Mitochondrial Neurogastrointestinal Encephalomyopathy Syndrome Treated with Stem Cell Transplant: A Case Series and Literature Review

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Abstract

Mitochondrial neurogastrointestinal encephalomyopathy syndrome is a rare autosomal recessive multisystem disorder caused by nuclear TYMP gene mutations, which leads to deficiency in thymidine phosphorylase enzyme. This deficiency then leads to mitochondrial dysfunction, which causes the features characteristic of this syndrome, including severe muscle wasting, gastrointestinal dysmotility, leukoencephalopathy, peripheral neuropathy, and ophthalmoplegia. Here, we present a case series of 3 patients with mitochondrial neurogastrointestinal encephalomyopathy from Saudi Arabia who underwent allogeneic stem cell transplant at King Faisal Specialist Hospital (Riyadh, Saudi Arabia). Two patients died within the first year of transplant, and the third is still alive but without improvement in clinical features. Allogeneic hematopoietic stem cell transplant-related mortality appears to be high; this may at least be partially related to established end-organ effects with decreased performance status. Although allogeneic hematopoietic stem cell transplant clearly affects correction of genetic and biochemical defects in mitochondrial neurogastrointestinal encephalomyopathy, its ability to reverse or improve established clinical manifestations has not been proven.

Key words: Autosomal recessive disorder, Failure to thrive, Thymidine phosphorylase

Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) syndrome is a rare autosomal recessive multisystem disorder caused by nuclear gene TYMP mutations, which leads to deficiency in thymidine phosphorylase enzyme.1 Thymidine phosphorylase deficiency results in systemic accumulation of thymidine and deoxyuridine (Figure 1), leading to mitochondrial dysfunction, which causes the features characteristic of this syndrome. These characteristics include severe muscle wasting, gastrointestinal dysmotility, leukoencephalopathy, peripheral neuropathy, and ophthalmoplegia.2 The average age of disease onset is 18 years (range, 5 mo to 35 y), but the first symptoms are mostly reported in childhood. The most frequent first feature of the disease is related to gastrointestinal dysmotility (found in 57% of patients). Symptoms include diarrhea, abdominal pain, nausea, vomiting, wasting, and failure to thrive.2

Figure 1. Proposed Mechanism of Mitochondrial Neurogastrointestinal Encephalomyopathy Syndrome

Abbreviations: dCMP, deoxycytidine monophosphate; dTDP, deoxythymidine diphosphate; dTMP, deoxythymidine monophosphate; dTTP, deoxythymidine triphosphate; mDNA, mitochondrial DNA

Mutation in nuclear TYMP gene leads to deficiency in thymidine phosphorylase (TP) enzyme, which results in systemic accumulation of thymidine (dThd) and deoxyuridine (dUMP) and leads to mitochondrial dysfunction.
Allogeneic hematopoietic stem cell transplantation (HSCT) may restore enzymatic levels, improving the clinical outcome of patients. Halter and associates published a common approach to allogeneic HSCT in MNGIE based on preliminary experience of participants of the first consensus conference (in Bern, Switzerland on November 7, 2008).

In this report, we present a review of the current literature and a case series of 3 patients with MNGIE from Saudi Arabia who underwent allogeneic HSCT at King Faisal Specialist Hospital (KFSHRC, Riyadh, Saudi Arabia). This work is the first report of MNGIE patients who underwent HSCT in the Middle East region.

Case 1
Case 1 was previously presented. A 26-year-old male patient had symptoms of watery diarrhea and abdominal pain over a period of 15 years. This was associated with difficulty in swallowing on a few occasions. At his first presentation to KFSHRC, a physical examination showed severe muscle wasting; his body mass index was 12 kg/m². Findings on physical examination included pallor, severe motor and sensory peripheral neuropathy of upper and lower limbs, bilateral sensory neural deafness, mild ptosis of the left eye, and ophthalmoplegia. Family history included consanguineous parents and 11 siblings (8 brothers and 3 sisters). One sister and another brother died as a result of a similar illness (chronic diarrhea and muscle wasting). Another sister was diagnosed with MNGIE but was still alive with similar symptoms (chronic diarrhea and muscle wasting).

