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Case Report

Mitochondrial Neurogastrointestinal Encephalopathy Disease: A Rare Disease Diagnosed in Siblings with Double Vision

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Abstract
Mitochondrial neurogastrointestinal encephalopathy disease (MNGIE) is a rare autosomal recessive condition characterized by gastrointestinal dysmotility, external ophthalmoplegia, leukoencephalopathy, and sensorimotor neuropathy. A 31-year-old man was referred for a 1-year history of horizontal diplopia related to a large exotropia from chronic progressive external ophthalmoplegia. MRI revealed a diffuse leukoencephalopathy and his 3-year history of chronic intermittent diarrhea, cachexia, and diffuse sensory more than motor peripheral neuropathy led to a unifying clinical diagnosis of MNGIE. This was later confirmed with genetic testing, which revealed a homozygous pathogenic mutation in the thymidine phosphorylase (TYMP) gene. His younger brother had an identical clinical syndrome and was similarly diagnosed. MNGIE diagnosis is important to establish to avoid unnecessary invasive testing for gastrointestinal, ophthalmological, and neurological symptoms and to ensure patients receive appropriate nutritional and genetic counselling. Gene therapy offers a potential future therapy for patients with this condition.

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Introduction

Mitochondrial neurogastrointestinal encephalopathy disease (MNGIE) is a rare autosomal recessive condition that usually presents in the first or second decade of life with an average age of onset of 17.9–18.5 years [1, 2]. The major clinical features required for diagnosis include gastrointestinal dysmotility, external ophthalmoplegia, eyelid ptosis, leukoencephalopathy, and sensorimotor neuropathy (usually mixed axonal and demyelinating) [3]. Patients often undergo referral to multiple specialists and have a protracted course before a diagnosis is ultimately made. They may also unnecessarily undergo several diagnostic and surgical procedures including laparotomies for their abdominal symptoms. Diffuse symmetric leukoencephalopathy characterized by confluent T2-hyperintensity in the white matter is almost always present on brain MRI, and may lead to diagnostic delay as other causes of this imaging pattern are investigated [3].

Here we present the cases of 2 brothers, aged 31 and 29, who developed gastrointestinal symptoms, cachexia, and double vision. Their presentation is unique as they developed symptoms in their late 20s, which is much later than most patients with MNGIE. There were many diagnostic errors that occurred and both patients underwent numerous investigations and abdominal surgeries and were given multiple diagnoses for their gastrointestinal symptoms. Awareness of MNGIE is important as all of these tests led to a delay in appropriate disease management. The older brother, case 1, presented to the neuro-ophthalmology clinic with a diagnosis of internuclear ophthalmoplegia, which we later on identified as MNGIE. Having similar symptoms that went undiagnosed, case 2 was referred to our clinic for similar assessment.

Case Presentation

Case1

A 31-year-old man was seen in neuro-ophthalmology consultation for double vision and suspected internuclear ophthalmoplegia. He had a past medical history of chronic intermittent diarrhea starting 3 years prior to presentation. Following extensive investigations including multiple colonoscopies, his condition was diagnosed as irritable bowel syndrome and medically managed with cholestyramine and diphenoxylate/atropine daily. One year prior to presentation, he developed abdominal pain and leucocytosis for which he underwent a laparotomy for small bowel obstruction. The distal small bowel and cecum were resected, whereby the procedure revealed chronic ruptured appendicitis without any evidence of inflammatory bowel disease. A few months later, he underwent right nephrectomy due to possible congenital atrophic right kidney, discovered during the investigation of recurrent UTIs for a year. As a child, he had a normal developmental history and academic performance.

One year prior to presentation, he developed intermittent horizontal binocular diplopia that was present in all directions of gaze and had increased in duration 6 months prior. He saw an ophthalmologist who noted bilateral limitation of adduction of each eye and suspected internuclear ophthalmoplegia. He therefore underwent MRI of the brain, which was initially reported to represent advanced multiple sclerosis but after later review was interpreted as a diffuse leukoencephalopathy, as shown in Figure 1a. A neuro-ophthalmology consultation was then requested to clarify the etiology of his double vision.

