ORIGINAL RESEARCH PAPER

Paediatric Medicine

KEY WORDS: Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE); intestinal pseudo-obstruction, ptosis, leukoencephalopathy.

A CASE REPORT OF INTESTINAL PSEUDO-OBSTRUCTION WITH BILATERAL PTOSIS AND LEUCOENCEPHALOPATHY

Dr Papiya Khawash MD(Paediatrics), MRCP, UK

Dr Adrita Khawash* DNB (Paediatrics), Post-graduate Trainee *Corresponding Author

ABSTRACT

Intestinal pseudo-obstructive symptoms, bilateral ptosis and ophthalmoplegia with leukoencephalopathy presenting in childhood are indicative of a multisystem disorder. A condition that can present with this symptom complex is MNGIE syndrome or mitochondrial neurogastrointestinal encephalomyopathy, a rare autosomal recessive disorder of mitochondrial function. Leukoencephalopathy is a hallmark of MNGIE syndrome and was present in all reported cases along with gastrointestinal dysmotility due to progressive degeneration of the muscles of the gastrointestinal tract, weakness of extra-ocular muscles causing ptosis and ophthalmoparesis, peripheral neuropathy and cachexia. Frequent misdiagnoses have been reported and in those patients presenting with ptosis and ophthalmoplegia, it has reportedly been diagnosed and treated initially as myasthenia gravis. Here we present the case of a 5 year old boy presenting with intestinal pseudo-obstruction, bilateral ptosis, myopathic facies, easy fatigability and leukoencephalopathic changes in brain MRI.

INTRODUCTION-

Intestinal pseudoobstruction and neuro-ophthalmologic abnormalities including ptosis with ophthalmoplegia and leukoencepalopathy presenting in early childhood are indicative of a multisystem disorder. Mitochondrial neurogastrointestinal encephalomyopathy or MNGIE syndrome, a rare autosomal recessive disorder in mitochondrial function, can present with this symptom complex; however, marked delay in diagnosis is common (1).

CASE DISCUSSION-

A 51/2 year old boy was admitted with complaints of vomiting, dehydration and non-passage of stool for 6 days. Abdominal examination showed hard elongated pipe-like faecal mass which was confirmed on ultrasonography. After correction of his dehydration he was given a bowel wash after rectal suppositories failed to remove impacted stool. Patient was also noted to have bilateral ptosis and 'tented' upper lip, characteristics of myopathic facies. He was born preterm (32 weeks) with low birth-weight (1.2 Kg). Past medical history revealed progressively worsening constipation and easy fatigability. There was no significant family history.

His routine blood tests including electrolytes, thyroid function test and serum creatinine phosphokinase (CPK) were normal. Nerve conduction velocity and repeated nerve stimulation tests were normal. Anti-acetylcholine receptor antibody was absent. CT chest was normal with no thymic mass. A bedside ice-pack test was done and based on clinical suspicion of juvenile myasthenia gravis, he was started on oral pyridostigmine. The ptosis improved but he developed convergent squint and generalized muscle weakness. Oral Prednisolone was started with significant clinical improvement of ptosis, muscle weakness and constipation. MRI of brain showed bilaterally symmetrical hyperintense lesions (on long TR images) involving cerebellar dentate nuclei, mid brain and basal ganglia. Signal change was also seen in diffusion weighted imaging but no obvious restricted diffusion (vide figure 1). MRI features were suggestive of a congenital metabolic disorder. The possibility of MNGIE disease was considered based on gastrointestinal and neurological symptoms and MRI findings but genetic testing was unfortunately not available. In view of clinical improvement, he was discharged home and was asked to follow-up regularly as out-patient.

