at death is reported to range between 35 and 37 years; survival 100% before 19
7 years and < 5% after 50 years.
- 8 • Death is mainly due to GI and liver complications (intestinal perforation, intestinal
9 bleeding, liver failure, aspiration pneumonia, complications due to small intestinal
10 bacterial overgrowth (SIBO) or infection related to central venous catheter for parenteral
11 nutrition) and cachexia.

12
13 Overall survival is the only outcome reported in the literature. Weight loss is an important
14 feature of MNGIE, but data on its prognostic role are lacking.

15

16 **3.2.2 Phenotypes of MNGIE**

17 MNGIE has two different presentations distinguished by age of onset: “Early Onset” (or
18 “Classic”) and “Late Onset” (Table 2). Severity can vary among family members. Available
19 data do not allow a differentiation of clinical phenotypes based on symptoms at onset (GI or
20 neurological). Neurological manifestations may be subtle and insidious leading to late
21 recognition by both patients and physicians. When GI symptoms are the first manifestation,
22 the diagnosis and consequently the appropriate treatment may be significantly delayed
23 because of misdiagnosis.

24 In clinical practice, the presence and/or severity of GI involvement are considered a negative
25 prognostic factor, for both morbidity and mortality. Apparently, there is no correlation

1 between genotype, phenotype and outcome. Residual TP activity of 10-15% has been
2 associated with moderate increases of nucleosides and “Late Onset” MNGIE compared to the
3 “Classic” form.

4

5 **3.2.3 Impact of different phenotypes on the natural history of MNGIE and outcomes**

6 Whether “Classic” (“Early Onset”) and “Late Onset” phenotypes have different disease
7 progression remain unsettled. All patients with Late Onset phenotype reported in the
8 literature were alive at follow-up ranging between 8 to 24 years. In the “Classic” phenotype,
9 age of onset is not related to life expectancy. At present, overall survival after onset is the
10 only available outcome reported in the literature.

11

12 **3.2.4 Events indicating disease progression**

13 The following events can be considered as important milestones related to progression: GI
14 sub-occlusive episode, decompressive percutaneous endoscopic gastrostomy (PEG),
15 aspiration pneumonia, abdominal surgical procedures, septic episode due to SIBO, need for
16 enteral tube feeding or PEG, onset of intestinal failure (and subsequent need of parenteral
17 nutrition), liver cirrhosis, loss of unaided walking ability. Recommended assessments to
18 monitor MNGIE progression are listed in Table 3.

19

20 **3.3 Position Statements on the Treatment of MNGIE**

21 The following statements are based on 25 Class IV level studies (one retrospective cohort,
22 one case series, 24 case reports) (Hirano et al 2006; la Marca et al 2006; Lara et al 2006;
23 Yavuz et al 2007; Moran et al 2008; Filosto et al 2012; Sicurelli et al 2012; Bax et al 2013;
24 Finkenstedt et al 2013; Hussein 2013; Ariaudo et al 2015; Casarez et al 2015; Halter et al
25 2015; Peedikayil et al 2015; De Giorgio et al 2016; Sivadasan et al 2016; Baker et al 2017;

1 D'Angelo et al 2017; Roeben et al 2017; Chandra et al 2018; Hanbali et al 2018; Levene et al
2 2018; Yadak et al 2018; Levene et al 2019; Kripps et al 2020) and expert opinion.

3

4 **3.3.1 Treatments effective in temporarily restoring the biochemical imbalance**

5 “Short term” is defined as a period of time required stabilizing a patient waiting for
6 permanent treatment or as compassionate use.

7 Overall, hemodialysis (HD), continuous ambulatory peritoneal dialysis (CAPD), EE-TP and
8 platelet infusion have been effective in achieving temporary improvement of the biochemical
9 imbalance in several MNGIE patients. However, there are practical limitations, safety issues
10 and unclear clinical effects associated with these approaches.

