Mitochondrial Neurogastrointestinal Encephalomyopathy Treated with Stem Cell Transplantation: A Case Report and Review of Literature

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Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disorder. The mutation in the ECGF1 gene causes severe deficiency of thymidine phosphorylase (TP), which in turn increases thymidine and deoxyuridine in the blood, serum, and tissue. The toxic levels of these products cause malfunction of the mitochondrial respiratory chain and mitochondrial DNA. Commonly, patients become symptomatic between 15 and 20 years of age (range 5 months to 35 years). The most commonly affected systems are gastrointestinal, followed by ocular, and nervous system. The disease is often fatal; high mortality rate is reported between 20 and 40 years of age. Treatment modalities that can increase thymidine phosphorylase activity and decrease thymidine and deoxy-uridine have shown symptomatic improvements in patients with MNGIE. Platelet transfusion, hemodialysis, peritoneal dialysis or allogeneic hematopoietic stem cell transplantation (HSCT) have been tried. The survival and long-term benefits of these measures are still not clear. Engrafted patients after stem cell transplantation have showed improvements in serum thymidine and deoxyuridine. We are reporting a case of MNGIE from Saudi Arabia, who underwent allogeneic hematopoietic stem cell transplantation. No MNGIE case has been previously reported from Saudi Arabia or the Gulf Arab countries. From the available literature, so far only 11 patients with MNGIE have undergone stem cell transplantation.

KEYWORDS: Mitochondrial neurogastrointestinal encephalomyopathy; MNGIE; Stem cell transplantation; Bone marrow transplantation

INTRODUCTION

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disorder characterized by severe muscle wasting, gastrointestinal dysmotility, leukoencephalopathy, peripheral neuropathy, and ophthalmoplegia. The mutations in the ECGF1 gene encoding thymidine phosphorylase (TP) cause alterations in the respiratory chain and mitochondrial DNA (mtDNA). The prognosis of this disease is limited; most patients die by the age of 35 years, but survival may range from 15 to 54 years.

Excessive thymidine alters mitochondrial nucleoside and nucleotide pools leading to impaired mitochondrial DNA replication, repair, or both. There is an assumption that therapies that can reduce thymidine levels might be helpful to MNGIE patients. In a limited number of patients, treatment modalities such as platelet transfusion, hemodialysis, and peritoneal dialysis have been tried. The survival and long-term benefits of these measures are still not clear. Engrafted patients after stem cell transplantation have showed improvements in serum thymidine and deoxyuridine. We are reporting a case of MNGIE from Saudi Arabia, who underwent allogeneic hematopoietic stem cell transplantation. No MNGIE case has been previously reported from Saudi Arabia or the Gulf Arab countries. From the available literature, so far only 11 patients with MNGIE have undergone stem cell transplantation.

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dialysis or stem cell transplantation were tried. The long-term benefit of these treatments for MNGIE is not clear.\textsuperscript{4-6} We report the first case of MNGIE from Saudi Arabia and the Gulf Arab states, and worldwide the 12th case of MNGIE treated with hematopoietic stem cell transplantation (HSCT). However, our patient died on day 24 after transplantation.

**CASE REPORT**

A 26-year-old male had been suffering from watery diarrhea and abdominal pain over a period of 15 years. There was no history of bleeding per rectum, melena or steatorrhea. Abdominal pain was scattered all over the abdomen and was mild in severity without any pattern, relieving or aggravating factors. He had difficulty in swallowing on a few occasions. Appetite was normal with no history of fever. The patient was a teetotaler and had no prior sexual exposure or drug addictions. The patient denied history of seizures, headache, arthralgia, chronic cough, chest pain or dyspnoea. He was unmarried and unemployed.

A physical examination showed severe muscle wasting. His body mass index was 12 kg/m\(^2\). The patient was pale. Findings on physical examination included severe sensory and motor peripheral neuropathy of upper and lower limbs; bilateral sensory neural deafness; mild ptosis of the left eye; and ophthalmoplegia. Cardiovascular, respiratory and abdominal examinations were unremarkable.

Patient had consanguineous parents. He had eight brothers and three sisters; two of them had died in road accidents. One sister and another brother died of similar illnesses (chronic diarrhea and muscle wasting). Another sister had chronic diarrhea and muscle wasting, and has been diagnosed with MNGIE. Figure 1 shows the pedigree diagram of the family tree.