On admission, laboratory results showed hemoglobin level of 104 g/L (135-180 g/L), creatinine level of 40 µmol/L (64-115 µmol/L), potassium of 2.8 mmol/L (3.5-5 mmol/L), calcium of 1.3 mmol/L (2.1-2.6 mmol/L), magnesium of 0.70 mmol/L (0.70-1 mmol/L), albumin of 27 g/L (32-48 g/L), phosphate of 0.78 mmol/L (0.8-1.45 mmol/L), lactic acid of 4.3 mmol/L (0.5-2 mmol/L), pyruvic acid of 217 µmol/L (30-90 µmol/L), alanine aminotransferase of 13 U/L (10-45 U/L), lactate dehydrogenase of 306 U/L (135-225 U/L), vitamin B6 level of < 3.5 µg/L (4.5-60.6 µg/L), vitamin E of 3.5 mg/L (5.5-15.5 mg/L), copper of 2.6 µmol/L (11-22 µmol/L), zinc of 10.2 µmol/L (10.6-19 µmol/L), antitissue transglutaminase of 8.9 U (0-20 U), and C reactive protein level of 0.2 mg/L.

Urine thymidine was 72 mM and plasma thymidine was 15289 nmol/L (normal < 700 nmol/L) (Baylor Medical Genetics Laboratories, Houston, TX, USA). A computed tomography scan of the chest and abdomen showed mild thickening of the terminal ileum, but liver, pancreas, adrenals, and other organs were normal. Upper gastrointestinal endoscopy showed features of reflux esophagitis; biopsy from the second part of the duodenum was normal. Colonoscopy revealed narrowed ileocecal valve, and biopsies of that area and the terminal ileum were normal. Capsule endoscopy was also normal.

A nerve conduction study showed severe peripheral sensory motor neuropathy, demyelinating in type with secondary axonal degeneration. Tympanometry was normal. An audiometry test confirmed severe bilateral sensory neural deafness. Visually evoked potentials after black and white square pattern reversal stimulation of the right and left eye, in turn recorded from the midoccipital region, were prolonged.

The genetic study was carried out by the Baylor Medical Genetics Laboratory at the Baylor College of Medicine. The TYMP sequence analysis (TYMP gene encoding thymidine phosphorylase enzyme) showed homozygous novel missense mutation, c833G>A (PG278D) mutation, at exon 7 location. A diagnosis of MNGIE was made.

Initial support measures included total parenteral nutrition, but the patient did not gain weight. A few months later, the patient underwent allogeneic HSCT. The patient’s Karnofsky score before HSCT was 50 (range, 0-100). The source of stem cells was granulocyte colony-stimulating factor (G-CSF)-stimulated bone marrow of HLA-identical male sibling donor. Conditioning regimen included busulfan (0.8 mg/kg intravenously every 6 h for 3 consecutive days starting at day -4) and fludarabine (25 mg/m²/d for a total of 5 days, starting on day -9). Graft-versus-host disease (GVHD) prophylaxis was with a short course of methotrexate and cyclosporine. Neutrophil (absolute neutrophil count) engraftment occurred on day 16 after HSCT, and platelet engraftment occurred on day 19 after HSCT. The frequency of diarrhea improved following HSCT, and post-HSCT course was uneventful until day 17 when the patient developed a skin rash that was due to drug allergy. On day 23 after bone marrow transplant, the patient had a fever; within a few hours, the patient developed respiratory failure.
and hypotension with features of septic shock and multiorgan failure. Bronchoscopic culture obtained from the respiratory tract was positive for Klebsiella pneumonia. The patient was given appropriate antimicrobials and other supportive measures. On day 24 after HSCT, the patient died of multiorgan failure secondary to sepsis. Biochemical and clinical improvement of MINGIE features after HSCT were not established.