11 Specifically:

- 12 • EE-TP seems to be effective on a monthly-based administration in terms of biochemical
13 and clinical improvement (4 patients out of 5); mild immunological reaction against
14 bacterial TP mainly with repeated infusions may occur (2 out of 5 patients). EE-TP is
15 currently under clinical evaluation.
- 16 • CAPD seems to be well tolerated with anecdotal biochemical efficacy; peritoneal
17 sclerosis due to repeated procedures may be a safety concern.
- 18 • HD has very short-term biochemical effects as nucleosides return to high levels a few
19 hours after the procedure. Disadvantages include the need of venous access, an intensive
20 procedure schedule (3-4 sessions per week) and the possible occurrence of hypotension,
21 fluid overload or infections.
- 22 • Platelet infusion has been reported to achieve some biochemical improvement. Safety
23 issues include allergic and immunological reactions.

24

1 We suggest consideration of EE-TP or CAPD in patients waiting for a permanent treatment
2 option, or for compassionate use.

3

4 **3.3.2 Effective treatments that permanently restore the biochemical imbalance**

5 Permanent treatment options are aimed at restoring TP resulting in the long-term clearance of
6 dUrd and dThd. The improved biochemical profile is expected to be associated with clinical
7 stabilization (i.e., halting tissue damage progression) or improvement.

- 8 • HSCT is effective in permanently restoring the biochemical imbalance. It requires
9 chemotherapy and immunosuppressive therapy and is associated with a high risk for
10 complications and mortality related to therapy, including graft versus host disease.
- 11 • OLT is effective for permanent restoration of the biochemical imbalance and it does not
12 require preoperative conditioning. Patients with severe malnutrition or previous episodes
13 of small bowel perforation, sub-occlusion or sepsis related to SIBO could be at high risk
14 of peri- and post-operative complications and should not be considered for OLT;
15 metabolic complications such as chronic kidney insufficiency, diabetes or cardiovascular
16 disease related to long-life immunosuppressive therapy may be long-term issues.

17

18 **3.3.3 Treatments that improve the patient's health in terms of quality of life (QoL) and** 19 **functional status**

20 Any temporary or permanent treatment should be considered as soon as diagnosis is
21 confirmed. EE-TP and CAPD are effective with some temporary improvement of QoL and
22 minimal complications. HSCT is effective in the long term for improving QoL and functional
23 status, although limited by a high post-treatment mortality rate (63%) in severely
24 symptomatic adult patients. OLT is effective in the long term for improving QoL and
25 functional status, although limited evidence is available.

1

2 **3.3.4 Appropriateness of treatments that temporarily or permanently restore the**
3 **biochemical imbalance**

4 Temporary treatments should be considered at any age based on clinical condition, before
5 permanent treatments, e.g. while waiting /on list for either HSCT or OLT. Once the diagnosis
6 is confirmed, permanent treatments are recommended as early as possible for both HSCT and
7 OLT according to eligibility criteria (e.g. severity). Ideal candidates should be those at an
8 early stage of MNGIE. In patients who are oligosymptomatic, either HSCT or OLT can be
9 considered. HSCT should be considered in pediatric patients and young adults with normal
10 liver function, mild or no GI manifestations (e.g. absence of intestinal pseudo-obstruction,
11 peritonitis, pancreatitis) and in case of matched donors with normal genotype. A busulphan-
12 based myeloablative regimen as a preparation to HSCT is recommended. OLT would be the
13 preferred permanent treatment option for patients with progressive liver involvement (i.e.
14 fibrosis and/or abnormal liver function). Transplant from a living donor can be considered
15 only if the donor's *TYMP* genotype is normal. In fully informed patients who are severely
16 affected by MNGIE and unlikely to survive permanent correction procedures, temporary
17 metabolite restorative treatments (EE-TP and CAPD) should be offered and discussed.

