Transient clinical improvement of a mitochondrial neurogastrointestinal encephalomyopathy-like syndrome after allogeneic haematopoietic stem cell transplantation

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Summary

Mitochondrial neurogastrointestinal encephalopathy (MNGIE), usually an autosomal-recessive inherited condition, causes gastrointestinal dysmotility, ophthalmoplegia, ptosis, leukoencephalopathy and neuropathy. The chromosome 22 disorder, due to mutations in the nuclear gene TYMP encoding thymidine phosphorylase (TP), leads to the accumulation of thymidine and deoxyuridine, with mitochondrial dysfunction.

This report describes a patient with an MNGIE-like syndrome with a heterozygous TYMP mutation who showed marked, but transient improvement postallogeneic haematopoietic stem cell transplantation (HSCT).

The patient, showing ptosis and ophthalmoplegia, was initially managed for myasthenia gravis. She developed gastrointestinal symptoms, dysarthria, dysphagia and weakness, and MNGIE was considered due to its low TP levels and improvement after platelet transfusions. She underwent HSCT, with dramatic improvement, but regressed 18 months later despite normal TP levels, platelet counts and full chimerism.

MNGIE may encompass a spectrum of disorders. TP deficiency alone is unlikely to explain all clinical signs, and other factors, including the possible development of anti-TP antibodies, which may play a role in the pathophysiology.

Background

We have been following this patient with a mitochondrial neurogastrointestinal encephalopathy (MNGIE)-like picture up for several years and were most impressed with her initial response to allogeneic haematopoietic stem cell transplantation. From being severely disabled, she was almost asymptomatic for 18 months post-transplant. Unfortunately, her symptoms then steadily returned. A number of reports on the successful treatment of MNGIE have been published, but we are unaware of a report that follows up a patient with an MNGIE picture for several years and finding regression of symptoms after superb initial response to haematopoietic stem cell transplantation (HSCT), in spite of normalised thymidine phosphorylase (TP) levels. This case highlights a number of unusual

aspects of MNGIE, including late age of onset, TP levels not as low as usually encountered and heterozygous TYMP gene mutation, possibly indicating a symptomatic carrier state.

Case presentation

MNGIE is usually an autosomal-recessive inherited condition, leading to gastrointestinal dysmotility, cachexia, external ophthalmoplegia, ptosis, leukoencephalopathy, peripheral neuropathy and mitochondrial abnormalities. The disorder, mapped to chromosome 22, is due to mutations in the nuclear gene encoding TP, an enzyme that catalyses the phosphorolysis of thymidine to thymine and deoxyribose 1-phosphate.[1–4] This leads to systemic accumulation of thymidine and deoxyuridine, with subsequent impaired mitochondrial DNA (mtDNA) replication or repair and mitochondrial dysfunction.[5] Mitochondrial oxidative phosphorylation becomes abnormal with subsequent ophthalmoparesis, ptosis, peripheral neuropathy, skeletal myopathy, gastrointestinal dysmotility and cachexia. While mitochondrial dysfunction presumably leads to the clinical deficits, the underlying abnormality is unclear.

MNGIE was first reported in 1976 as 'congenital oculoskeletal myopathy' with abnormal mitochondria,[6] and several other acronyms have been used for this condition,[1] until the term MNGIE, coined by Bardosi in 1987, found widespread acceptance.[7]

Therapy for MNGIE is aimed at reducing toxic nucleosides. Platelets contain high levels of TP, and platelet infusions reduce nucleoside overload, transiently restoring TP.[8] Allogeneic stem cell transplantation was proposed as a possibility to permanently restore more TP levels, and the first allogeneic stem cell transplantation, reported in 2006,[5 9] showed an almost total correction of thymidine and deoxyuridine levels. Clinical response was less clear, possibly since mitochondrial damage was already widespread.[9] Other proposed treatment modalities include haemodialysis and peritoneal dialysis.[10–15]

This report describes the clinical presentation and follow-up of a patient with an MNGIE-like syndrome who showed marked but transient clinical improvement postallogeneic stem cell transplantation.

A 39-year-old woman presented in 2000 with progressive ptosis and ophthalmoplegia. She had been managed elsewhere for myasthenia gravis for several years, undergoing a thymectomy and being treated with pyridostigmine, prednisone, cyclophosphamide, immunogloblulins and plasma exchange, with no improvement in her symptoms and signs.

At the end of 2003, age 42 years, she was referred to our specialised neuromuscular clinic with progressive worsening of symptoms. She was an adopted child with untraceable biological parents. She had three healthy children. She complained of progressive ptosis, diplopia, dysphagia, mild generalised weakness, distal paraesthesias and increased perspiration at night. Twenty years prior, she had experienced episodic seizures. Gastrointestinal complaints were initially absent.

On examination, her mini-mental state examination was 38/38. She had marked ptosis, almost totally on the right, with normal visual acuity and an external ophthalmoplegia with

restriction of upward gaze and left-sided lateral rectus palsy; pupils were normal. Facial weakness and mild dysarthria were present. Power was mildly decreased , reflexes were brisk and the sensory examination was normal. The possibility of a mitochondrial disorder was considered.

