Mitochondrial neurogastrointestinal encephalopathy disease (MNGIE)

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ABSTRACT

Mitochondrial neurogastrointestinal encephalopathy (MNGIE) is a rare autosomal recessive condition. Deficiency of thymidine phosphorylase disrupts the nucleoside pool, with progressive secondary mitochondrial DNA damage. MNGIE is clinically diagnosable because of a distinctive tetrad of gastrointestinal dysmotility, progressive external ophthalmoplegia, demyelinating neuropathy and asymptomatic leucoencephalopathy. The diagnosis may be confirmed genetically or biochemically. Misdiagnosis is frequent, but early and accurate recognition allows the possibility of novel transplant therapies capable of rectifying the biochemical defects. Its management remains difficult in the face of progressive disability and the risks of treatment.

Mitochondrial neurogastrointestinal encephalopathy (MNGIE), despite its rarity, is worthy of the attention of the practical neurologist. It has distinctive clinical features which when recognised allow a confident diagnosis before biochemical or genetic confirmation.

MNGIE is an autosomal recessive disorder in which *TYMP* gene mutations cause thymidine phosphorylase deficiency.[1–3] An Italian study estimated its minimum prevalence to be 0.15/1 000 000.[4] Thymidine phosphorylase deficiency increases thymidine and deoxyuridine concentrations in plasma and tissues. The resulting intramitochondrial deoxynucleotide pools are unbalanced, thus impairing mitochondrial DNA (mtDNA) replication. It is therefore a disorder caused by nuclear gene mutations but with secondary mitochondrial dysfunction.

DIAGNOSTIC TETRAD

Although the four main clinical features of MNGIE occurring together would usually be diagnostic, a patient presenting with only one of these features may confound any specialist, from gastroenterologist to psychiatrist, from radiologist to ophthalmologist. The onset of symptoms is usually before the age of 30 years, but presentations may range from infancy to the fifth decade.[5] The diagnosis is often delayed, which may lead to inappropriate treatments. A small subgroup of patients with less severe enzyme deficiency present later and have a more benign progression.[6 7]

Gastrointestinal dysmotility and cachexia

Progressive gut symptoms are the most common presentation of MNGIE and are almost always present even if the patient consults because of other features.[5] Gastrointestinal dysfunction is usually the major cause of medical morbidity and mortality. Any part of the gastrointestinal tract may be affected, from the pharynx to the large intestine. It manifests in various combinations of dysphagia, nausea, vomiting, gastroparesis, early satiety, abdominal cramps, intestinal pseudo-obstruction and diarrhoea. Inevitably, this leads to progressive weight loss and cachexia. Most, but not all, patients have short stature.

The most common form of dysmotility in MNGIE manifests in the small intestine with failure of peristalsis, which may result in bacterial overgrowth or pseudo-obstruction. Diverticula of the small intestine may perforate.

Gastroenterologists may struggle with the diagnosis of MNGIE if the associated neurological features are not recognised. Patients frequently are initially considered to have anorexia nervosa, inflammatory bowel disease or other diagnoses.

Progressive external ophthalmoplegia

Ptosis and ophthalmoplegia are usually present (figure 1); initially, the only manifestation may be mild ptosis. As in other mitochondrial diseases, the slowly progressive ophthalmoplegia may be asymptomatic, without diplopia.

Neuropathy

Nearly all MNGIE patients have a peripheral neuropathy, with rare exceptions.[7] This can be prominent and

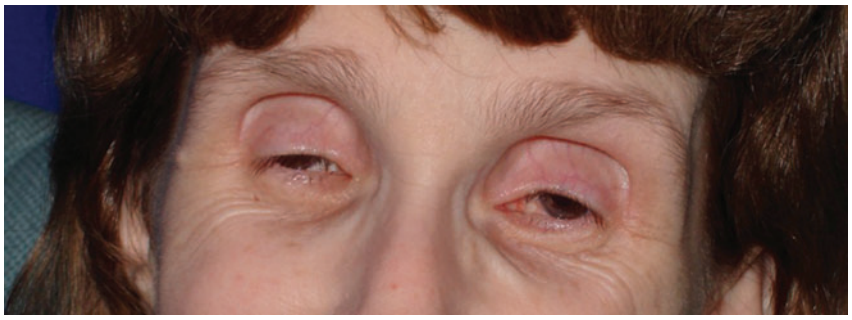

Figure 1 The figure shows asymmetrical ptosis and a divergent squint of the patient described in case 2. Cachexia can also be seen.