18

19 **3.3.5 Assessments predicting the effect of treatment**

20 The following assessments may be predictive of effects of treatment:

- 21 • Serial plasma levels of dThd and dUrd
22 • Serial TP activity measurement in buffy coat (only for HSCT)

23 The clinical outcome after treatment depends upon the patient's disease status prior to
24 treatment. Assessments evaluating the disease status at the time of diagnosis may indicate
25 whether a proposed treatment is likely to be effective. The extent of hepatic, GI involvement

1 and cachexia are key indicators of survival, therefore assessments evaluating these aspects
2 may be predictive of treatment outcome. Several clinical outcome assessments may be used
3 to monitor the effect of treatment. Some of these assessments were discussed in the
4 “Prognosis” section.

5

6 **4 DISCUSSION**

7 This is the first consensus statement on MNGIE, prompted by the severity of a condition that,
8 although very rare, affects mainly young adults causing substantial reduction of life
9 expectancy and QoL. Several potentially useful treatments can be offered to patients, and
10 more may be soon available. It is important to coordinate the work of clinicians and
11 researchers in order to generate new useful evidence and provide patients with reliable and
12 consistent information about their condition.

13

14 **4.1 Main findings**

15 The ICC developed over two days. During the first day one representative of each of the three
16 EWG presented (in a meeting open to the general audience) the results of a systematic search
17 of the literature relative to the topic. Each representative summarized the scientific evidence
18 and proposed conclusions. Presentations were followed by discussion, moderated by the chair
19 of the Jury and by a methodologist, during which disagreements were resolved and tentative
20 recommendations were drafted. No disagreement required formal voting. Multi-stakeholder
21 involvement in the public discussion was ensured by involving patients’ advocacy
22 organizations.

23

24 **4.2 Strengths and limitations**

1 MNGIE is genetically determined and gene therapies are still at a pre-clinical stage.
2 Nevertheless, promising treatments that could potentially modify the course of the condition
3 are emerging. The efficacy of available treatments is still not completely defined, and
4 probably influenced by the stage of the disease. Due to the rarity of the condition, the
5 evidence on MNGIE is limited to few case reports and small case series. The ICC aimed at
6 reaching for the first time an evidence-based consensus involving researchers, patients and
7 their families and healthcare providers on the clinical and instrumental hallmarks of MNGIE,
8 its expected course and the main criteria guiding the choice of the most appropriate treatment
9 in individual patients. Research priorities were also identified (Appendix 5) along with the
10 newborn promoting collaboration and networks.

11 Our process had several limitations. First, since the available evidence is scanty and of low
12 quality, the provided guidance is mainly based on the opinion of experienced clinicians and
13 researchers, and therefore subject to bias. Adopting a rigorous and explicit methodology and
14 warranting the possibility of discussion in every stage of the process through public
15 presentations compensated this limitation. In order to avoid a prevailing view by medical
16 experts, we ensured a formal participation of a leading patient advocacy association among
17 the stakeholders in the jury that formulated the guidance and prompted questions and
18 comments by patients and their families in the audience during discussion. Personal interests,
19 that could bias the point of view of individuals, were declared by each participant. Secondly,
20 there was a partial overlapping in the composition of the scientific workgroups and the SC,
21 since some of the members of the formers were also part of the latter. This could have been a
22 potential source of bias that we mitigated by creating groups as large as possible, facilitating
23 a plurality of views within different areas. Due to the rarity of MNGIE and its recent
24 discovery, the number of knowledgeable researchers and clinicians was low. Although the

1 conference was international and almost all invited persons accepted the invitation, the total
2 number of participants did not allow a complete separation of roles.
3

