



Mitochondrial Neurogastrointestinal Encephalopathy (MNGIE) Disease: a case Report of a rare Autosomal Recessive Inheritance with a poor Prognosis

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ABSTRACT

Mitochondrial Neurogastrointestinal Encephalopathy Disease; Synonyms: MNGIE Syndrome, Mitochondrial Neurogastrointestinal Encephalopathy Syndrome, Myoneurogastrointestinal Encephalopathy Syndrome, Thymidine Phosphorylase Deficiency; is characterized by progressive gastrointestinal dysmotility and cachexia manifesting as early satiety, nausea, dysphagia, gastroesophageal reflux, postprandial emesis, episodic abdominal pain and/or distention, and diarrhea; ptosis/ophthalmoplegia or ophthalmoparesis; hearing loss; and demyelinating peripheral neuropathy manifesting as paresthesias. The clinical diagnosis of MNGIE disease is based on the presence of severe gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoplegia, sensorimotor neuropathy, asymptomatic leukoencephalopathy as observed on brain MRI, and family history consistent with autosomal recessive inheritance. Management is supportive and includes attention to swallowing difficulties and airway protection; dromperidone for nausea and vomiting; celiac plexus block with bupivacaine to reduce pain; bolus feedings, gastrostomy, and parenteral feeding for nutritional support; antibiotics for intestinal bacterial overgrowth; morphine, amitriptyline, gabapentin, and phenytoin for neuropathic symptoms; specialized schooling arrangements; and physical and occupational therapy.

Keywords: MNGIE - dysmotility – Syndrome – vomiting – Myoneurogastrointestinal.



Case Illustration

Twenty five years old male, born and living in the New Valley Governorate, single, worker in a restaurant, with no special habits of medical importance. His complaint is colicky abdominal pain and weight loss. The condition started 2 years ago with gradual onset, progressive course in the form of diffuse abdominal pain, colicky in nature, not radiating, increased by meals “any type of meals” and relieved by self induced vomiting of semi digested food following meals by 30-60 minutes. There is associated constipation “1 motion every 3 days” with passage of small amount of hard stools not associated with blood, mucous, or tenesmus. The condition was associated with loss of weight about 20Kg; with loss of appetite. Year later the patient began to feel numbness and tingling sensation affecting both hands and feet of gradual onset, progressive course associated with unsteady gait “sensation of walking on cotton” with no observed motor weakness, or other neurological

symptoms. Patient sought medical advice repeatedly in which medical treatment in the form of antispasmodics for abdominal pain and multi vitamins, Carbamazepine “200mg/day for 6 months” for neurological symptoms were prescribed with no improvement of condition. The patient was referred to our department. The condition was not associated with other GIT manifestations, fever, perception of body masses or symptoms suggestive of other system affection. Regarding his family history there was no similar condition in the family with negative consanguinity.

Examination:

The patient is fully conscious, normal vital signs, under built, BMI (16.8) kg/m², well oriented to time, place and persons, cooperative, with no special decubitus, waddling gait. He is a febrile all through hospital stay. Head and neck revealed cachectic face with prominent zygomatic bones,

posed eyelids without squint. No pallor, jaundice or cyanosis. Neck veins are not congested. Equal carotid pulsations on both sides with no audible bruit. No thyroid or parotid swellings. Central trachea No lymphadenopathy. Oral examination showed red glazed tongue, angular stomatitis, no telangectasia, pigmentations, gum bleeding, hypertrophy, or oral ulcers. Neurological examination showed ptosis with no other cranial nerve affection. Wasted muscles of both upper and lower limbs. Grade 4/5 motor power. Hypotonia, hyporeflexia affecting both proximal and distal muscles with absent pathological reflexes or sphincteric affection. Sensation and coordination examination revealed glove and stock hypoesthesia. Positive Romberg test with loss of vibration sense. Abdominal examination represents scaphoid abdomen with no organomegaly or ascites. There is increased intestinal sounds (15-20) /min. Free PR examination. No symptoms suggestive other systems affection.

Laboratory work up: Urine and stools repeated were free. Hb was 10.4 g/dl and CBC revealed

moderate normocytic normochromic anemia RBC's show anisopoikilocytosis. ESR first hour was: 30CRP was negative.

Biochemical profile showed no abnormality apart from low total proteins which were 5.1 g/dl as well as low albumin 3.1 g/dl. LDH was 223 U/L and normally it is up to 247. Blood electrolytes, fasting blood sugar and Coagulation profiles normal were all within the normal ranges.