Case 2
A 17-year-old male patient with a history of repeated attacks of vomiting and severe weight loss presented to KFSHRC for further treatment. The patient was diagnosed with MNGIE based on a positive test for homozygous mutation TYMP gene c1048c>T:pGlu350X, which was the same mutation as shown in his previously deceased brother who was also diagnosed with MNGIE syndrome and unfortunately died just 2 weeks before a bone marrow transplant. The patient’s family history showed consanguineous parents and 4 brothers with MNGIE syndromes, 3 who had died previously. On his first visit to KFSHRC, a physical examination showed severe muscle wasting. Body mass index was 14.5 kg/m². The patient’s neurologic examination showed that his sensory, motor, and cranial nerves were intact.

Laboratory results on initial presentation were as follows: hemoglobin level of 156 g/L (135-180 g/L), creatinine 40 µmol/L (64-115 µmol/L), potassium 4.5 mmol/L (3.5-5 mmol/L), calcium 2.37 mmol/L (2.1-2.6 mmol/L), magnesium 0.87 mmol/L (0.70-1 mmol/L), albumin 44.5 g/L (32-48 g/L), alanine aminotransferase 17.5 U/L (10-45 U/L), and lactate dehydrogenase 250 U/L (135-225 U/L). Magnetic resonance imaging (MRI) of the brain showed diffuse white matter signal intensity changes. A nuclear medicine gastric emptying study showed significantly delayed gastric emptying of solid food. The patient underwent HSCT shortly after his initial presentation to KFSHRC. His Karnofsky score before HSCT was 80%. The source of stem cells was G-CSF-stimulated bone marrow of HLA-identical mother. The conditioning regimens for stem cell transplant were busulfan (0.8 mg/kg/6 h for 4 consecutive days starting on day 5 before stem cell infusion) and fludarabine (30 mg/m²/d for a total of 5 days starting on day 6 before stem cell infusion). For GVHD prophylaxis, the patient received short course treatment with methotrexate and cyclosporine together with antithymocyte globulin. Neutrophil engraftment occurred on day 13 after HSCT, and platelet engraftment occurred on day 12 after HSCT. During the first 30 days post-HSCT, the patient developed grade 2 mucositis; otherwise, the recovery was uneventful. The patient was discharged on day 22 and continued regular follow-up with the bone marrow transplant clinic. Four months after HSCT, biochemical testing for thymidine phosphorylase enzyme and genetic testing for c1048C and c1048c>T alleles were conducted, and the results were within normal range. Unfortunately, the patient’s nutrition status did not improve during that time and he continued to have severe weight loss. His body mass index remained low at 12.5 kg/m² at 5 months post-HSCT. Six months after HSCT, the patient developed steroid-refractory grade IV liver GVHD that was treated with multiple lines of immunosuppression, including cyclosporine and azathioprine, which resulted in a partial response. Ten months after HSCT, he was admitted to the intensive care unit with septic shock secondary to pneumonia and died shortly after admission.

Case 3
Case 3 was a 27-year-old male patient and the brother of case 2 in this series. He presented with a history of diarrhea, occasional vomiting, cachexia, and severe weight loss. The patient was diagnosed with MNGIE based on a positive test for homozygous mutation TYMP gene c1048c>T:pGlu350X, which was the same mutation seen in his brother (case 2). Family history is as mentioned for case 2. On presentation to KFSHRC, the patient’s physical examination showed severe muscle wasting. Body mass index was 12.5 kg/m². He had no signs or symptoms of neurologic abnormalities.