1 5 REFERENCES

- 2 Ariaudo C, Daidola G, Ferrero B, et al (2015) Mitochondrial neurogastrointestinal
3 encephalomyopathy treated with peritoneal dialysis and bone marrow transplantation. *Journal*
4 *of nephrology* 28: 125-127.
- 5 Baker MK, Schutte CM, Ranchhod N, Brittain D, van Rensburg JE (2017) Transient clinical
6 improvement of a mitochondrial neurogastrointestinal encephalomyopathy-like syndrome
7 after allogeneic haematopoietic stem cell transplantation. *BMJ case reports* 2017.
- 8 Bax BE, Bain MD, Scarpelli M, Filosto M, Tonin P, Moran N (2013) Clinical and biochemical
9 improvements in a patient with MNGIE following enzyme replacement. *Neurology* 81: 1269-
10 1271.
- 11 Bragge P, Clavisi O, Turner T, Tavender E, Collie A, Gruen RL (2011) The Global Evidence
12 Mapping Initiative: scoping research in broad topic areas. *BMC medical research*
13 *methodology* 11: 92.
- 14 Cabrera-Pérez R, Torres-Torronteras J, Vila-Julà F, et al (2015) Prospective therapeutic approaches
15 in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *Expert Opinion on*
16 *Orphan Drugs* 3: 1167-1182.
- 17 Cabrera-Pérez R, Vila-Julà F, Hirano M, Mingozi F, Torres-Torronteras J, Marti R (2019) Alpha-1-
18 Antitrypsin Promoter Improves the Efficacy of an Adeno-Associated Virus Vector for the
19 Treatment of Mitochondrial Neurogastrointestinal Encephalomyopathy. *Human gene therapy*
20 30: 985-998.
- 21 Candiani G, Colombo C, Daghini R, et al (2009) *Sistema Nazionale Linee Guida. Manuale*
22 *Metodologico. Come realizzare una conferenza di consenso.* , Milan: Zadig publishing.
- 23 Carrozzo R, Hirano M, Fromenty B, et al (1998) Multiple mtDNA deletions features in autosomal
24 dominant and recessive diseases suggest distinct pathogeneses. *Neurology* 50: 99-106.
- 25 Casarez VQ, Zavala AM, Owusu-Agyemang P, Hagan K (2015) Anesthetic Management of a Child
26 with Mitochondrial Neurogastrointestinal Encephalopathy. *Case reports in anesthesiology*
27 2015: 453714.
- 28 Chandra VS, Lakshmi BS, Padmavathi Devi SVV, et al (2018) Mitochondrial Neurogastrointestinal
29 Encephalomyopathy: A Nonrenal Indication for Peritoneal Dialysis. *Indian J Nephrol* 28:
30 310-313.
- 31 Corazza G, Pagan C, Hardy G, Besson G, Lombes A (2019) MyoNeuroGastroIntestinal
32 Encephalopathy: Natural History and Means for Early Diagnosis. *Gastroenterology* 156:
33 1525-1527.e1524.
- 34 D'Angelo R, Rinaldi R, Carelli V, et al (2016) ITA-MNGIE: an Italian regional and national survey
35 for mitochondrial neuro-gastro-intestinal encephalomyopathy. *Neurological sciences : official*
36 *journal of the Italian Neurological Society and of the Italian Society of Clinical*
37 *Neurophysiology* 37: 1149-1151.
- 38 D'Angelo R, Rinaldi R, Pironi L, et al (2017) Liver transplant reverses biochemical imbalance in
39 mitochondrial neurogastrointestinal encephalomyopathy. *Mitochondrion* 34: 101-102.
- 40 De Giorgio R, Pironi L, Rinaldi R, et al (2016) Liver transplantation for mitochondrial
41 neurogastrointestinal encephalomyopathy. *Annals of neurology* 80: 448-455.
- 42 Filosto M, Scarpelli M, Tonin P, et al (2012) Course and management of allogeneic stem cell
43 transplantation in patients with mitochondrial neurogastrointestinal encephalomyopathy.
44 *Journal of neurology* 259: 2699-2706.
- 45 Filosto M, Scarpelli M, Tonin P, et al (2011) Pitfalls in diagnosing mitochondrial
46 neurogastrointestinal encephalomyopathy. *Journal of inherited metabolic disease* 34: 1199-
47 1203.
- 48 Finkenstedt A, Schranz M, Bosch S, et al (2013) MNGIE Syndrome: Liver Cirrhosis Should Be Ruled
49 Out Prior to Bone Marrow Transplantation. *JIMD reports* 10: 41-44.
- 50 Garone C, Tadesse S, Hirano M (2011) Clinical and genetic spectrum of mitochondrial
51 neurogastrointestinal encephalomyopathy. *Brain : a journal of neurology* 134: 3326-3332.