may be a presenting feature. In other patients, it may be asymptomatic and evident only on examination or identified only on nerve conduction studies.

MNGIE neuropathy has neurophysiological features of demyelination, although biopsy shows both demyelination and axonal loss. Demyelinating neuropathy is uncommon in other forms of mitochondrial disease. Clinically and electrically, it may masquerade as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)[8] and even lead to ineffective use of immunomodulatory drugs. While usually symmetrical, sensorimotor and distal, the neuropathy may be asymmetrical, even unilateral, and sometimes painful. Although in the early stages the neuropathy may fluctuate in severity, it eventually progresses, leading to disability.

Case report 1

A young woman had presented at the age of 14 years with painful foot numbness and bilateral foot drop. The symptoms had initially progressed and then improved. Examination showed severe weakness and wasting of ankle dorsiflexors and toe flexors, and mild weakness of intrinsic hand muscles and finger extensors. There was no proximal weakness initially, but this developed slowly over time. She had stocking sensory loss to all modalities, areflexia and mild ptosis. Nerve conduction studies showed conduction block, cerebrospinal fluid (CSF) showed an elevated protein concentration, and nerve biopsy identified evidence of demyelination and remyelination with onion bulb formation. A neuromuscular specialist diagnosed CIDP and recommended immunotherapy. Treatment was withheld because her twin sister had developed similar symptoms. Subsequently, weight loss and gastrointestinal dysmotility led to her review. MR scan of brain showed white matter disease and this, together with progressive ophthalmoplegia, led to a clinical diagnosis of MNGIE, later confirmed genetically.

Asymptomatic leucoencephalopathy

The MR scan of the brain in people with MNGIE shows diffusely abnormal cerebral white matter (figure 2). Absence of this feature makes MNGIE highly unlikely. There is usually no clinical correlate such as spasticity or

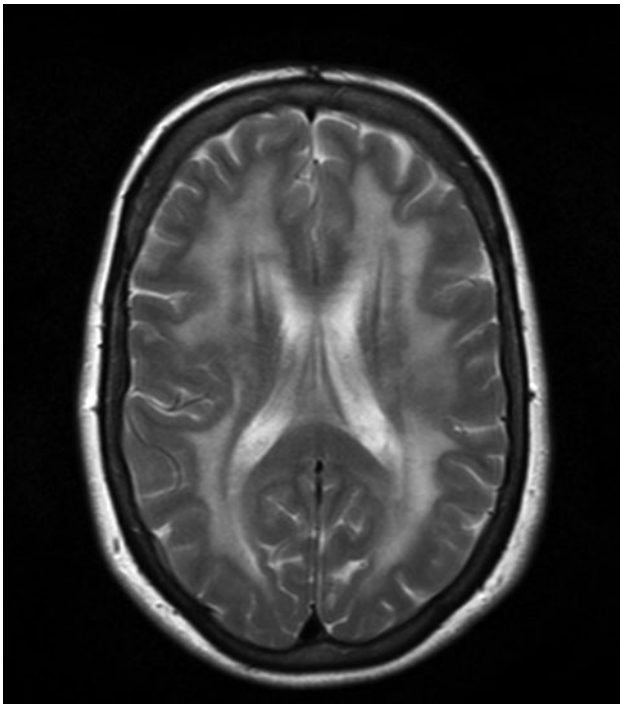

Figure 2 MR brain, T2 weighted. This demonstrates the diffuse asymptomatic leucoencephalopathy present in the patient described as case 2, typical of mitochondrial neurogastrointestinal encephalopathy.

cognitive manifestations. Some reports have indicated occasional cognitive or psychological problems,[5 9] but these problems need further study before we can be certain that such features are an intrinsic part of the condition.

