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# A complex case of mitochondrial disease in a 7-year-old child

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## Introduction

Mitochondrial diseases are a rare but important cause of human illness. Only about 18 cases are reported from the Southeast Asia region, hence it is difficult to determine the true burden of the disease (1). Estimated prevalence of mitochondrial disease is 1 : 10000 and a further 1:200 at risk of being mutation carriers (2). These disorders result from mutations in both the nuclear DNA and the mitochondrial DNA (mtDNA). Its phenotypic spectrum largely depends on the altered oxidative phosphorylation pathways, resulting from defective proteins and their functions due to the said mutations (3).

mtDNA has distinctive features setting it apart from nuclear DNA (nDNA). It has a genetic code which differs from nDNA, has information tightly packed with no introns, subject to spontaneous mutations at a higher rate than nDNA with less efficient repair mechanisms. It is also inherited maternally *i.e.* non-mendelian. It also displays heteroplasmy and threshold effects in which each cell has a chance of getting either normal, mixed or mutant genes and a critical number of mutant genomes should be passed to express the disease (6).

Therefore, management of a patient with mitochondrial disease varies and case specific. In this case report we discuss a complex case of mitochondrial disease in a young child.

## Case presentation

A 7-year-old, male, third-child of non-consanguineous healthy parents, who is being followed up for neurodevelopmental regression for the past 1 year, presented with feeding difficulties over 3 days and respiratory distress progressively worsening over 2 days and a status epilepticus which lasted 2 hours till medically intervened.

Being well until 2 years back, he initially presented at the age of 5 with progressive difficulty in walking with a left lower limb weakness, which gradually deteriorated to involve all 4 limbs over next 2 months. He developed vomiting, swallowing difficulties, excessive sleepiness, emotional lability and generalized seizures and episodic headaches; associated with developmental regression of all developmental domains. His growth parameters revealed height, weight and body mass index less than 3$^{rd}$ centile with head circumference at the 10$^{th}$ centile for age (Figure 1 & 2).

On examination, he was drowsy with a Glasgow Coma Scale of 8 (E-3, M-4. V-1); was in respiratory distress having a respiratory rate of 46/min with intercostal and subcostal recessions and deep laboured breathing with equal air entry and no added sounds. Abdomen and Cardiovascular examination were clinically normal except for a high blood pressure of 130/90 mmHg (more than 99$^{th}$ centile for age). Neurological examination of the limbs revealed a generalized hypotonia with wasting, normal reflexes and power of 2 with bilateral foot drop, down going plantars without clonus. Cranial nerves, cerebellum and higher functions were unable to be examined. Fundoscopy revealed peripheral retinal degeneration and features suggestive of retinitis pigmentosa.