- 1 Giordano C, Sebastiani M, Plazzi G, et al (2006) Mitochondrial neurogastrointestinal
2 encephalomyopathy: evidence of mitochondrial DNA depletion in the small intestine.
3 *Gastroenterology* 130: 893-901.
- 4 Gramegna LL, Pisano A, Testa C, et al (2018) Cerebral Mitochondrial Microangiopathy Leads to
5 Leukoencephalopathy in Mitochondrial Neurogastrointestinal Encephalopathy. *AJNR*
6 *American journal of neuroradiology* 39: 427-434.
- 7 Gronseth GS, Woodroffe LM, Getchius TSD (2011) *Clinical Practice Guideline Process Manual*.
8 *American Academy of Neurology*
- 9 Halter JP, Michael W, Schupbach M, et al (2015) Allogeneic haematopoietic stem cell transplantation
10 for mitochondrial neurogastrointestinal encephalomyopathy. *Brain : a journal of neurology*
11 138: 2847-2858.
- 12 Hanbali A, Rasheed W, Peedikayil MC, Boholega S, Alzahrani HA (2018) Mitochondrial
13 Neurogastrointestinal Encephalomyopathy Syndrome Treated with Stem Cell Transplant: A
14 Case Series and Literature Review. *Experimental and clinical transplantation : official*
15 *journal of the Middle East Society for Organ Transplantation* 16: 773-778.
- 16 Hirano M, Marti R, Casali C, et al (2006) Allogeneic stem cell transplantation corrects biochemical
17 derangements in MNGIE. *Neurology* 67: 1458-1460.
- 18 Hussein E (2013) Non-myeloablative bone marrow transplant and platelet infusion can transiently
19 improve the clinical outcome of mitochondrial neurogastrointestinal encephalopathy: a case
20 report. *Transfusion and apheresis science : official journal of the World Apheresis*
21 *Association : official journal of the European Society for Haemapheresis* 49: 208-211.
- 22 Ionasescu VV, Thompson HS, Aschenbrener C, et al (1984) Late-onset oculogastrointestinal muscular
23 dystrophy. *American Journal of Medical Genetics* 18: 781-788.
- 24 Kipper K, Hecht M, Antunes NJ, et al (2020) Quantification of Plasma and Urine Thymidine and 2'-
25 Deoxyuridine by LC-MS/MS for the Pharmacodynamic Evaluation of Erythrocyte
26 Encapsulated Thymidine Phosphorylase in Patients with Mitochondrial Neurogastrointestinal
27 Encephalomyopathy. *Journal of clinical medicine* 9.
- 28 Kripps K, Nakayuenyongsuk W, Shayota BJ, et al (2020) Successful liver transplantation in
29 mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *Molecular genetics and*
30 *metabolism* 130: 58-64.
- 31 la Marca G, Malvagia S, Casetta B, et al (2006) Pre- and post-dialysis quantitative dosage of
32 thymidine in urine and plasma of a MNGIE patient by using HPLC-ESI-MS/MS. *Journal of*
33 *mass spectrometry : JMS* 41: 586-592.
- 34 Lara MC, Weiss B, Illa I, et al (2006) Infusion of platelets transiently reduces nucleoside overload in
35 MNGIE. *Neurology* 67: 1461-1463.
- 36 Levene M, Bain MD, Moran NF, et al (2019) Safety and Efficacy of Erythrocyte Encapsulated
37 Thymidine Phosphorylase in Mitochondrial Neurogastrointestinal Encephalomyopathy.
38 *Journal of clinical medicine* 8.
- 39 Levene M, Pacitti D, Gasson C, Hall J, Sellos-Moura M, Bax BE (2018) Validation of an
40 Immunoassay for Anti-thymidine Phosphorylase Antibodies in Patients with MNGIE Treated
41 with Enzyme Replacement Therapy. *Molecular therapy Methods & clinical development* 11:
42 1-8.
- 43 Marti R, Spinazzola A, Tadesse S, Nishino I, Nishigaki Y, Hirano M (2004) Definitive diagnosis of
44 mitochondrial neurogastrointestinal encephalomyopathy by biochemical assays. *Clinical*
45 *chemistry* 50: 120-124.
- 46 Marti R, Verschuuren JJ, Buchman A, et al (2005) Late-onset MNGIE due to partial loss of thymidine
47 phosphorylase activity. *Annals of neurology* 58: 649-652.
- 48 Massa R, Tessa A, Margollicci M, et al (2009) Late-onset MNGIE without peripheral neuropathy due
49 to incomplete loss of thymidine phosphorylase activity. *Neuromuscular disorders : NMD* 19:
50 837-840.
- 51 Millar WS, Lignelli A, Hirano M (2004) MRI of Five Patients with Mitochondrial
52 Neurogastrointestinal Encephalomyopathy. *American Journal of Roentgenology* 182: 1537-
53 1541.
- 54 Mohamed S, Caporali L, De Giorgio R, Carelli V, Contin M (2014) HPLC-UV analysis of thymidine
55 and deoxyuridine in plasma of patients with thymidine phosphorylase deficiency. *Journal of*