At the neuro-ophthalmology consultation, he appeared cachexic and weighed 46 kg and was 177 cm tall (BMI 14.7 kg/m^2). He reported no family history of neurological or oculomotor syndromes except a grandfather with Parkinson disease. He had normal afferent visual

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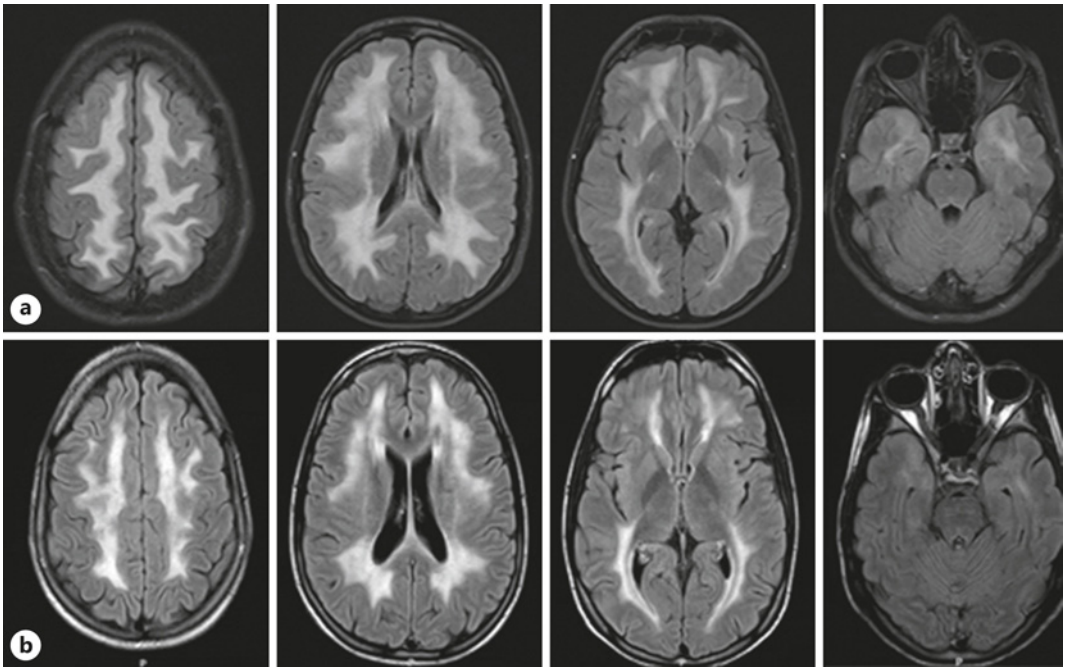

Fig. 1. Axial and sagittal MRI FLAIR images demonstrating a diffuse leukoencephalopathy of case 1 (**a**) and case 2 (**b**).

function with a visual acuity of 20/20 in each eye and normal Humphrey visual field testing. Dilated fundus examination was normal. External examination revealed bilateral ptosis with recruitment of the frontalis muscles. There was a large exotropia of 40 prism diopters (PD) in the primary position. The exotropia was fairly comitant, measuring 35 PD in both left and right gaze. He had diffuse limitation of extraocular movements, as shown in Figure 2a. Neurological examination revealed diffuse muscle atrophy, particularly in the proximal upper and lower limbs with relative sparing of his distal leg, forearm, and hand muscles. There was moderate weakness (4/5 on the Medical Research Council scale) in proximal upper and lower limb muscles, with normal distal strength. He had reduced vibration sensation at the big toes, which normalized by the ankle. Joint position sense was normal and sensation to pinprick was normal throughout. Nerve conduction studies and electromyography demonstrated a mixture of a diffuse predominantly axonal, but mixed axonal and demyelinating, sensorymotor peripheral neuropathy, along with evidence of a proximal myopathy (small motor unit potentials with early recruitment in proximal muscles).