Case report 2

A young woman reported having had low weight in her teenage years, with anorexia and vomiting more prominent from the age of 18, leading to a psychiatric consultation exploring the possibility of anorexia nervosa. From the age of 28, she developed ptosis and ophthalmoplegia; muscle biopsy showed features of mitochondrial disease. She was assessed by a neuromuscular specialist and neurophysiological studies identified an asymptomatic demyelinating

neuropathy; MR scan of the brain (figure 2) showed asymptomatic white matter disease. The clinical diagnosis of MNGIE was later confirmed genetically. Her neuropathy progressed to distal weakness and wasting (figure 3), and she became unable to walk unaided. The gastrointestinal problems progressed to the point that she required total parenteral nutrition. A haemopoietic stem cell transplant, with her sister as the donor, was initially successful, leading to a marked improvement in biochemistry and some marginal improvement in neurophysiology. However, she had advanced disability and succumbed to infection 3 years later.

Additional clinical features

Although the diagnostic tetrad is constant in established disease, additional clinical features may emerge.[5] A mitochondrial myopathy may cause clinically important proximal myopathy, which, together with the neuropathy, contributes to immobility. Some patients develop hearing loss. Various gastrointestinal complications may arise beyond the bowel problems, including hepatic steatosis or even cirrhosis. Laboratory abnormalities may include raised CSF protein and lactic acidosis.

DIAGNOSIS

The diagnosis may be made confidently in the presence of the clinical tetrad. However, confirmation is still required because other forms of mitochondrial myopathy can cause gut problems, progressive external ophthalmoplegia and/or neuropathy, including phenotypes associated with the m.3243A>G mutation and the nuclear DNA disorders of *POLG* and *RRM2B* (although without typical MR brain scan appearances). Further, it is best to diagnose MNGIE early, and this may be before all the features are present. Patients initially need an MR scan of the brain and neurophysiology, as these are almost always abnormal, even when there are no associated clinical features.

Sequencing the *TYMP* gene may provide genetic confirmation if two pathogenic variants are found, and if not, deletion/duplication analysis may be required. Availability of this analysis varies with time and location, and it may be necessary to use a multigene panel. If there is difficulty obtaining genetic analysis, or if there is doubt about the pathogenicity of variants, then it is wise to investigate biochemically with assay of thymidine phosphorylase activity,[10] or plasma or urine concentrations of thymidine and deoxyuridine.[11] Muscle biopsy is not usually necessary but will usually show changes in mitochondrial myopathy.

The *TYMP* gene currently appears on 15 different genetic panels available in the UK (https://panelapp.genomicsengland.co.uk/panels/entities/TYMP), including those for gastrointestinal disorders, white matter disorders and others. The wider use of such genetic investigations makes it likely that in the future neurologists will see patients with MNGIE earlier in their disease course.

PATHOPHYSIOLOGY

It is not completely understood how thymidine phosphorylase deficiency creates the specific phenotype of MNGIE, but the likely sequence of pathophysiology is as follows:

1. Biallellic loss of function mutations in *TYMP*.
2. Impaired function of thymidine phosphorylase, typically.

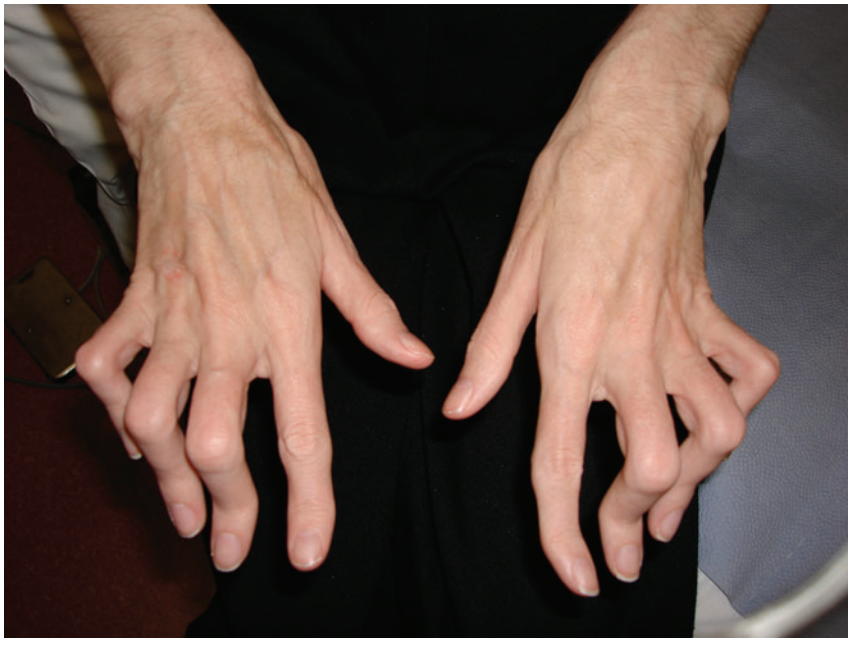

Figure 3 The hands of the patient described in case 2, demonstrating the results of a progressive neuropathy.

   a. <8% of the control mean.
   b. <18% of the control mean in late-onset disease.[6]
3. Accumulation of thymidine and deoxyuridine homogeneously in plasma and cellular compartments.
4. Imbalance of nucleotide pools within mitochondria (increased deoxythymidine triphosphate (dTTP) appears to cause deoxycytidine triphosphate (dCTP) reduction).
5. Accumulation of mtDNA point mutations and deletions, and depletion (mtDNA has no repair mechanism).
6. Progressively impaired mitochondrial function.
7. Tissue-specific manifestations:
   a. Gut. The most prominent gastrointestinal abnormalities occur in the external longitudinal layer of the muscularis propria with atrophy, vacuolisation and fibrosis of the smooth muscle cells because of mtDNA depletion.[12]
   b. Progressive external ophthalmoplegia. Eye muscles are highly energy-dependent and sensitive to mitochondrial dysfunction.
   c. Nerve. The uneven demyelination probably results from patchy accumulation of mitochondrial abnormalities. Abnormal mitochondria become apparent in Schwann cells and axons.[13]
   d. Brain. Gramegna *et al*,[14] inferring from MR spectroscopy and autopsy data, speculated that the leucoencephalopathy resulted from endothelial failure due to thymidine toxicity and mtDNA depletion, causing blood–brain barrier dysfunction and microangiopathy. This leads to increased white matter water content and the resulting MR appearance.

PROGNOSIS

MNGIE is a progressive multisystem disorder, with gastrointestinal and neurological problems being the most troublesome. Even patients initially asymptomatic from neuromuscular perspective develop progressive neurological disability due to a combination of disabling peripheral neuropathy and proximal weakness from mitochondrial myopathy. Garone *et al*[5] found that morbidity and mortality were high in those aged 20–40 years, with average age of death being 35 years. Some patients with less severe thymidine phosphorylase dysfunction have a better prognosis.[6 7]

MANAGEMENT

General

This multisystem disorder requires a multidisciplinary approach from several specialities and therapists. Gastroenterologists are central to the medical management. Prokinetic agents may help; abdominal pain may require medication. In patients with bacterial overgrowth, antibiotics may be indicated. Coeliac plexus and splanchnic nerve block may help some patients.[15] If conservative measures addressing dysphagia or dysmotility are inadequate, gastrostomy, jejunostomy or total parenteral nutrition are required.

In patients presenting with abdominal emergencies, it may be difficult to differentiate pseudo-obstruction (best treated conservatively) from other causes such as peritonitis (eg, from a perforated diverticulum) or bowel obstruction, which require intervention. Appropriate caution and investigation may reduce unnecessary intervention.