1 *chromatography B, Analytical technologies in the biomedical and life sciences* 949-950: 58-
2 62.

3 Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews
4 and meta-analyses: the PRISMA statement. *BMJ (Clinical research ed)* 339: b2535.

5 Moran NF, Bain MD, Muqit MM, Bax BE (2008) Carrier erythrocyte entrapped thymidine
6 phosphorylase therapy for MNGIE. *Neurology* 71: 686-688.

7 Nair R, Aggarwal R, Khanna D (2011) Methods of formal consensus in classification/diagnostic
8 criteria and guideline development. *Seminars in arthritis and rheumatism* 41: 95-105.

9 Nishigaki Y, Martí R, Copeland WC, Hirano M (2003) Site-specific somatic mitochondrial DNA
10 point mutations in patients with thymidine phosphorylase deficiency. *The Journal of clinical*
11 *investigation* 111: 1913-1921.

12 Nishino I, Spinazzola A, Papadimitriou A, et al (2000) Mitochondrial neurogastrointestinal
13 encephalomyopathy: An autosomal recessive disorder due to thymidine phosphorylase
14 mutations. *Annals of neurology* 47: 792-800.

15 Oz G, Alger JR, Barker PB, et al (2014) Clinical proton MR spectroscopy in central nervous system
16 disorders. *Radiology* 270: 658-679.

17 Pacitti D, Levene M, Garone C, Nirmalanathan N, Bax BE (2018) Mitochondrial
18 Neurogastrointestinal Encephalomyopathy: Into the Fourth Decade, What We Have Learned
19 So Far. *Frontiers in genetics* 9: 669.

20 Peedikayil MC, Kagevi EI, Abufarhaneh E, Alsayed MD, Alzahrani HA (2015) Mitochondrial
21 Neurogastrointestinal Encephalomyopathy Treated with Stem Cell Transplantation: A Case
22 Report and Review of Literature. *Hematology/oncology and stem cell therapy* 8: 85-90.

23 Roeben B, Marquetand J, Bender B, et al (2017) Hemodialysis in MNGIE transiently reduces serum
24 and urine levels of thymidine and deoxyuridine, but not CSF levels and neurological function.
25 *Orphanet journal of rare diseases* 12: 135.

26 Scarpelli M, Ricciardi GK, Beltramello A, et al (2013) The role of brain MRI in mitochondrial
27 neurogastrointestinal encephalomyopathy. *Neuroradiol J* 26: 520-530.

28 Sicurelli F, Carluccio MA, Toraldo F, et al (2012) Clinical and biochemical improvement following
29 HSCT in a patient with MNGIE: 1-year follow-up. *Journal of neurology* 259: 1985-1987.