Laboratory results on initial presentation were as follows: hemoglobin level of 119 g/L (135-180 g/L), creatinine of 40 µmol/L (64-115 µmol/L), potassium of 4.5 mmol/L (3.5-5 mmol/L), calcium of 2.39 mmol/L (2.1-2.6 mmol/L), magnesium of 0.90 mmol/L (0.70-1 mmol/L), albumin of 39.4 g/L (32-48 g/L), alanine aminotransferase of 17.5 U/L (10-45 U/L), and lactate dehydrogenase of 209 U/L (135-225 U/L). Brain MRI showed moderate diffuse periventricular and deep white matter changes. A nuclear medicine gastric emptying study showed significantly delayed gastric emptying of solid food.
gastric emptying of solid food. An ultrasonographic scan of the abdomen showed fatty liver. An audiometry examination was done and showed moderately severe sensorineural hearing loss in the right ear and moderately to moderately severe mixed hearing loss in the left ear.

The patient underwent HSCT shortly after his initial presentation to our institution. Karnofsky score before HSCT was 80%. Stem cell source was G-CSF-stimulated bone marrow of HLA-identical father. Conditioning regimen was with busulfan and fludarabine as in case 2. A short-course treatment with methotrexate and ciclosporine was used for GVHD prophylaxis. Neutrophil and platelet engraftment occurred on day 14 and day 13 after HSCT. During the first 30 days after bone marrow transplant, the patient had diarrhea secondary to Clostridium difficile infection and grade 4 mucositis. The patient also had 1 grand mal epilepsy seizure during his conditioning regimen, which was managed with lorazepam. The patient was discharged on day 22 and continued regular follow-up with the bone marrow transplant clinic. At 3 months after HSCT, the patient’s plasma thymidine level was < 700 nmol/L (within normal range). Genetic testing for c1048C and c1048c>T alleles in the bone marrow was done 6 months after HSCT, and the results were within a normal range. The patient is now alive, 14 months after HSCT. His general condition continues to be poor with severe muscle wasting and weight loss, but he has no signs of GVHD at present.

Discussion

Mitochondrial neurogastrointestinal encephalomyopathy syndrome is a rare autosomal recessive disorder with around 200 cases reported in the literature. The syndrome was described for the first time in 1976 by Okamura and associates. It is caused by a TYMP gene mutation that leads to deficiency in thymidine phosphorylase enzyme, causing accumulation of thymidine and deoxyuridine with an end result of mitochondrial dysfunction (57%).

The clinical presentation of patients with MNGIE can be heterogenous and have a wide spectrum of phenotypes. Garone and associates published an epidemiologic study of 102 patients with MNGIE, showing that the most common presentation of such patients is related to gastrointestinal dysmotility (100%), with ocular symptoms being the second most common (96%). Although gastrointestinal and ocular manifestations are the most common symptoms, the initial manifestation can be in the form of peripheral neuropathy or hearing loss.

Zimmer and associates proposed a diagnostic algorithm for MNGIE. They suggested to start with a brain MRI; a finding of diffuse hyperintensity in the cerebral white matter is considered an important diagnostic clue for MNGIE. Absence of diffuse leukoencephalopathy on brain MRI makes TYMP mutations unlikely and indicates alternative diagnoses. Diagnostic confirmation of MNGIE is performed by specialized biochemical assessment of preferably plasma thymidine and deoxyuridine levels or by enzymatic assessment of thymidine phosphorylase activity in buffy coats.

There are multiple publications in the literature describing different methods of therapy for MNGIE syndrome. Lara and associates demonstrated that infusion of platelets from healthy donors to patients with MNGIE restored transiently circulating thymidine phosphorylase and reduced plasma thymidine and deoxyuridine levels, suggesting that treatments to achieve permanent restoration of circulating thymidine phosphorylase, such as allogeneic stem cell transplant or gene transfer, may be therapeutic. On the other hand, Spinazzola and team used hemodialysis in 2 patients with MNGIE and showed that hemodialysis reduced circulating concentrations of thymidine in both patients but only transiently. Yavuz and colleagues tried continuous ambulatory peritoneal dialysis on a patient with MNGIE, which resulted in improvements in gastrointestinal symptoms; however, the benefit was also transient.