Specific therapies

The pathogenesis of MNGIE is a systemic metabolic derangement of nucleosides. There are several suggested approaches to correct the abnormal biochemistry,[16] but each has associated problems.

The systemic accumulations of deoxythymidine (dThd) and deoxyuridine (dUrd) can be corrected transiently with continuous ambulatory peritoneal dialysis[17] or by haemodialysis. Platelet infusions (containing thymidine phosphorylase) will also temporarily improve nucleoside concentrations. There is currently a trial of erythrocyte encapsulated thymidine phosphorylase.[18] Although impractical as a long-term therapy, the presence of thymidine phosphorylase in donor platelet and leucocytes stimulated thoughts of whether allogeneic haemopoietic stem cell transplantation might be a more definitive treatment. Several groups have attempted this, as summarised by Halter *et al*.[19] Of 24 patients, only 9 were alive at the time of the survey. Deaths were attributed to the transplant in nine patients and to MNGIE itself in six. The authors concluded that allogeneic haemopoietic stem cell transplantation can alter the natural course of MNGIE.

More recently, liver transplantation has been technically successful[20 21] both surgically and in restoring nucleoside levels. The authors consider that it may be safer than allogeneic haemopoietic stem cell transplantation.

Before embarking on such therapies, clinicians should thoroughly study the patient's medical status. Patients should be carefully counselled, with care to disclose full information of the dangers of allogeneic haemopoietic stem cell transplantation or liver transplantation when compared with the poor prognosis with conservative management. Success is more likely in psychologically robust patients with donors who are well human leucocyte antigen (HLA) matched, and in patients who receive the transplant before they have developed severe organ damage.. Transplant therapies clearly require further study and development.

CONCLUSION

A clinical diagnosis of MNGIE is usually possible with understanding of the cardinal clinical features. Following confirmation of the diagnosis, it is important to assess the patient fully with a multidisciplinary team to provide supportive care. Despite this, there is generally a poor prognosis and life expectancy. If the patient remains in general good functional state, they may wish to explore the possibilities of allogeneic haemopoietic stem cell transplant and liver transplant, including the timing of such therapy.

Key points

- A confident diagnosis of MNGIE can be made in the presence of the clinical tetrad of gut dysmotility, progressive external ophthalmoplegia, demyelinating neuropathy and asymptomatic leucoencephalopathy.
- The diagnosis is usually confirmed genetically, but biochemical testing may also be used.
- Good management requires careful assessment and a multidisciplinary team.
- Selected patients may benefit from allogeneic haemopoietic stem cell transplant or liver transplant, but these new therapies require further evaluation and optimisation.

FURTHER READING

1 Hirano M. Mitochondrial neurogastrointestinal encephalopathy disease, 22 April 2005. In: Pagon RA, Adam MP, Ardinger HH *et al*, eds. *GeneReviews()*. Seattle: University of Washington, 2016: 1993–2017. Available http://www.ncbi.nlm.nih.gov/pubmed/20301358 (Updated 14 Jan 2016)

2 Halter JP, Michael W, Schüpbach M, *et al*. Allogeneic haematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalomyopathy. *Brain* 2015;138:2847–2858. doi:10.1093/brain/awv226

3 Garone C, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. *Brain* 2011;134:3326–3332. doi:10.1093/brain/awr24

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REFERENCES

1 Nishino I, Spinazzola A, Hirano M. Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder. *Science (80-)* 1999;283:689–92.

2 Nishino I, Spinazzola A, Papadimitriou A, *et al*. Mitochondrial neurogastrointestinal encephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. *Ann Neurol* 2000;47:792–800.

3 Hirano M. Mitochondrial neurogastrointestinal encephalopathy disease, 22 April 2005. In: Pagon RA, Adam MP, Ardinger HH *et al*, eds. *GeneReviews()*. Seattle: University of Washington, 2016: 19932017. Available http://www.ncbi.nlm.nih.gov/pubmed/20301358 (Updated 14 Jan 2016)

4 D'Angelo R, Rinaldi R, Carelli V, *et al*. ITA-MNGIE: an Italian regional and national survey for mitochondrial neuro-gastrointestinal encephalomyopathy. *Neurol Sci* 2016;37:1149–51.