30 Sivadasan A, Muthusamy K, Patil AK, Mathew V, Alexander M (2016) Pearls & Oy-sters:
31 Mitochondrial neurogastrointestinal encephalomyopathy: Diagnosis and response to
32 peritoneal dialysis. *Neurology* 86: e147-e150.

33 Spinazzola A, Martí R, Nishino I, et al (2002) Altered thymidine metabolism due to defects of
34 thymidine phosphorylase. *The Journal of biological chemistry* 277: 4128-4133.

35 Torres-Torronteras J, Cabrera-Perez R, Barba I, et al (2016) Long-Term Restoration of Thymidine
36 Phosphorylase Function and Nucleoside Homeostasis Using Hematopoietic Gene Therapy in
37 a Murine Model of Mitochondrial Neurogastrointestinal Encephalomyopathy. *Human gene*
38 *therapy* 27: 656-667.

39 Torres-Torronteras J, Cabrera-Perez R, Vila-Julia F, et al (2018) Long-Term Sustained Effect of
40 Liver-Targeted Adeno-Associated Virus Gene Therapy for Mitochondrial
41 Neurogastrointestinal Encephalomyopathy. *Human gene therapy* 29: 708-718.

42 Torres-Torronteras J, Viscomi C, Cabrera-Perez R, et al (2014) Gene therapy using a liver-targeted
43 AAV vector restores nucleoside and nucleotide homeostasis in a murine model of MNGIE.
44 *Molecular therapy : the journal of the American Society of Gene Therapy* 22: 901-907.

45 Valentino ML, Martí R, Tadesse S, et al (2007) Thymidine and deoxyuridine accumulate in tissues of
46 patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *FEBS Lett*
47 581: 3410-3414.

48 Yadak R, Boot MV, van Til NP, et al (2018) Transplantation, gene therapy and intestinal pathology in
49 MNGIE patients and mice. *BMC Gastroenterology* 18: 149.

50 Yadak R, Cabrera-Pérez R, Torres-Torronteras J, et al (2018) Preclinical Efficacy and Safety
51 Evaluation of Hematopoietic Stem Cell Gene Therapy in a Mouse Model of MNGIE.
52 *Molecular therapy Methods & clinical development* 8: 152-165.

53 Yavuz H, Ozel A, Christensen M, et al (2007) Treatment of mitochondrial neurogastrointestinal
54 encephalomyopathy with dialysis. *Archives of neurology* 64: 435-438.

1

2

1 **Table 1** - Recommended brain MRI protocol.

MRI technical requirements
Brain MRI should be performed using a magnetic field of at least 1.5T with a slice thickness =3-5mm for 2D acquisition or \leq 3 mm for 3D reconstruction
MRI protocol
<ul style="list-style-type: none"> • Axial 2D T2 FLAIR/T2-weighted
<ul style="list-style-type: none"> • Sagittal 2D T2-FLAIR/T2-weighted
<ul style="list-style-type: none"> • 3D T2-FLAIR/T2-weighted in alternative to axial and sagittal T2-FLAIR/T2-weighted
<ul style="list-style-type: none"> • Axial DWI
<ul style="list-style-type: none"> • Axial T2* or SWI
<ul style="list-style-type: none"> • Axial 2D or 3D T1-weighted before and after contrast *
<ul style="list-style-type: none"> • Single voxel proton MRS sequence in white matter with signal intensity changes **
Description of leucoencephalopathy (Fig. 2)
<p>White matter hyperintensity in T2-weighted imaging, usually bilateral, patchy and/or diffuse, periventricular and/or subcortical. It may be cloud-like in the early stage of the disease.</p> <p>White matter hyperintensity generally spares U fibers, does not have mass effect or contrast enhancement and must be mostly symmetrical. Its reversibility after therapy is still under debate.</p> <p>The involvement of corpus callosum, white matter capsules, basal ganglia, thalami, midbrain, pons, and cerebellar white matter in general has been observed in patients with long standing condition.</p>

2 * MNGIE patients show no post-contrast enhancement in contrast with some white matter disorders;

3 ** MNGIE patients show normal metabolite ratios: this is not the case for most brain white matter

1 disorders(Oz et al 2014). Abbreviations: DWI, diffusion-weighted imaging; FLAIR, Fluid-attenuated
2 Inversion Recovery; MRS, Magnetic Resonance Spectroscopy; SWI, Susceptibility-Weighted
3 Imaging.
4
5

1 **Table 2** - Features of “Classic” and “Late Onset” phenotype of MNGIE.