On admission, laboratory results were as follows: hemoglobin 104 gm/L (135–180); creatinine 40 \(\mu\)mol/L (64–115); potassium 2.8 mmol/L (3.5–5); calcium 1.3 mmol/L (2.1–2.6); magnesium 0.23 mmol/L (0.70–1); albumin 27 gm/L (32–48); phosphate 0.78 mmol/L (0.8–1.45); lactic acid 4.3 mmol/L (0.5–2); pyruvic acid 217 \(\mu\)mol/L (30–90); ALT 13 U/L (10–45); LDH 306 U/L (135–225); vitamin B6 < 3.5 \(\mu\)g/mL (4.5–60.6); vitamin E 3.5 mg/L (5.5–15.5); copper 2.6 \(\mu\)mol/L (11–22); zinc 10.2 \(\mu\)mol/L (10.6–19); anti tissue trans-glutaminase 8.9 units (0–20); CRP 0.2 mg/L.

Urine thymidine was 72 mmol/mol and plasma thymidine 15289 nano-mols/L (Normal < 700 nano-mols/L). (Baylor Medical Genetics Laboratories; Texas).

The stool examination for ova, parasites, and stool for *Clostridium difficile* were negative. Celiac serology, serum QuantiFERON test, purified protein derivative (PPD) skin test and serology for HIV 1 and 2 were negative. A CT scan of the chest and abdomen with and without contrast showed mild thickening of the terminal ileum, but normal liver, pancreas, adrenals, and other organs. The upper endoscopy showed features of reflux esophagitis. The biopsy from the second part of the duodenum was normal. The colonoscopy revealed narrowed ileoecal valve, and biopsy from that area and the terminal ileum was normal. The capsule endoscopy was also normal.

![Figure 1. Pedigree diagram of the family tree showing autosomal recessive pattern of inheritance.](image-url)
The manometry study of the esophagus (Figure 2) showed severe dysmotility of the esophagus. Gastric emptying was significantly delayed for emptying of solid food with a T-1/2 of 101 min.

The nerve conduction study showed severe peripheral sensory-motor neuropathy, demyelinating in type with secondary axonal degeneration. Tympanometry was normal. Audiometry (Figure 3) confirmed severe bilateral sensory neural deafness. The visual evoked potential after black and white square pattern reversal stimulation of the right and left eye, in turn recorded from the mid occipital region, were prolonged.

Electromyography (EMG) needle study of the distal and proximal muscles showed significant neurogenic changes in the distal muscle with pronounced signs of a chronic partial denervation with signs of reinnervation. In the proximal muscle, the EMG needle study showed more myopathic changes.
Sympathetic skin responses were absent after electrical stimulation of contra-lateral median nerve. Absent sympathetic skin response from left plantar skin was also noted after right tibial nerve stimulation.

Electroencephalogram (EEG) showed a few short runs of low voltage 5 Hz activity temporally with shift to left-side predominance during drowsiness and hyperventilation. A Magnetic resonance imaging (MRI) of the brain (Figure 4) showed typical findings of leukoencephalopathy.

The genetic study was carried out by Baylor College of Medicine, Medical Genetics Laboratories, Houston, Texas. The TYMP sequence analysis (TYMP gene encode thymidine phosphorylase enzyme) showed homozygous novel missense mutation, c 833G > A (P G278D) mutation at exon 7 location.

A diagnosis of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) was made in our patient.

Total parental nutrition was given to improving his inadequate nutritional status, but the patient did not gain weight. After a few months’ stay in the hospital, the patient underwent hematopoietic stem cell transplantation (HSCT). The patient’s Karnofsky score was 50 (range 0–100) before HSCT. The patient’s source of stem cells was granulocyte colony-stimulating factor (G-CSF) stimulated bone marrow of HLA-identical male sibling donor.

The conditioning regimens for stem cell transplantation were busulfan and fludarabine. Busulfan was given through intravenous route as dose of 0.8 mg/kg, six hourly for three consecutive days. The first dose of busulfan was given four days prior to bone marrow transplantation (BMT). Fludarabine was given at a dose of 25 mg/m² daily; the first dose was started nine days prior to BMT, and then given daily for a total of five days.

Graft versus host disease (GVHD) prophylaxis was the standard dose of methotrexate/cyclosporine. The absolute neutrophil count (ANC) engraftment happened on day 16 post-BMT and platelet engraftment on day 19 post-BMT.

Post-HSCT period was uneventful until day 17. The frequency of diarrhea improved following HSCT. On day 17, the patient developed a skin rash that was due to drug allergy. On day 23 post-BMT, the patient’s temperature spiked. Within a few hours, the patient developed respiratory failure and hypotension with features of septic shock and multi-organ failure. Bronchoscopy showed copious secretion from the respiratory tracts, and culture was positive for Klebsiella pneumonia. The patient was given appropriate antimicrobials and other supportive measures. On day 24 post-HSCT, the patient died of multi-organ failure secondary to sepsis. Biochemical and clinical improvement of the patient following HSCT was not established.