He saw his gastrointestinal specialist and additional bloodwork including those measuring vitamin levels was performed. He was found to be anemic with a hemoglobin of 129 g/L (normal 140–180 g/L) and deficient in magnesium at 0.40 mmol/L (normal 0.70–1.10 mmol/L), calcium at 2.13 mmol/L (normal 2.20–2.62 mmol/L), 25-hydroxy vitamin D at 14 nmol/L (normal 25–200 nmol/L), and vitamin B12 at 212 pmol/L (normal 222–652 pmol/L). His parathyroid hormone levels were elevated at 9.9 pmol/L (normal 1.3–7.6 pmol/L), while his albumin was normal at 42 g/L. He continued supportive treatment and vitamin supplementation to correct these deficiencies. Diphenoxylate/atropine was discontinued due to low energy and fatigue, and he was started on loperamide 2 mg as needed up to twice daily.

Case 2

The younger sibling of case 1 was referred for neuro-ophthalmic evaluation after experiencing similar symptoms. He was a 29-year-old man with over a decade of gastrointestinal

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Fig. 2. External photographs demonstrating bilateral ptosis and diffuse external ophthalmoplegia of case 1 (**a**) and case 2 (**b**).

issues and low body weight. Around 13 years prior to presentation, his gastrointestinal symptoms started with reports of early satiety, cramping, diarrhea, nausea, and vomiting. He saw a gastrointestinal specialist and received a diagnosis of superior mesenteric artery syndrome, which prompted a bypass surgery where a portion of the artery around the duodenum was removed. Initially, he felt better but his symptoms returned, including continuing to lose weight and being intolerant to many foods.

Two years prior to presentation, he underwent gastroscopy for abdominal cramps which was unremarkable. Due to persistent abdominal discomfort, he underwent CT of abdomen and pelvis with clusters of enlarged lymph nodes found in the right lower quadrant of the abdomen. This prompted a referral to a hematologist who did not think that it was representative of an underlying diagnosis of lymphoma, and a repeat CT of the abdomen and pelvis revealed stability in these lesions 1 year later. He also underwent a hepatobiliary iminodiacetic acid scan which was consistent with biliary dyskinesia. A laparoscopic cholecystectomy was performed in an attempt to alleviate his symptoms, but was not successful. The source of his abdominal discomfort and diarrhea was not yet established and he was prescribed cholestyramine which did not improve his symptoms. He also endorsed weakness in his arms and legs for years prior to presentation, but this did not limit his mobility and there were no associated sensory changes. He also reported binocular diplopia at near distances for 2 years prior to presentation for which an optometrist prescribed him prism glasses for convergence insufficiency. He denied double vision at distance with his contact lenses but experienced intermittent binocular diplopia when looking right and left.

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Neuro-ophthalmic assessment revealed a visual acuity of 20/20 in both eyes with normal Humphrey visual fields and color vision. Fundoscopy examination revealed normal optic nerve and retinae in both eyes. He had mild ptosis in both eyes. In addition, there was a diffuse limitation of eye movement (−1) in all directions. He had an exotropia of 10 PD in primary position, which increased to 18 PD at the extremes of gaze and 25 PD at 33 cm, as shown in Figure 2b. Neurological examination revealed diffusely reduced muscle bulk and evidence of bilateral temporal wasting. On cranial nerve exam, he had limited frontalis movement that could be due to impaired activation. There was no evidence of lower facial weakness or tongue atrophy. On motor exam, he had diffuse atrophy in both arms. He had at least antigravity strength in upper extremity muscles and normal hip movements. MRI of the brain was performed and this revealed diffuse and nearly symmetric and diffuse white matter signal alteration in both cerebral hemispheres in keeping with a leukodystrophy pattern, as shown in Figure 1b.

He underwent additional bloodwork that revealed anemia with a hemoglobin of 107 g/L (normal 135–175 g/L) and a deficiency in magnesium at 0.35 g/L (normal 0.70–1.00 g/L), calcium at 2.01 mmol/L (2.15–2.60 mmol/L), and a low albumin at 30 g/L (normal 35–50 g/L). Nutritional supplementation was initiated, and the patient worked with a dietician and gastrointestinal specialist.