Electromyography showed no decremental responses on repetitive stimulation and the patient had a normal needle examination. Brain MRI showed a leukoencephalopathy with increased T2 signal in the subcortical white matter, most prominent in the left frontal lobe. Acetylcholine receptor antibodies and anti-MuSk antibodies were negative; creatine kinase levels, vitamin B_{12}, thyroid function, electrolytes and liver functions were normal. The full blood count showed a mild anaemia. A muscle biopsy showed type 1 fibre predominance but no ragged red fibres. On electron microscopy, abnormal mitochondria with widely spaced cristae were seen, supporting a diagnosis of a mitochondrial disorder. Blood lactate and pyruvate levels were intermittently raised. Extensive serological studies for autoimmune disorders were negative.

A year later, the patient had developed dysphagia with regurgitation and abdominal bloating, and preferred a soft diet. The neurological symptoms were essentially unchanged, with an additional development of right-hand clawing.

By the end of 2005, she had lost 24 kg and complained of exertional dyspnoea. She had severe ptosis, worse on the right, with marked ophthalmoplegia and a tendency of the eyes to converge. Bilateral clawing of the hands was seen, worse on the right, but without fixed contractures. There was some proximal weakness, but reflexes were still 1 to 2+; coenzyme Q10 was started.

In 2007, she also developed severe dysarthria; she choked frequently and complained of progressive dyspnoea and diplopia. She was on a liquid diet. On examination, she could count up to 11 on one breath; eye movements were as before, with additional nystagmus. She was severely dysarthric and hoarse; deep tendon reflexes were now decreased. A polyethylene glycoltube was considered, and bilevel positive airway pressure ventilatory support was recommended at night. Lung function testing showed most flow-volume parameters to be at approximately 50% of predicted values. Gastrointestinal studies revealed dysmotility.

Investigations

The diagnosis of mitochondrial neurogastrointestinal encephalomyopathy was considered, and a low thymidine phosphorylase level of 1.52 nmol/mg in buffy coat (normal: 2.28–6.89) with elevated thymidine levels in urine and blood further suggested this. The patient received a series of platelet transfusions, given daily for 5 days, which led to a dramatic improvement of clinical signs. Some improvement was first noted on the second day of treatment. Further improvement occurred and lasted for a few days after transfusion, with regression of symptoms thereafter. Genetic studies were subsequently performed and revealed a heterozygous TYMP mutation.

Differential diagnosis

Although atypical features were present, the overall picture appeared to be most consistent with MNGIE. Encouraged by the response to platelet transfusions and concerned by her deteriorating functionality and overall condition, her treating team elected to proceed with allogeneic haematopoietic stem cell transplantation.

Treatment

Early in 2010, she underwent allogeneic haematopoietic stem cell transplantation from a matched unrelated donor. She had myeloablative conditioning with BuMelCy (bulsulphan 3.2 mg/kg/day intravenous (IVI) days 1–3, melphalan 70 mg/m^2 days 3 and 4 and fludarabine 40 mg/m^2 x days 4–6). Prophylactic platelet support was given throughout the cytopenic phase. She engrafted rapidly (neutrophils day 11) and platelet transfusions were stopped when her count incremented stably over 50×109/L. Muscle weakness progressively improved. Post-transplant graft-versus-host disease prophylaxis was according to our protocol (mabcampath 12 mg ex vivo 'in-the-bag' and tacrolimus 1 mg/day from day −1 to day +84). Her post-transplant care was complicated by chronic graft-versus-host disease of the skin (grade 1, extensive) responding to corticosteroids (1 mg/kg/dayx7 days, weaned over 14 days). Furthermore, she developed pulmonary aspergillosis, treated with liposomal amphotericin followed by voriconazole after 2 weeks (at 3 mg/kg for a further 10 weeks). Clear improvement of her deficits, present before haematopoietic stem cell transplantation, began approximately 3 months after transplantation.

Five months post-transplant, she was re-examined. She was, at the time, on cortisone and cotrimoxazole for chronic graft-versus-host disease. The improvement was dramatic: the ptosis had disappeared and no diplopia was present. She had good muscle power and was able to keep both arms extended for 100 s. She could count up to 27 on a single breath. Deep tendon reflexes had returned; she had been able to resume work and stopped bilevel positive airway pressure ventilation. Lung function flow-volume parameters were at approximately 90% of predicted values.

Nine months later, on sirolimus and cortisone for chronic graft-versus-host disease, grade 2localised to the skin of her forearms, she was still doing well; a year post-transplant, now on mycophenolate mofetil, she only had very mild right-sided ptosis.