5 Garone C, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. *Brain* 2011;134:3326–32.

6 Marti R, Verschuuren JJGM, Buchman A, *et al*. Late-onset MNGIE due to partial loss of thymidine phosphorylase activity. *Ann Neurol* 2005;58:649–52.

7 Massa R, Tessa A, Margollicci M, *et al*. Late-onset MNGIE without peripheral neuropathy due to incomplete loss of thymidine phosphorylase activity. *Neuromuscul Disord* 2009;19:837–40.

8 Bedlack RS, Vu T, Hammans S, *et al*. MNGIE neuropathy: five cases mimicking chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2004;29:364–8.

9 Carod-Artal FJ, Herrero MD, Lara MC, *et al*. Cognitive dysfunction and hypogonadotrophic hypogonadism in a Brazilian patient with mitochondrial neurogastrointestinal encephalomyopathy and a novel ECGF1 mutation. *Eur J Neurol* 2007;14:581–5.

10 Martí R, Spinazzola A, Tadesse S, *et al*. Definitive diagnosis of mitochondrial neurogastrointestinal encephalomyopathy by biochemical assays. *Clin Chem* 2004;50:120–4.

11 Fairbanks LD, Marinaki AM, Carrey EA, *et al*. Deoxyuridine accumulation in urine in thymidine phosphorylase deficiency (MNGIE). *J Inherit Metab Dis* 2002;25:603–4.

12 Giordano C, Sebastiani M, De Giorgio R, *et al*. Gastrointestinal dysmotility in mitochondrial neurogastrointestinal encephalomyopathy is caused by mitochondrial DNA depletion. *Am J Pathol* 2008;173:1120–8.

13 Said G, Lacroix C, Planté-Bordeneuve V, *et al*. Clinicopathological aspects of the neuropathy of neurogastrointestinal encephalomyopathy (MNGIE) in four patients including two with a Charcot-Marie-Tooth presentation. *J Neurol* 2005;252:655–62.

14 Gramegna LL, Pisano A, Testa C, *et al*. Cerebral mitochondrial microangiopathy leads to leukoencephalopathy in mitochondrial neurogastrointestinal encephalopathy. *Am J Neuroradiol* 2018;39:427–34.

15 Teitelbaum JE, Berde CB, Nurko S, *et al*. Diagnosis and management of MNGIE syndrome in children: case report and review of the literature. *J Pediatr Gastroenterol Nutr* 2002;35:377–83.

16 Bax BE. Mitochondrial neurogastrointestinal encephalomyopathy: approaches to diagnosis and treatment. *J Transl Genet Genomics* 2020;4:1–16.

17 Yavuz H, Özel A, Christensen M, *et al*. Treatment of mitochondrial neurogastrointestinal encephalomyopathy with dialysis. *Arch Neurol* 2007;64:435–8.

18 Bax, Levene, Bain, *et al*. Erythrocyte encapsulated thymidine phosphorylase for the treatment of patients with mitochondrial neurogastrointestinal encephalomyopathy: study protocol for a multi-centre, multiple dose, open label trial. *J Clin Med* 2019;8:1096.

19 Halter JP, Michael W, Schüpbach M, *et al*. Allogeneic haematopoietic stem cell transplantation for mitochondrial neurogastrointestinal encephalomyopathy. *Brain* 2015;138:2847–58.

20 Kripps KA, Nakayuenyongsuk W, Shayota BJ, *et al*. Successful liver transplantation in mitochondrial neurogastrointestinal encephalomyopathy (MNGIE). *Mol Genet Metab* 2020;130:58–64.

21 De Giorgio R, Pironi L, Rinaldi R, *et al*. Liver transplantation for mitochondrial neurogastrointestinal encephalomyopathy. *Ann Neurol* 2016;80:448–55.