He continued to be well on subsequent follow-ups but was readmitted after three months with vomiting, constipation for 7 days and repeated convulsions. His mother gave a history of recent rapid loss of previously achieved developmental milestones. He had external opthalmoplegia and generalized progressive muscle weakness. He developed intractable seizures on admission and required sedation and ventilator support. EEG was abnormal and suggestive of diffuse cerebral dysfunction. MRI brain showed abnormal T2/Flair hyperintensity bilaterally at striatum, substantia nigra, periaqueductal gray area and both dentate nucleus with asymmetrical involvement of inferior olivary nucleus. Patchy areas of diffusion restriction were noted bilaterally at striatum, dentate nuclei and central tegmental tract (vide figure 2). These MRI features which had markedly deteriorated were suggestive of mitochondrial leukoence phalopathy. Clinically the patient continued to deteriorate on ventilator support and expired within 48 hours of readmission.

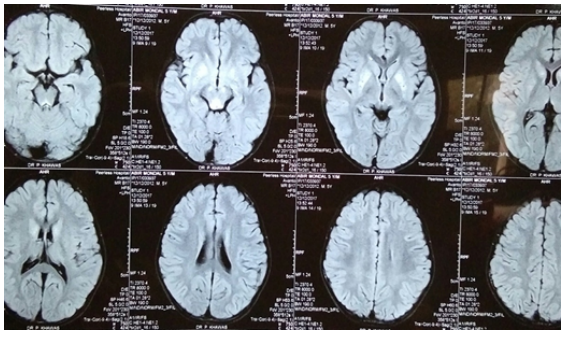

Figure 1 – MRI brain showing initial leucoence phalopathic changes.

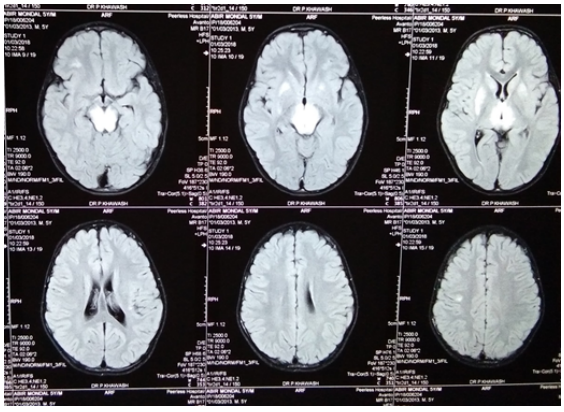

Figure 2 – MRI brain showing later leucoencephalopathic changes.

DISCUSSION –

The symptom complex of intestinal pseudo-obstruction and neuro-ophthalmological features of bilateral ptosis and MRI findings of this case are suggestive of MNGIE syndrome. Classically, MNGIE affects mainly the gastrointestinal and nervous systems causing intestinal dysmotility, pseudoob struction, cachexia and neuro-ophthalmologic abnormalities including ptosis, ophthalmoplegia, peripheral neuropathy and leukoencephalopathy(2,3). However, MNGIE patients with incomplete or atypical clinical presentations have been described and frequent misdiagnoses of the condition have been reported (4,5). In a patient presenting with ptosis and ophthalmoplegia, it has reportedly been initially diagnosed and treated as myasthenia gravis(6,7); similar to the case under discussion.

MNGIE is an autosomal recessive disorder of mitochondrial function due to TYMP gene mutations that cause loss of thymidine phosphorylase activity resulting in marked elevation of thymidine and deoxyuridine levels, nucleotide pool imbalance, subsequent instability of mitochondrial DNA (mtDNA) and impairment of the mitochondrial respiratory chain (8). It is an extremely rare disorder affecting males and females equally. The prevalence is unknown. More than 120 individuals with features consistent with MNGIE disease has been reported since it was first described (9). Patients develop symptoms at a mean age of 18 years with disease onset ranging from five months to more than 50 years of age. The disease course is relentlessly progressive leading to death at a mean age of 35 years (2).

