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Mitochondrial Neuro-Gastrointestinal Encephalopathy (MNGIE), Index of Suspicion

Mona Faramawy[1], Najla Al Kuwaiti[1], Abdulla Al-Amri[2] and Amar Al Shibli[2]

[1]*Department of Academic Affairs/Pediatrics Resident, UAE*
[2]*Department of Pediatric Consultant, Tawam Hospital, Al Ain, UAE*

Abstract

Mitochondrial neuro-gastrointestinal encephalomyopathy (MNGIE), is an autosomal recessive disease, is one of the mitochondrial disorders, and is a multisystem disease clinically defined by progressive ophthalmoplegia, peripheral neuropathy, leukoencephalopathy, mitochondrial abnormalities and severe gastrointestinal involvement. Mitochondrial disorders have clinical manifestations reflecting the fact that nearly all organ systems utilize oxidative metabolism. Clinical features often involve tissues with high energy requirements such as central and peripheral nervous systems, and eye, muscle, kidney and endocrine organs.. To the best of our knowledge there is no case report of this syndrome from Middle East and since this presents with diagnostic difficulties so is being reported.

Keywords: Mitochondrial neurogastrointestinal encephalomyopathy; Intestinal pseudoobstruction

Introduction

Mitochondrial disorders have clinical manifestations reflecting the fact that nearly all organ systems utilize oxidative metabolism. Clinical features often involve tissues with high energy requirements such as central and peripheral nervous systems, and eye, muscle, kidney and endocrine organs [1,2]. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive multisystem disorder characterized by eye manifestation including external ophthalmoplegia and/or ptosis, progressive gastrointestinal dysmotility and abdominal pain, postprandial emesis, cachexia, demyelinating peripheral neuropathy, symmetrical and distal weakness more prominently affecting the lower extremities, and leukoencephalopathy [3,4]. MNGIE has also been reported to be particularly associated with Chronic Intestinal Pseudo-obstruction (CIP) along with other symptoms such as malnutrition [5].

Mitochondrial genetic defects should be considered in the differential diagnosis of unexplained chronic gastrointestinal symptoms accompanied by neurological findings [2]. The disease is caused by mutations in the gene encoding thymidine phosphorylase endothelial cell growth factor 1 (ECGF1) [3,4] leading to loss of activity of the enzyme [6]. TP is an important factor involved in the control and maintenance of the pyrimidine nucleoside pool of the cell [6,7]. Diagnosis is established by muscle biopsy. Mitochondrial changes in muscle fibers are mitochondrial proliferation (ragged red fibers) [8]. Due to bizarre symptomatology the diagnosis of this disease is often delayed [9]. This autosomal recessive disease is uncommon, with < 70 reported patients [10].

Diagnosing a case with MNGIE needs to have high index of suspicion as the disorder is rare and having heterogeneous presentation. Here, we are describing a case of MNGIE that was presented with multisystem presentations.

Case Report

We are reporting a case who presented at age of 8 years with recurrent abdominal distention with suspected intestinal pseudo obstruction along with severe failure to thrive and malnutrition. She also had Global developmental delay with Quadriplegic cerebral palsy and brain atrophy due to unknown etiology. She was having bilateral cataract, nystagmus associated with visual impairment along with hearing loss.

The patient was not able to tolerate any kind of feeding and used to develop abdominal distention and bowel dilatation with smallest amount of feeding. The patient was evaluated and followed by the gastroenterologist where she was diagnosed with chronic pseudo-obstruction due to absence of any evidence of mechanical obstruction (Figure 1).

There was electrolytes imbalance including hypocalcemia, hypomagnesemia, hypophosphatemia, hypokalemia, Vitamin D deficiency and hypoalbuminemia. Explorative laparotomy due to the suspicion of intestinal obstructions, ileostomy and gastrostomy were performed yet the patient didn't tolerate enteral feeding and currently she is depended on the total parenteral nutrition (TPN). She was born at 7 month gestation by vaginal delivery with birth weight 2.08 Kg with no known perinatal complications including asphyxia. Serology during pregnancy were all negative. Since the age of 6 months she started to progressively show signs of global developmental delay and poor visual fixation. Neurologically, she had features suggestive of early spastic cerebral palsy. There were no dysmorphic features apart from flat occipital and short upper segment of arms and legs. Parents were cousins. There was no family history of deaths or chronic diseases. MRI brain showed decrease in the periventricular white matter and atrophy of frontal and parietal lobes. This clinical picture was highly suggestive MNGIE disease caused by TYMP mutation. Genetic study was done and mtDNA isolated from fibrobalst was screened after having the family consent. A rare sequence variation was found (Figure 2).