Abdominal ultrasonography predicts that the stomach, small intestine is seen dilated with normal wall thickness and preserved wall layering pattern. The small bowel loops show increased diameter of 2 cm, increased peristalsis, with normal wall thickness. There is mild thickening of the terminal ileum of 0.5 cm with preserved wall layering pattern with minimal inter bowel fluid. There was extensive mesenteric adenopathy. The nodes are oblong isoechoic the largest is 2.5*1 cmes (photos 1&2).

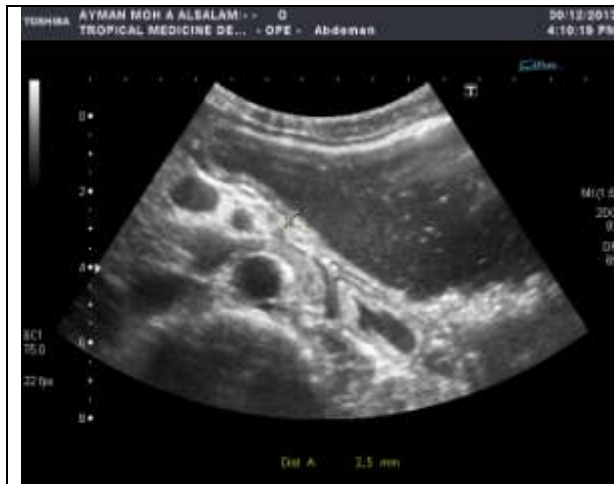


Photo (1): US dilatation of the stomach



Photo (2): US dilatation of the intestine with interbowel fluid

CT abdomen and pelvis revealed minimal ascites otherwise Normal CT appearance of the abdomen and pelvis.

Upper endoscopy with gastric and duodenal biopsies revealed grade B reflux esophagitis with atrophic gastric and duodenal mucosa with signs of inflammation. Histopathological examination showed mild chronic active gastritis associated with H.Pylori, moderate chronic non specific duodenitis with no malignancy.

CT enterography detected diffuse thickening enhanced bowel walls mainly small bowel, they are seen matted together with no clear mesenteric fat planes in between. Associated omental thickening is noted. Multiple subcentimetric mesenteric LNs are seen. Picture is impressive of inflammatory etiology, IBD or TB enteritis should be considered (photo 3).

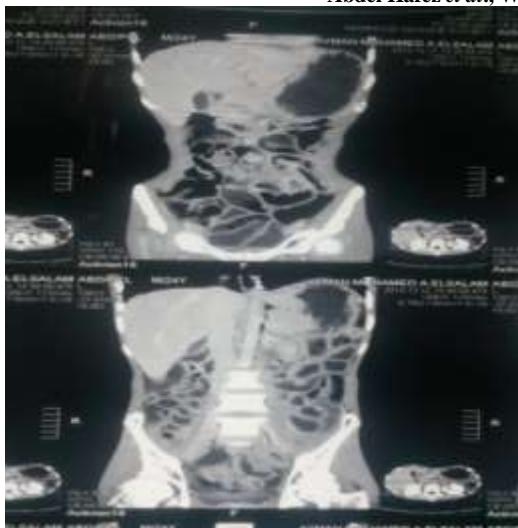


Photo (3): CT enterography revealed dilatation of the GIT with inter bowel fluid

Colonoscopy: Done up to terminal ileum. Tight ileocecal valve passed with difficulty with normal looking mucosa of the terminal ileum with no other abnormality detected.

Work up for TB as ADA in ascitic fluid, examination for acid fast bacilli; CT Chest and Tuberculin test all were negative.

Work up for Crohn's disease: ANCA-C; ANCA-P; ASCA all were negative.

Work up for lymphoma: B2 Microglobulin and LDH were negative.

LN biopsy from intra-abdominal LN: revealed no evidence of TB; Crohn's or lymphoma.

Diagnostic analysis of 20 cc of ascitic fluid: concluded that it is transudate and bacteriologically free.

Surgical consultation decided resection of the ileal stricture. So the operation was done and reported presence of ileal stricture with bowel loops dilated behind. Excision of terminal ileum with ileocolic anastomosis was done.

Ileal biopsy: showed

Gross appearance: Ileal segment 19 cm along with attached cecal segment 4*4 cm. Ileal end circumference was 3.5 cm ileal mucosa showed no gross abnormalities and ileocecal valve mucosa was mamillated. Grayish white tan lobulated firm swelling measured 2.5*2.5

Microscopic examination concluded Ileocecal valve serosal adhesions, Ileocolic lymphoid hyperplasia. Sections from the LNS revealed reactive follicular hyperplasia with no evidence of specific infection or malignancy.