Leukoencephalopathy is a hallmark of MNGIE, so far reported in all patients (2,4). Brain MRI usually shows symmetric and confluent T2-hyperintensity in white matter of semioval centres with sparing of subcortical U-fibres, and sometimes in cerebellar white matter, splenium of corpus callosum, basal ganglia and thalami (4,10). In mitochondrial disorders a correlation between brain imaging and genotype and/or biochemical findings can be difficult to demonstrate (11). The clinical presentation may be disproportionate to the extent of white matter involvement and the extension and distribution of leukoencephalopathy do not clearly correlate with age and clinical picture, hence are not considered reliable markers of disease severity in MNGIE (4).

MNGIE is a devastating progressive disease that leads inevitably to death if not treated. Apart from symptomatic and supportive care, therapeutic approaches including dialysis and enzyme replacement therapy (ERT) have been tried with transient improvement. Allogeneic hematopoietic stem cell transplantation and Orthotopic liver transplantation can restore normal enzyme activity but are associated with transplant-related complications. Other potential therapeutic approaches include adeno-associated viral vector and hematopoietic stem-cell gene therapy (12).

REFERENCES-

1. Teitelbaum, J. E.; Berde, C. B.; Nurko, S.; Buonomo, C.; Perez-Atayde, A. R.; Fox, V. L. Diagnosis and Management of MNGIE Syndrome in Children: Case Report and Review of the Literature. Journal of Pediatric Gastroenterology and Nutrition: September 2002 - Volume 35 - Issue 3 - p 377-383.
2. Garone C, Tadesse S, Hirano M. Clinical and genetic spectrum of mitochondrial neurogastrointestinal encephalomyopathy. Brain. 2011;134:3326–3332.
3. Hirano M, Nishigaki Y, Martí R. Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE): a disease of two genomes. Neurologist. 2004;10:8–17.
4. Scarpelli M, Ricciardi GK, Beltramello A, et al. The Role of Brain MRI in Mitochondrial Neurogastrointestinal Encephalomyopathy. The neuroradiology journal. 2013;26(5):520- 530.
5. Filosto M, Scarpelli M, Tonin P, et al. Pitfalls in diagnosing mitochondrial neurogastrointestinal encephalomyopathy. J Inherit Metab Dis. 2011;34:1199–1203.
6. Malcolm Kevin Baker, Clara Maria Schutte, Neelay Ranchhod, David Brittain, J E van Rensburg. Transient clinical improvement of a mitochondrial neurogastrointestinal encephalomyopathy-like syndrome after allogeneic haematopoietic stem cell transplantation. BMJ Case Reports 2017: doi:10.1136/bcr-2016-218276.
7. Thomas P.Chapman, Gina Hadley, Carl Fratter, Sue N. Cullen, Bridget E. Bax, Murray D. Bain, Robert A. Sapsford, Joanna Poulton, Simon P. Travis. Unexplained gastrointestinal symptoms: think mitochondrial disease. Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, ISSN: 1878-3562, Vol: 46, Issue: 1, Page: 1-8. Publication Year:2014. https://doi.org/10.1016/j.dld.2013.04.008
8. Nishino I, Spinazzola A, Hirano M. Thymidine phosphorylase gene mutations in MNGIE, a human mitochondrial disorder. Science. 1999; 283:689–692.
9. Hirano M. Mitochondrial Neurogastrointestinal Encephalopathy Disease. 2005 Apr 22 [Updated 2016 Jan 14]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993- 2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1179/
10. Barragán-Campos HM, Vallée J, Lô D, et al. Brain magnetic resonance imaging findings in patients with mitochondrial cytopathies. Arch Neurol. 2005;62:737–742.
11. Diogo L, Cordeiro M, Garcia P, et al. Value of brain magnetic resonance imaging in mitochondrial respiratory chain disorders. Pediatr Neurol. 2010;42:196–200.
12. Yadak R, Sillevis Smitt P, van Gisbergen MW, van Til NP, de Coo IF. Mitochondrial neurogastrointestinal encephalomyopathy caused by thymidine phosphorylase enzyme deficiency: from pathogenesis to emerging therapeutic options. Frontiers in cellular neuroscience. 2017 Feb 15;11:31.