The first allogeneic HSCT in a MNGIE patient was done in 2006 by Hirano and associates. They performed reduced intensity allogeneic stem cell transplant in 2 patients. Although engraftment in the first patient was not successful, the second patient achieved mixed donor chimerism, which partially restored thymidine phosphorylase activity in buffy coat and lowered plasma nucleosides. The conclusion from this experience was that allogeneic HSCT can correct biochemical abnormalities in the blood of patients with MNGIE, but clinical efficacy remains unproven.

In 2011, Halter and associates published a common approach to allogeneic HSCT in MNGIE...
based on preliminary experience of participants of the first consensus conference (Bern, Switzerland; November 7, 2008). In this report, 9 patients with MNGIE received allogeneic stem cell transplant; recovery of thymidine phosphorylase activity was observed in these patients. Although the observation period in most of these patients was too short to evaluate a clinical benefit, it was sufficient to show biochemical improvement.

In a report from 2012, 2 patients with MNGIE underwent allogeneic HSCT and also showed biochemical improvement with recovery of thymidine phosphorylase activity. According to this report, there was also a clinical improvement in gastrointestinal symptoms but not with neurologic assessment. Both patients died from infection (15 and 8 months after transplant).

Here, we reported 3 patients with MNGIE who underwent allogeneic HSCT in one center (KFSHRC). Similar to previous experiences, our results showed improved biochemical profiles in the patients but very little clinical improvement. Currently, 1 patient (case 3) is still alive but without showing improvements in severe weight loss and muscle wasting. The other 2 patients died of transplant-related complications at 24 days and 10 months after HSCT.

Table 1 shows a summary of selected MNGIE patients who received allogeneic SCT from fully matched related donors that were published in the literature along with the 3 current cases in this series. In general, although patients with MNGIE who have undergone allogeneic HSCT worldwide have shown biochemical improvement, patients do not live long after transplant.

Although allogeneic HSCT is considered a therapeutic option in MNGIE patients who have a suitable matched donor, transplant-related mortality appears to be high; this may at least be partially related to established end-organ effects with decreased performance status. Although allogeneic HSCT clearly effects correction of genetic and biochemical defects in MNGIE, its ability to reverse or improve established clinical manifestations has not been proven. More studies are clearly required to confirm the role of HSCT in improving patient status and chances of survival. Furthermore, increased awareness of this disease among physicians is essential so that these patients are diagnosed early in the course of the disease and potential experimental treatment may be offered before they reach an irreversible state.

Table 1. Summary of Selected Patient With Mitochondrial Neurogastrointestinal Encephalomyopathy Syndrome Who Received Allogeneic Stem Cell Transplant From Fully Matched Related Donors

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex</th>
<th>Age at HSCT, y</th>
<th>GI Manifestation</th>
<th>Neuro-Ophth Manifestation</th>
<th>Conditioning</th>
<th>GVHD Prophylaxis</th>
<th>HSC Source</th>
<th>GVHD Clinical Improvement</th>
<th>Dead or Alive</th>
<th>Last Follow-up After HSCT, d</th>
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<td>30</td>
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<td>Flu/Cy/ATG</td>
<td>Sir/MMF</td>
<td>PBSC</td>
<td>No</td>
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<td>Yes</td>
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<td>CsA/MMF</td>
<td>BM</td>
<td>Acute</td>
<td>Yes</td>
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<td>CsA/MTX</td>
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<td>In vitro TCD</td>
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<td>23</td>
<td>Yes</td>
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<td>Flu/Bu/alemtuzumab</td>
<td>CsA</td>
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<td>Yes</td>
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Abbreviations: ATG, antithymocyte globulin; BM, bone marrow; Bu, busulfan; CsA, cyclosporine; Cy, cyclophosphamide; F, female; Flu, fludarabine; GI, gastrointestinal; M, male; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; Neuro-ophth, neuro-ophthalmology; PBSC, peripheral blood stem cells; Sir, sirolimus; Tac, tacrolimus; TCD, T-cell depletion

References