After operation : There is no improvement of symptoms despite removal of the stricture. Patient still hypokalemic. Neurological manifestations

remain the same despite B12 replacement. At this time suspicion of Ogilvie syndrome, Hirschsprung's disease or Intestinal hypogangliosis was raised so revision of ileal slides for functional causes was done and revealed normal ganglia pattern, no evidence of functional obstruction and the outer longitudinal muscle fibers are replaced by fibrous tissue in some areas.

Follow up ultrasound: There is dilation of the stomach, duodenum, and small bowel down to the pelvis.

The bowel loops have increased diameter of 2cm width, normal wall thickness with excessive peristalsis. Small amount of inter bowel fluid is seen with extensive adhesions within.

Barium meal follows through revealed delayed emptying of the stomach with excess gastric secretions. Dilated duodenal loops with effacement and lost mucosal pattern.

All the small bowel loops are seen dilated with loss of the normal mucosal pattern and excess intestinal secretions with flocculation of the contrast media. No evidence of the intestinal obstruction or adhesions.

These findings are of diffuse small bowel inflammatory process which could be atypical Crohn's or infiltrative disease as amyloidosis or collagen disease (photo 4).

MR Enterography: represented dilated stomach, duodenum, most of the small bowel loops with mesenteric thickening, adhesions, lymphadenopathy and reduced caliber of small bowel segments associated with mild ascites with the possibility of underlying inflammatory condition are to be considered (photo 5).



Photo (4): BMFT revealed all the small bowel loops are seen dilated with loss of the normal mucosal pattern.

Photo (5): MR Enterography revealed dilated stomach, duodenum, most of the small bowel loops with mesenteric thickening.

Reconsultation for full neurological reassessment raised the possibility of *mitochondrial neuro gastrointestinal encephalopathy* (MNGIE) disease which is a rare disease, so asked for nerve conduction study and EMG as well as MRI brain with contrast.

Nerve conduction test and EMG showed sensorimotor polyneuropathy affecting the lower limbs more than upper limbs.

MRI brain with contrast revealed bilateral diffuse cerebral and cerebellar as well as brain stem white matter disease with small right occipital encephalomalacia and bilateral basal ganglia lesions. The possibility of mitochondrial disease is considered for further clinical correlation.

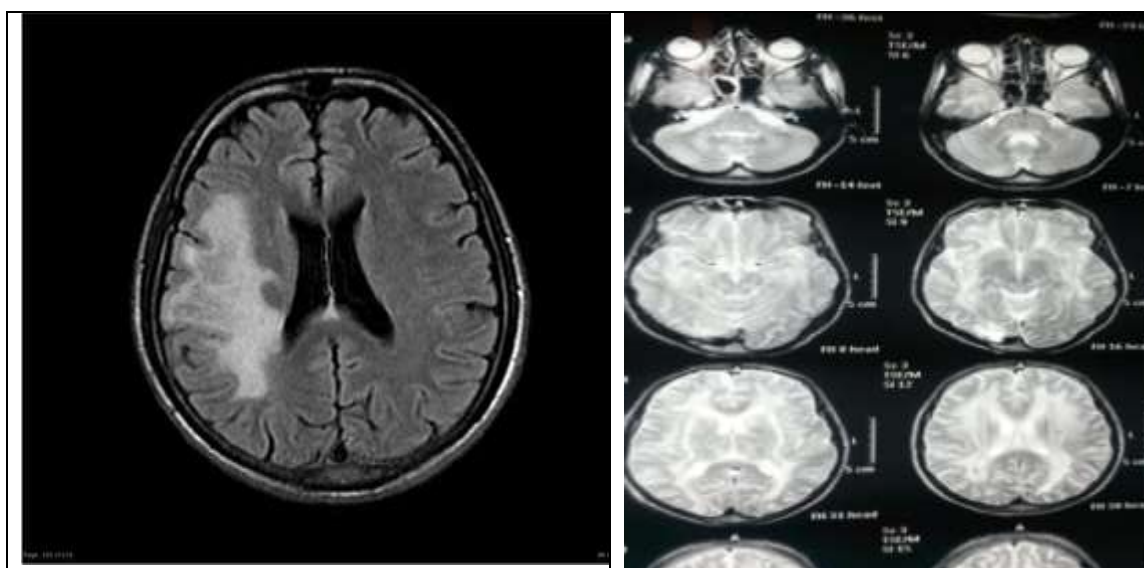


Photo (6): MRI brain with contrast revealed bilateral diffuse and symmetrical cerebral and cerebellar white matter abnormal high T2 and FLAIR signal.