Discussion

Mitochondrial neurogastrointestinal encephalomyopathy is a rare autosomal recessive multisystem disorder. At present, 87 sporadic or familial cases have been reported and 52 different mutations identified [11]. It is associated with multiple deletions and depletion of mtDNA in skeletal muscle [2,12,13].The major clinical finding in our case was the chronic intestinal pseudo-obstruction. This presentation was also noted to be the major finding in MNGIE cases reported by Coşkun et al. [2] and Yaflar et al. [4] from Turkey. Another study from Paris

***Corresponding author:** Mona Faramawy, Department of Academic Affairs/ Pediatrics Resident, UAE, Tel: +971 3 767 7444; E-mail: mfaramawy@seha.ae

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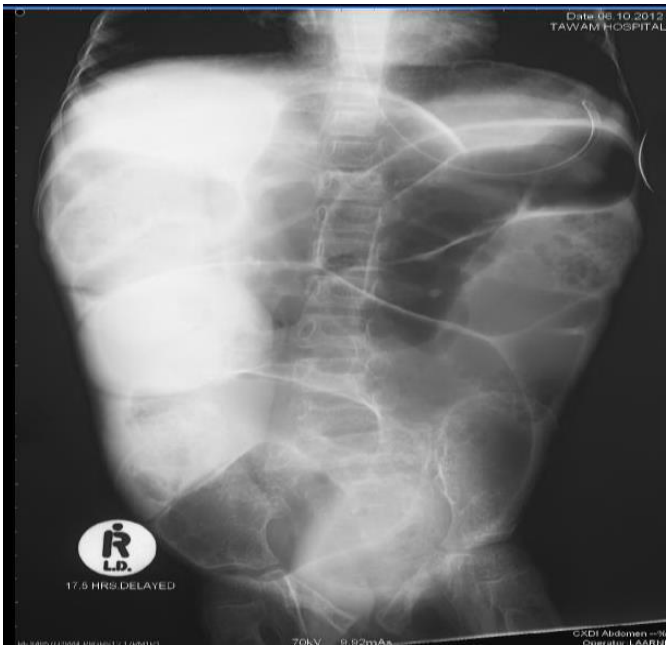
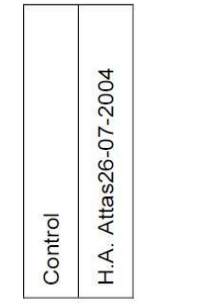


Figure 1: Barium follow through showing no evidence of mechanical obstruction with dilatation of the loops.



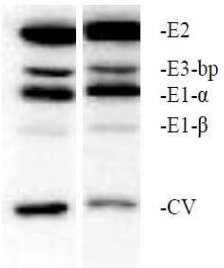


Figure 2: Result of the pyruvate dehydrogenase complex Westren Blot diagnostics M12/0488.

[14], reported that chronic intestinal pseudo obstruction (CIPO) with neurological symptoms was found in 3 cases defining complete MNGIE syndrome. Visceral involvement in MNGIE may be myogenic, neurogenic, or both, even if myogenic involvement appeared to be more frequent. The visceral myo-neuropathy is directly related to mitochondrial dysfunction in the gut. Thus, systemic treatments which restore normal mitochondrial functions, or which more specifically lower thymidine plasma level, might be theoretically effective for improving digestive symptoms in MNGIE [14]. To date, the basis of the management of severe CIPO syndrome remains the classical association of prokinetic drugs and home parenteral nutrition [14] however, although our patient was started on prokinetics she did not show any signs of improvement in regards to her CIPO and she ended being TPN dependent.

In Regards to neurological examination, all individuals with MNGIE disease have peripheral neuropathy. In some, the first symptoms are paresthesias and weakness. The weakness is usually symmetrical and distal [12]. The most common neurological features of MNGIE are peripheral neuropathy, ptosis, ophthalmoparesis and hearing loss [3]. As indicated in several cases, neuropathy was clinically mild, and this was the case in our patient as well, While EMG - conduction velocities for our patient on both lower and right upper extremities were within Normal for age and the compound muscle action potential (CMAPs) were also within normal for age; however the amplitudes were relatively diminished in both peroneal and ulnar nerves. There was no evidence of demyelinating process. But the Relatively low amplitudes in the peroneal and ulnar nerve were suggestive of axonal problem. On the other hand, our patient was suffering from severe neurological impairment in a form of Quadriplegic Cerebral Palsy with brain atrophy along with Microcephaly that was not explained by any antenatal or perinatal CNS insult as she had uneventful antenatal course and further investigations after birth were unremarkable including TORCH screening that was negative, such severe form of neurological defect was not commonly described in published cases and literature.

MRI of our index case was evident of mild decrease in the periventricular white matter proving the leukoencephalopathy which fits the characteristics of those reported by Nishino et al. [15]. Cranial nerve involvement in MNGIE usually takes the form of ophthalmoplegia and sensorineural hearing impairment [16]. Blindness and bilateral cataract were the main ocular involvement in our patient and an audiology examination of the patient showed sensorineural hearing impairment.

Conclusion

Mitochondreal Neuro-Gastro Intestinal Encephalopathy is a very rare mitochondrial disorder. Difficult to be diagnosed clinically unless keeping high index of suspicion. Clinicians need to be aware of this rare clinical situation in a setting of intestinal pseudo obstruction and neurological abnormalities in order to manage effectively.

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