Outcome and follow-up

On follow-up in July 2011, she had clearly regressed. Diplopia and ptosis were again present as were the gastrointestinal symptoms and dyspnoea. She was on a low dose of mycophenolate. There was no evidence of bone marrow rejection and platelet transfusions once again reversed the symptoms. She showed bilateral ptosis, external ophthalmoplegia with lateral rectus weakness and mild upgaze paralysis. She was able to keep her arms extended for only 10 s and had clear muscle weakness globally. Deep tendon reflexes were reduced. TP levels were retested, but remained normal at 3.15 nmol/mg in spite of the recurrence of symptoms and signs. Platelet count was normal, she had full chimerism and interphase fluorescence in situ hybridization confirmed her megakaryocytes to be male. Her

symptoms and signs have persisted until recent follow-up. Non-availability of certain studies locally and financial constraints have precluded additional studies, such as thymidine levels and repeated TP levels.

Discussion

The patient presented here showed severe clinical involvement which had only started late in life. She improved markedly on allogeneic HSCT within weeks post-transplant, maintaining this improvement for 18 months. Her pre-HSCT biochemical work-up showed decreased but not absent TP levels. It is possible that our patient's good response to allogeneic HSCT was the result of a partial deficiency of TP in the presence of a MNGIE carrier state with a heterozygous TYMP mutation. Several patients have been described in the literature with low TP levels,[11 12] and generally the evidence currently suggests that a TP activity of 20% of normal may still prevent clinical disease, and below this, there is a correlation between clinical signs and degrees of TP deficiency. Our patient, however, was symptomatic with a TP level of approximately 50% of normal.

Bone marrow transplants previously performed on patients with absent TP had limited success. According to a 2011 consensus conference proposal for a standardised approach to allogeneic HSCT, nine patients with MNGIE had been treated with allogeneic HSCT. While biochemical abnormalities were rapidly corrected, clinical improvement was not that well-documented.[13] In the study of Halter *et al* retrospectively examining patients who received HSCT for MNGIE, only 9 of 25 patients were alive 27 months to 8.5 years after HSCT. The median age of transplantation was 25 years. Clinical improvement was normally seen only after 6 months, but a large number of patients may still deteriorate in spite of HSCT.[14] Our patient's initial excellent response may suggest that this treatment modality may have better results in patients with only partial TP deficiency and HSCT, as the only form of possible curative treatment currently available should still be considered.

After a symptom-free interval of 18 months, some of the patient's symptoms unfortunately returned. The TP levels performed at the time of clinical relapse, however, were still normal, suggesting that other factors also play a role in the development of clinical symptoms and signs in patients with MNGIE or MNGIE-like syndromes.

Our patient showed some clinical differences compared with other patients with MNGIE. She did not present with gastrointestinal symptoms—these only developed about 4 years after the initial neurological symptoms. A similar case[15] of a 60-year-old woman with near-absent TP activity and only subclinical gastroparesis, with neurological symptoms since childhood, has been described. Our patient also had no initial electromyography evidence of a peripheral neuropathy, although distal paraesthesias were present. A patient with late-onset MNGIE without neuropathy has been reported in 2009.[12]This patient had, like our patient , only an incomplete loss of TP activity, suggesting that this could protect against developing a peripheral neuropathy.

Intriguingly, our case responded to platelet transfusions initially and then to HSCT, but then later relapsed with another subsequent improvement after platelet transfusions. The improvement after HSCT correlated with a normalisation of TP levels. A possible explanation

for this could be the development of neutralising antibodies against the specific antigenic constituents of the HSCT produced TP.

The variation of clinical findings and response to treatment suggest that MNGIE encompasses a spectrum of presentations. The biochemical defect of TP alone is unlikely to explain all the clinical signs, and other factors, including the possible development of anti-TP antibodies post-HSCT, may play a role in the pathophysiology of this disorder. Alterations in thymidine and deoxyuridine balance appear to be critical for mitochondrial maintenance[16] and changes in these levels appear to be of pathogenic significance, leading to mitochondrial point mutations, deletions and depletions. MNGIE has usually been associated with an autosomal-recessive homozygous TYMP gene mutation, although similar phenotypes have been associated with RRM2B, MGME1 and other abnormalities.[17]

Learning points

- Considering the diagnosis of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) in patient with non-responsive myasthenia gravis, haematopoietic stem cell transplantation (HSCT) may be of value in MNGIE-like syndromes.
- The effect of HSCT is possibly transient.
- MNGIE may encompass a spectrum of disorders: our patient was found to have a heterozygous TYMP gene mutation, possibly indicative of a carrier status. The level of pretreatment thymidine phosphorylase activity would also be consistent with this. To our knowledge, a severe MNGIE phenotype has not yet been reported in association with a TYMP carrier status.

Footnotes

- Contributors MKB was involved in the conception and design of this study, and helped with the final writing up; CMS was responsible for the drafting and writing up of the manuscript as well as the final editing; NR was involved in the acquisition of data and literature review of the subject; DB was involved in data collecting, final reporting and editing of the manuscript, while E J vR was responsible for the genetic studies and information.
- Competing interests None declared.
- Patient consent Obtained.
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