Objective: To study the effect of continuous ambulatory peritoneal dialysis on nucleoside levels and clinical course in a patient with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE).

Patient: We studied a patient with genetically verified MNGIE, who prior to treatment had lost weight progressively, developed amenorrhea, vomited multiple times daily, and had abdominal pain.

Intervention: The patient was treated with peritoneal dialysis for 3 years, and the effect on symptoms and plasma concentrations of thymidine and deoxyuridine were monitored.

Results: Dialysis stopped vomiting and reduced abdominal pain, and the patient gained 5 kg in weight and started to menstruate again. Symptoms returned if dialysis was paused. Dialysis did not affect plasma nucleoside levels.

Conclusions: This study shows an unambiguous clinical benefit of peritoneal dialysis on gastrointestinal symptoms in MNGIE. Dialysis did not affect nucleoside levels, indicating elevated thymidine and deoxyuridine levels are not solely responsible for the pathogenesis of MNGIE.

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MITOCHONDRIAL NEUROGASTROINTESTINAL ENCEPHALOMYOPATHY (MNGIE) is a rare autosomal recessive multisystem disorder characterized by external ophthalmoplegia, gastrointestinal dysmotility and pain, cachexia, peripheral neuropathy, and leukoencephalopathy. The disease is caused by mutations in the gene encoding thymidine phosphorylase (ECGF1).1 Thymidine phosphorylase is a cytosolic enzyme that regulates pyrimidine nucleoside levels by phosphorolytic catabolism of deoxyuridine and thymidine to uracil and thymine and 2-deoxy-D-ribose 1-phosphate. ECGF1 mutations cause severe loss of enzyme function in patients with MNGIE, resulting in very high concentrations of the nucleosides, thymidine, and deoxyuridine in extracellular fluids.1,2 Altered thymidine and deoxyuridine metabolism has been proposed to destabilize mitochondrial DNA (mtDNA) by interfering with mtDNA repair and replication.2

Despite significant progress in the molecular characterization of this disease, treatment for the condition is still lacking. In this study, we report the use of continuous ambulatory peritoneal dialysis (CAPD) as a treatment for MNGIE.

REPORT OF A CASE

A girl with consanguineous parents presented with episodic vomiting and epigastric pain at age 15 years. She was cachectic (weight, 28 kg; height, 154 cm) and had a low blood pressure (85/65 mm Hg). The patient had generalized muscle weakness and atrophy, mild bilateral ophthalmoplegia and ptosis, and absent tendon reflexes in the lower extremities.

Plasma lactate levels were slightly elevated (18.4 mg/dL [2.04 mmol/L]; reference range, 3-12 mg/dL [0.33-1.33 mmol/L]). Radiography after barium ingestion showed an excess of gastric fluid and gastroptosis (Figure 1), but the intestinal passage appeared normal on imaging. Electrophysiological studies revealed diffuse, mixed sensorimotor polyneuropathy. Brainstem auditory evoked potential study results were nor-
mal, but visual evoked potential studies showed pro-
longed P100 latency. T2-weighted brain magnetic reso-
nance imaging showed increased signal affecting the
periventricular white matter of the frontoparieto-
occipital regions (Figure 2). On suspicion of MNGIE,
we measured plasma thymidine and deoxyuridine levels
and sequenced all introns and exons of ECGF1, using
methods previously described.3

![Figure 1. Contrast radiograph demonstrating marked gastroptosis.](image)

![Figure 2. T2-weighted brain magnetic resonance image of the patient, demonstrating diffusely increased signal in the periventricular white matter.](image)

The patient was treated with intravenous fluids, dom-
peridone, and metiamide with good effect on the eme-
sis, but in the following year, vomiting got worse, so that
she always vomited after meals. After a vomiting epi-
sode, the patient developed a generalized tonic-clonic sei-
zure. At that time (age 16 years), hemodialysis began 3
times weekly via first femoral, then brachial, catheters.
After 2 months of hemodialysis, treatment was shifted
to CAPD because CAPD can be performed continu-
ously, is better tolerated by most patients, and can be per-
fomed outside the hospital. Continuous ambulatory peri-
toneal dialysis is performed with 1200 mL of 1.5% glucose
dialysis fluid every 3 hours. The procedure of emptying
and refilling the peritoneum with dialysis fluid takes 10
minutes and is performed by the patient. At the time of
publication, the patient had been treated with CAPD for
3 years. Only a few CAPD-related problems occurred dur-
ing this period (leaking dialysis fluid from the catheter,
1 episode of mild peritonitis, and occasional right shoul-
der pain).

Magnetic resonance imaging and visual evoked
potential and brainstem auditory evoked potential
studies were repeated after 2 years of CAPD. Plasma
levels of thymidine and deoxyuridine were measured
before, during, and after 1 hemodialysis and 4 CAPD
treatments. Thymidine and deoxyuridine levels were
also measured in dialysis fluid during 3 CAPD treat-
ments. Samples were injected into a high-performance
liquid chromatograph (Alliance model 2690; Waters
Corporation, Milford, Mass) equipped with a photodi-
oide array detector (model 996; Waters Corporation)
operating at 254 nm and recording UV-visible absorp-
tion spectra (200-400 nm). All compounds were iden-
tified by their retention times and by comparison of
their absorption spectra with those of commercially
available products.

**GENETIC AND METABOLIC FINDINGS**

Sequencing of ECGF1 revealed homozygosity for a pre-
viously described splice-site mutation (IVS9-1G>A),1 con-
firming the diagnosis of MNGIE. The parents and an
asymptomatic sister of the proband were heterozygous
for this mutation.