So we are confronted with a case of MENGI. The patient received symptomatic and supportive treatment and he is better now after improving his nutritional status through PEPTAMEN Nestle which is nutritive formula

DISCUSSION

Our patient is 25 years old male with generalized colicky abdominal pain. Vomiting “induced”, Loss of weight 20 kg. Constipation with neurological manifestations. The possibility of gastric outlet obstruction, Crohn’s disease, Lymphoma, Intestinal Tuberculosis or Celiac disease was raised. All were exclude through the different imaging procedures, endoscopies, biopsies and complete laboratory assessment. Surgical interference was not improving the condition. So that we thought about the MNGIE disease which is a rare disease affecting fewer than 70 cases that have been reported [1]. There is an estimated incidence of one in 4,000 live births suffering from mitochondrial diseases [2].

The clinical diagnosis of MNGIE disease is based on the presence of severe gastrointestinal dysmotility, cachexia, ptosis, external ophthalmoplegia, sensorimotor neuropathy, asymptomatic leukoencephalopathy as observed on brain MRI [3], and family history consistent with autosomal recessive inheritance [4]. Direct evidence of MNGIE disease is provided by increase in plasma thymidine concentration greater than 3 $\mu\text{mol/L}$ and increase in plasma deoxyuridine concentration greater than 5 $\mu\text{mol/L}$. Thymidine phosphorylase enzyme activity in leukocytes is less than 10% of the control mean [5]. Molecular genetic testing of TYMP, the gene encoding thymidine phosphorylase, detects mutations in

approximately 100% of affected individuals [6]. Management is supportive and includes attention to swallowing difficulties and airway protection; dromperidone for nausea and vomiting; celiac plexus block with bupivacaine to reduce pain; bolus feedings, gastrostomy, and parenteral feeding for nutritional support; antibiotics for intestinal bacterial overgrowth; morphine, amitriptyline, gabapentin, and phenytoin for neuropathic symptoms; specialized schooling arrangements; and physical and occupational therapy [7].

Conclusions

MNGIE disease is inherited in a rare autosomal recessive manner with a poor prognosis. Fewer than 70 cases have been reported. No ethnic prevalence for MNGIE disease has been observed. Gestation and delivery are normal. The earliest reported age of onset is five months. Onset is between the first and fifth decades. No specific management, only we can manage its manifestations with prevention of secondary complications such as attention to swallowing abnormalities and diverticulosis. Medications that are primarily metabolized in the liver should be used with caution. Possible future treatments include decreasing plasma thymidine concentration by reducing renal reabsorption of thymidine (i.e., blocking the Na⁺/thymidine transporter), by dialysis, and by enzyme replacement therapy (ERT).

REFERENCES

1. Moran NF, Bain MD, Muqit MM, Bax BE. Carrier erythrocyte entrapped thymidine phosphorylase therapy for MNGIE. *Neurology*. 2008; 71:686–8.
2. Driessen JJ. Neuromuscular and mitochondrial disorders: what is relevant to the anaesthesiologist? *Curr Opin Anaesthesiol*. 2008; 21 (3):350-355.
3. Finsterer J. Mitochondrial disorders, cognitive impairment and dementia. *J Neurol Sci*. 2009; 283:143–8.
4. Nishino I, Spinazzola A, Papadimitriou A, Hammans S, Steiner I, Hahn CD, Connolly AM, Verloes A, Guimaraes J, Maillard I, Hamano H, Donati MA, Semrad CE, Russell JA, Andreu AL, Hadjigeorgiou GM, Vu TH, Tadesse S, Nygaard TG, Nonaka I, Hirano I, Bonilla E, Rowland LP, DiMauro S, Hirano M. Mitochondrial neurogastrointestinalencephalomyopathy: an autosomal recessive disorder due to thymidine phosphorylase mutations. *Ann Neurol*. 2000; 47:792–800.
5. Valentino ML, Martí R, Tadesse S, López LC, Manes JL, Lyzak J, Hahn A, Carelli V, Hirano M. Thymidine and deoxyuridine accumulate in tissues of patients with mitochondrial neurogastrointestinalencephalomyopathy (MNGIE). *FEBS Lett*. 2007; 581:3410–4.
6. Nishigaki Y, Marti R, Copeland WC, Hirano M. Site-specific somatic mitochondrial DNA point mutations in patients with thymidine phosphorylase deficiency. *J Clin Invest*. 2003; 111:1913–21.
7. Zimmer V, Feiden W, Becker G, Zimmer A, Reith W, Raedle J, Lammert F, Zeuzem S, Hirano M, Menges M. Absence of the interstitial cell of Cajal network in mitochondrial neurogastrointestinalencephalomyopathy. *Neurogastroenterol Motil*. 2009; 21:627–31.