**DISCUSSION**

Okamura initially described MNGIE in 1976. It is a well-characterized autosomal recessive disorder. Most of the patients have gastrointestinal dysmotility, cachexia, peripheral neuropathy, and diffuse leukoencephalopathy. Though other diseases can have different clinical features that are seen in MNGIE, diffuse leukoencephalopathy is typical for MNGIE. Leukoencephalopathy is clinically silent, but some patients can have mild neurological symptoms such as headache, seizure, cognitive impairment, dementia, or psychiatric symptoms. MRI findings of the
leukoencephalopathy appears as hyperintense on T2-weighted or fluid-attenuated inversion recovery images. In the early stages of the condition, these results may be patchy, but eventually become diffuse and confluent.  

From a review of a cohort of 102 MNGIE patients collected from 1988 to 2011, significant mortality was reported between the ages of 20 and 40 years. In 1999, Nishino et al identified the gene mutation responsible for MNGIE. They identified the responsible mutation of MNGIE as homozygous or compound heterozygous mutations in the gene specifying thymidine phosphorylase (TP), located on chromosome 22q13.32-qter. The mutation leads to extremely low activity of TP in leukocytes.

Very low TP activity eventually ends up in systemic accumulation of thymidine and deoxyuridine that causes mitochondrial DNA instability. Treatments that can achieve the restoration of TP activity might be possible options. The in-vitro experiment by Laura et al with platelet transfusion in two patients partially restored TP catabolism of thymidine and deoxyuridine in both patients. The infused platelets provided TP activity, and the effect should be transient.

Spinazzola and team tried hemodialysis in another two MNGIE patients in 2002. Patient A underwent one dialysis, and patient B underwent three consecutive weekly dialysis treatments. Hemodialysis reduced circulating concentrations of thymidine in both patients. However, the effect was transient. Three hours after dialysis, levels of the nucleoside returned to pretreatment values. In 2006, there was another attempt to reduce the blood thymidine level with hemodialysis in a patient with MNGIE. A significant reduction in thymidine levels in the plasma and urine was observed during and after dialysis. However, the researchers noted a progressive reduction of the initial thymidine level after several dialysis trials.

In 2007, a 16-year-old girl with MNGIE was treated with continuous ambulatory peritoneal dialysis for three years. She showed marked improvements in her symptoms. While she was on dialysis, her vomiting and abdominal pain improved, and she had a weight gain of 5 kg. Interruption of dialysis returned the symptoms.

In 2006, Hirano et al. performed allogeneic stem cell transplantation to correct biochemical derangements in two MNGIE patients. Patient A had primary non-engraftment of donor cells with spontaneous autologous recovery. After 86 days of transplantation, this patient died from disease progression complicated by sepsis and respiratory failure. At 6.5 months after the transplant, Patient B reported less severe abdominal pain, improved swallowing ability, and decreased numbness in her hands and feet. In both patients, improvement of TP activity and reduction of thymidine and deoxyuridine was observed.

Between 2007 and 2009, seven more MNGIE patients were treated with hematopoietic stem cell transplantation. The data of the post-transplant engrafted patients suggest biochemical recovery of the TP activity, but the clinical usefulness of transplantation was difficult to judge because of short observation period.

In 2012, two more MNGIE patients underwent HSCT. Both patients achieved full donor chimerism, and in both, improvements of TP activity and decrease in urine nucleoside concentration was observed. Both patients showed improvement in gastrointestinal dysmotility, abdominal cramps and diarrhea post-HSCT. Neurological assessment remained unchanged. However, the first patient died 15 months after HSCT due to gastrointestinal obstruction and shock; the second patient died eight months after the procedure due to respiratory distress following septic shock.

Worldwide, so far twelve patients have undergone HSCT for MNGIE, including our patient from Saudi Arabia. In engrafted patients, an improvement in biochemical parameters of MNGIE was noted. The 12 patients who had undergone HSCT for MNGIE did not survive for a long period. With available information, the long-term benefit of bone marrow transplantation in MNGIE is still unknown. Often, MNGIE patients are diagnosed at an advanced stage. Identifying these patients at a younger age and offering them HSCT might improve their quality of life and survival.

In conclusion, we have reported a case of MNGIE, a disease which is often fatal. Stem cell transplantation is considered one treatment modality. More study is required to confirm the role of transplantation in improving the patient’s well-being and chances of survival. Awareness of this disease among physicians is essential so that these patients are diagnosed early and experimental treatment can be offered before they reach an irreversible state.

CONFLICT OF INTEREST
No conflict of interest exists for this paper.
REFERENCES