Both brothers had a similar clinical history of longstanding gastrointestinal dysfunction, cachexia, ophthalmoplegia, asymptomatic leukodystrophy with the older sibling having a documented mixed axonal and demyelinating, sensory-motor peripheral neuropathy. Further questioning revealed that their parents shared the same first cousin and this made a genetically inherited condition very likely. Although the age of onset was older than typically seen, the clinical picture was characteristic of MNGIE and confirmatory genetic testing was performed. Both brothers were found to be carrying a homozygous mutation in the thymidine phosphorylase (TYMP) gene (formally known as ECGF1), c.647C>T, p.(Ala216Val), and their parents were both heterozygous. This mutation was predicted to be pathogenic and categorized as ACMG category 2. This homozygous mutation was previously reported in a patient with MNGIE syndrome [4].

Given that the nutritional and gastrointestinal symptoms were most prominent, both brothers worked closely with a dietician, gastrointestinal specialists, and genetics specialists. Given that their weight and overall symptoms were stable 1 year after diagnosis, the risks of hematopoietic stem cell transplantation were thought to outweigh the benefits. This was to be considered in the future should their symptoms worsen.

One year after diagnosis, both siblings remained stable with respect to their weight, neurological and ophthalmological symptoms. The older sibling was referred for strabismus surgery given that his diplopia continued to be bothersome. Both brothers have given their written informed consent to publish their case and images.

Discussion

MNGIE is a rare, mitochondrial genetic condition that is difficult to diagnose and often goes unrecognized. It is an autosomal recessive multisystem condition with a prevalence of 0.1 in 100,000 in the European population that predominantly affects mitochondrial DNA synthesis [5]. Although the pathophysiology of MNGIE involves dysfunction in the mitochondria, it results from a mutation in the TYMP gene, which is located in the nuclear genome on chromosome 22 and encodes thymidine phosphorylase [3]. Thymidine phosphorylase catalyzes the phosphorolysis of thymidine or deoxyuridine to thymine or uracil and deoxyribose-phosphate [3]. Dysfunction of thymidine phosphorylase leads to the accumulation of

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thymidine and deoxyuridine, creating an imbalance in the nucleotide pool required for mitochondrial DNA replication. This has an effect on post-mitotic tissues that continuously turn over mitochondria and replicate mitochondrial DNA but do not replicate nuclear DNA. The diagnosis of MNGIE can therefore be established by detection of biallelic pathogenic variants in TYMP, markedly reduced levels of thymidine phosphorylase activity, or elevated plasma levels of thymidine and deoxyuridine [3, 6].

MNGIE normally manifests between the first and second decade of life and presents with gastrointestinal dysfunction, excessive weight loss, ptosis, external ophthalmoplegia, peripheral neuropathy, and leukoencephalopathy on MRI [6]. Gastrointestinal symptoms include dysmotility, pain, discomfort, nausea, intestinal pseudo-obstruction, and bowel diverticulitis [7]. Histological findings of gastrointestinal samples of individuals with MNGIE show very large mitochondria, also known as "megamitochondria," and a depletion in mitochondrial DNA in smooth muscle cells and ganglion cells, possibly explaining the mechanism behind gut dysmotility [8]. MNGIE patients have a high demand for energy as ATP molecules are constantly being consumed by the dysfunctional mitochondria. This leads to excessive weight loss and weakness and wasting in muscles with high energy demand. These muscles primarily depend on oxidative phosphorylation to generate ATP for movement. Extraocular muscles are 1 such example that have a very high oxygen demand, explaining the occurrence of external ophthalmoplegia and ptosis in these patients [9]. The most common ocular findings of MNGIE are ophthalmoplegia and ptosis, which are present in essentially all patients at the time of diagnosis but are the first symptoms in only 22–41% of the cases [2, 10, 11]. A less common ocular finding of MNGIE is pigmentary retinopathy which is found in around 6% of patients [10]. Exotropia has been the only pattern of strabismus described in the literature. This is likely a result of the medial rectus muscle being more affected by mitochondrial dysfunction than the lateral rectus muscle [12]. The medial rectus muscle is bulkier and is more fatigable and is an early muscle involved in ocular myasthenia gravis [12]. Despite the high prevalence of ophthalmoplegia, many patients do not complain of diplopia [3, 7, 13]. However, a number of patients, including our cases, reported diplopia at the time of presentation [9]. Strabismus surgery has been shown to improve ophthalmoplegias that are due to mitochondrial disorders, but no systematic studies have investigated its effectiveness in MNGIE patients [14, 15]. A case report of a patient with MNGIE without diplopia showed improvement in external ophthalmoplegia after strabismus surgery [13]. Overall, the ophthalmoplegia and ptosis findings of MNGIE are similar to the chronic progressive external ophthalmoplegia seen in other mitochondrial disorders, such as maternally inherited Leigh syndrome, Kearns-Sayre syndrome, and mendelian progressive external ophthalmoplegia [16].