Thymidine and deoxyuridine levels were decreased
by hemodialysis from 13 and 22 µmol/L before dialysis
to 7 and 9 µmol/L after. Continuous ambulatory peri-
toneal dialysis, however, had no measurable effect on
nucleoside levels (Figure 3), and the levels of these
metabolites were elevated 100-fold or more compared
with concentrations found in healthy subjects (ie,
<0.05 µmol/L). Concentrations of the nucleosides in
the dialysate were on average one third of plasma levels
(Figure 3), and it can be calculated that approximately
100 µmol of both thymidine and deoxyuridine were
removed daily by dialysis. Thymine and uracil were not
detected in plasma or dialysate at any time. Plasma lac-
tate levels ranged between 33 mg/dL [3.66 mmol/L] and
52 mg/dL [5.77 mmol/L] during the course of CAPD
treatment and were only decreased by 17% on average
after each dialysis session.
EFFECT OF DIALYSIS ON SYMPTOMS AND SIGNS

Before hemodialysis, the patient vomited after every meal. Hemodialysis reduced the frequency of vomiting to once every 2 to 3 days.

Continuous ambulatory peritoneal dialysis stopped vomiting completely. If the quantity of dialysis fluid was decreased or dialysis was missed, typically because of a long period of sleeping, the patient consistently developed nausea, weakness, and vomiting. Epigastric pain almost disappeared with the treatment, and the anorexia she had before dialysis treatment improved markedly, so that parenteral food supplementation has not been needed. After starting CAPD, her weight increased by 5 kg to 33 kg, and she started to menstruate again. Her height remained unchanged. Her blood pressure also increased with treatment to an average 100/65 mm Hg. Despite the progressive nature of the disease, the patient is able to climb stairs more easily and walk longer distances than she could 3 years ago before treatment. The level of ophthalmoplegia, the absent tendon reflexes, and findings on brain magnetic resonance imaging and results of visual evoked potential and brainstem auditory evoked potential studies after 2 years of CAPD treatment did not change.

The 2 major findings of the present study are that peritoneal dialysis has a sustained beneficial effect on the severe gastrointestinal symptoms in MNGIE and that this improvement occurred in the face of unchanged extracellular levels of thymidine and deoxyuridine. The findings are important because they represent the first report, to our knowledge, of a significant treatment response in MNGIE and because they clearly indicate that, in addition to imbalanced nucleoside pools, the pathogenesis of MNGIE may be caused by other metabolic factors.

Cachexia and early death are characteristic of MNGIE. The most debilitating symptoms of MNGIE are the gastrointestinal manifestations (nausea, anorexia, vomiting, abdominal pain, diarrhea) that lead to poor quality of life and severe weight loss. Gastrointestinal symptoms develop in nearly all patients with MNGIE, and they are often the presenting symptoms, as in our patient.1,2,4-6 Most gastrointestinal symptoms in MNGIE stem from dysmotility of the small intestine. The dysmotility is in part caused by a pronounced visceral myopathy of the external layer of the muscularis propria,6 but an intestinal autonomic neuropathy may also play a role.7 Intestinal dysmotility is likely also the cause of the frequent occurrence of diverticula in MNGIE, which may cause fatal peritonitis.7 The poor quality of life and early death in patients with MNGIE call for treatment, but so far, therapy has largely been supportive, including total parenteral nutrition, pain relief, and treatment of infections. Abdominal pain was treated with some success in a patient by celiac plexus neurolysis.4 Treatment with intravenous immunoglobulin and corticosteroids has been unsuccessful.5

High extracellular concentrations of thymidine and deoxyuridine have been proposed to induce nucleoside pool imbalance in mitochondria that compromise mtDNA replication and repair, resulting in a progressive development of deletions, point mutations, and depletion of mtDNA.2,5 Possible therapies for MNGIE could therefore be enzyme replacement or removal of excess thymidine and deoxyuridine from the extracellular space. Hemodialysis has previously been studied in 3 patients with MNGIE.5,10 The treatment was only given 1 to 3 times in each patient, so that the effect of the treatment on the patients’ symptoms could not be assessed. The hemodialysis was discontinued in the patients because plasma nucleoside levels had returned to pretreatment values 3 hours after dialysis.3

Recently, 2 studies have shown partial correction of the excessive nucleoside levels in the plasma of patients with MNGIE by either infusing platelets from healthy subjects or by performing allogenic stem cell (bone marrow) transplantation.11,12 These interesting treatments provide “proof of principle” that potentially toxic nucleosides can be removed in vivo, but the clinical effect of the treatments is unknown.

We investigated the effect of continued dialysis treatment on symptoms and nucleoside levels in a patient with MNGIE. Stimulated by a very favorable clinical response to hemodialysis, the patient was treated with CAPD for more than 2 years with marked improvements in clinical status. The patient gained weight and could eat without vomiting or getting abdominal pain. She started to menstruate again and could walk longer distances than before. When dialysis was paused, the patient invariably started to vomit again, thus verifying the treatment response. Interestingly, the plasma nucleoside levels were unchanged by CAPD, and basal levels of the nucleosides on dialysis treatment were still highly elevated. Dialysis removed approximately 100 µmol of thymidine and deoxyuridine every day, indicating a very high production rate of these metabolites in patients with MNGIE. Since nucleoside levels, as well as urine output, were un-
changed by CAPD, renal excretion of the nucleosides was probably also unchanged.

Our findings suggest that CAPD should be considered as a treatment for patients with MNGIE to alleviate the debilitating gastrointestinal symptoms. Long-term studies are warranted to assess the effect of the treatment on other symptoms in MNGIE. Furthermore, the study suggests that symptoms in MNGIE are not solely due to imbalanced nucleoside pools causing mtDNA instability. In keeping with this, deletions and point mutations of mtDNA in muscle were lacking in 17 of 18 patients with newly diagnosed MNGIE, even though their muscles were clinically affected.13

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