<i>Classic phenotype (n=161)*</i>	<i>Late Onset phenotype (n=8)*</i>
Age of onset <40 years old	Age of onset ≥40 years old
Leukocyte TP enzymatic activity: 0-10% Plasma levels: dThd >4 and/or dUrd >5 μmol/L	Leukocyte TP enzymatic activity: 10-30% Plasma levels: dThd 0.05-4 and/or dUrd 0.05-5 μmol/L
GI symptoms 100%	GI symptoms 100%
Leukoencephalopathy 100%	Leukoencephalopathy 100%
Polyneuropathy 92-100%	Polyneuropathy 60%
Ocular signs 74-100%	Ocular signs 100%
Hearing loss 39-45%	Hearing loss 75%

2 *Number of cases described at the time of the ICC.

3

1 **Table 3** - Recommended assessments to monitor MNGIE progression.

Clinical/instrumental assessments of disease course	Parameters	Frequency of assessment (months)
GI symptoms severity	Abdominal pain (assessed with VAS), diarrhea, vomiting, oral intake (assessed with diary)	3
Metabolic assessment	FGF21*, GDF15*, blood lactate	6
Body weight and body composition trajectory	BMI, prealbumin, albumin, CRP, BIA (bioimpedentiometry)	3
Polyneuropathy	Electroneurography	12
Hepatic function and imaging	LFTs, PT, INR, liver function impairment (assessed with Child-Pugh score), ultrasound,	3
	elastography	6
Quality of life (QoL)	SF36	6
Fatigue	FSS or FIS	6
Functional status	Karnofsky/Lansky Performance Status Scale	6
Leukoencephalopathy	Brain MRI (no contrast agent required)	24

1 Abbreviations: BIA, bioelectrical impedance analysis; BMI, body mass index; CRP, C-reactive
2 protein; FGF, fibroblast growth factor 21; FSS, fatigue severity scale; FIS, fatigue impact scale; GDF,
3 growth differentiation factor 15; GI, gastrointestinal; INR, international normalized ratio; LFTs, liver
4 function tests; MRI, magnetic resonance imaging; PT, prothrombin time; SF, short form 36. VAS,
5 visual analogue scale.

6 * FGF21 and GDF15 are ancillary biomarkers of mitochondrial myopathy due to mtDNA
7 maintenance defects recently established for their usefulness in documenting natural history of
8 progression or improvements (after therapy) marking skeletal muscle in mitochondrial myopathies
9 (Lehtonen JM, Forsström S, Bottani E, et al. FGF21 is a biomarker for mitochondrial translation and
10 mtDNA maintenance disorders. *Neurology* 2016;87:2290-2299).

11

12 **FIGURE LEGEND**

13 Fig. 1 - Diagnostic algorithm in MNGIE.

14

15 Fig. 2 - Brain MRI examination from a 27-year-old severely affected MNGIE male patient.

16 A) Axial T2-FLAIR shows bilateral and symmetrical diffuse cerebral white matter
17 hyperintensity, with relative sparing of subcortical U fibers and patchy bilateral
18 hyperintensities in the basal ganglia, thalami and corpus callosum. B) Hyperintensities are also
19 seen bilaterally in the pons and cerebellar white matter. (Courtesy of Prof Raffaele Lodi and
20 Dr. Laura Ludovica Gramegna, IRCCS Istituto delle Scienze Neurologiche di Bologna).

21

22