Distal paresthesia, weakness, and reduced nerve conduction velocities in motor and sensory neurons on electromyography are the most common neurological symptoms. However, the hallmark neurological symptom of MNGIE is leukoencephalopathy of the cerebral white matter on MRI which does not manifest in any symptoms [7]. Other less common symptoms that may occur include seizures, sensorineural hearing impairment, endocrine dysfunction, immunodeficiency, and cardiac manifestations such as prolonged QT interval, cardiac arrest, and supraventricular tachycardia [17].

Early diagnosis is important to avoid unnecessary investigations and treatment with respect to double vision, peripheral nerve symptoms, and gastrointestinal issues. Many MNGIE patients undergo unnecessary exploratory abdominal surgeries, such as laparotomies, before they are diagnosed, and this has associated risks from the procedure and risks associated with anesthesia [17]. Patients diagnosed with MNGIE should undergo nutritional and genetic counselling [3]. Similarly, both of our cases experienced gastrointestinal manifestations and cachexia before reaching the final diagnosis. They had extensive exploratory tests

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and surgeries done during this time which did not improve their condition. As MNGIE presents mostly in the first or second decade of life, the late presentation and diagnosis of the disease in our patients is worth noting [3]. Both of our cases developed their initial symptoms in their late 20s, demonstrating that MNGIE can manifest in older individuals. They had a milder form of the condition, which is a likely reason for their later presentation. Our first case was diagnosed after a referral for internuclear ophthalmoplegia and a misinterpretation of diffuse leukodystrophy as advanced multiple sclerosis. The diagnosis was established with genetic testing for the TYMP gene, which revealed a pathogenic homozygous mutation. The second case had similar symptoms as case 1 and after genetic testing was diagnosed with the same condition.

MNGIE is a progressive disease with a poor prognosis. In a previous study of 102 patients with MNGIE, the average age of death was 35 years (range 14–54 years) [18]. Causes of death included pneumonia due to aspiration, peritonitis from intestinal rupture, suicide, and electrolyte imbalance [18]. Prospects for therapy include reduction of thymidine and deoxyuridine plasma levels, which can theoretically be achieved through dialysis or decreasing the rate of renal reabsorption. The former was unsuccessful since plasma levels of the nucleosides returned to pre-dialysis levels a few hours later [19]. Additional treatment prospects include enzyme replacement through infusion of a stabilized thymidine phosphorylase enzyme, hematopoietic stem cell replacement from adult donors or cord blood, or gene therapy. The first attempts at gene therapy via allogeneic stem cell transplantation showed initial success in 1 patient; further long-term follow-up is necessary [19]. Hematopoietic stem cell transplantation has been shown to increase thymidine phosphorylase activity and reduce disease progression; however, there is a high change of complications associated with transplantation. Recently, liver transplantation has been shown in 4 patients to be promising in restoring thymidine phosphorylase levels and stopping the progression of MNGIE symptoms, but further studies are needed to assess the long-term benefits and complications [20].

In conclusion, MNGIE is a rare autosomal recessive disease that should be suspected in patients with a combination of chronic progressive external ophthalmoplegia, leukoencephalopathy, severe gastrointestinal dysmotility, and sensorimotor neuropathy. Treatment is aimed at symptomatic relief of double vision, nutritional counselling, and ongoing monitoring by gastroenterology specialists since gastrointestinal complications associated to cachexia are frequent causes of death in patients with MNGIE.

Statement of Ethics

This study complies with the guidelines for human studies and was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The subjects have given their written informed consent to publish their case and their images for publication.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.F. prepared the manuscript and gave final approval. C.D.K. prepared the manuscript and gave final approval. J.A.M. conceived and designed the study conception, prepared manuscript, and gave final approval.

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