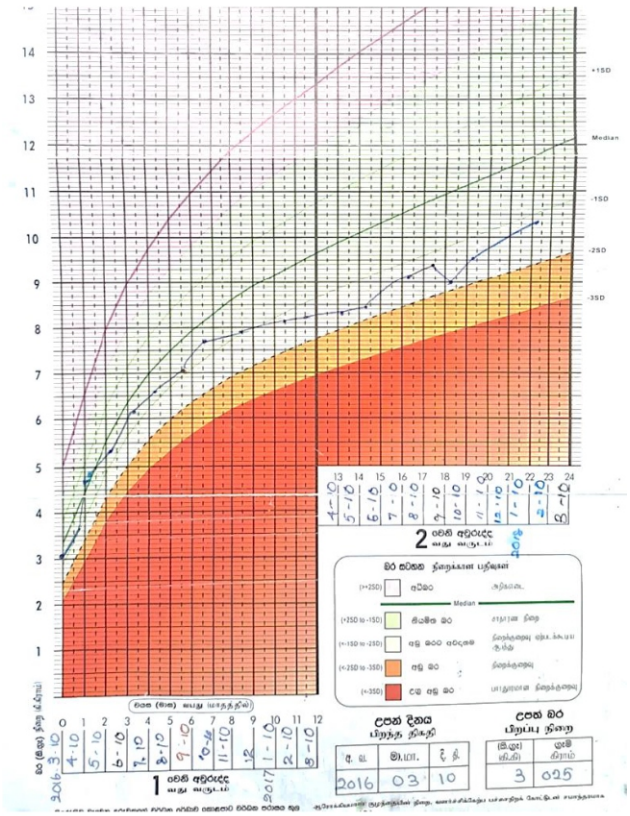

**Figure 1:** Child's development record - first 2 years of life

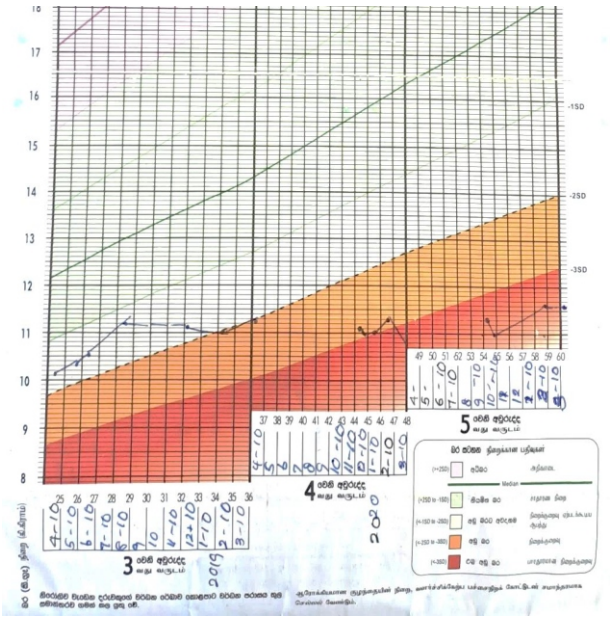

**Figure 2:** Child's development record - first 3rd to 5th year of life

His full blood count revealed white cell count of $14.65x10^3/\mu l$ (Ref. 4.5-13.5 $x10^3$) with 54% (Ref. 40-70%) neutrophils and 30% (Ref. 25 - 50%) lymphocytes with hemoglobin of 12.4 g/dL (Ref. 11.5-15.5) and platelet count of 288,000/$mm^3$ (Ref.150,000 - 450,000). Blood picture showed only occasional macrocytes with no abnormal cells. Bone marrow aspiration showed normocellular reactive marrow. Both erythrocyte sedimentation rate and C-Reactive Protein were normal. Serum $Na^+$, $K^+$, $Ca^{2+}$, $Mg^{2+}$ and $PO_4^{3-}$ were normal. He had a random blood sugar of 62 mg/dL (normal <140) and fasting blood sugar of 50 mg/dL (Ref.70 - 99).

Venous blood gas during the acute state showed a pH of 7.01 (Ref. 7.32 - 7.43) with $pCO_2$ of 20 mmHg (Ref. 40 - 50), $HCO_3^-$ of 7 mEq/L (Ref. 22 - 26) with markedly high lactate level of 17.7 mmol/L (Ref. 0.5 - 2.3) indicative of severe lactic acidosis.

He had normal liver functions including a aspartate transaminase level of 32 U/L (Ref. 15 - 40), alanine transaminase 35 U/L (Ref. 10 - 35), alkaline phosphatase 125 U/L (Ref. 130 - 560), serum bilirubin 4 µmol/L (Ref. 3 - 17), gamma glutamyl transferase 24 U/L (Ref. 5 - 25) and total protein level of 74 g/L (Ref. 60 -80) with normal albumin and globulin level and ratio. Renal functions including serum creatinine 31 µmol/L (Ref. 30 - 70), blood urea of 4.9 mmol/L (Ref. 2.5 - 6.5) and uric acid of 147 µmol/L (Ref. 130 - 360) were normal with a serum ammonia of 22 µmol/L (Ref. 10 - 47). His Creatine phosphokinase level was elevated at 445 µg/L (Ref. 10 - 120). Ultrasound of the kidney showed increased cortical echogenicity suggestive of bilateral renal parenchymal disease. Urine full report did not reveal any cells or proteinuria.

He had a normal coagulation screen including a prothrombin time of 14.3 seconds (Ref. 11 - 15), activated partial thromboplastin time of 36 seconds (Ref. 25 - 38) with international normalized ratio of 0.96 (Ref. 0.8 - 1.2). His cerebrospinal fluid (CSF) analysis revealed a clear and colorless sample having 1 polymorph (Ref. 0 - 5), 3 lymphocytes (Ref. 0 - 5) and 8,400 red blood cells per high power field (Ref. 0 if non-traumatic), with high protein level of 350 mg/dL (Ref. 15 - 45) with a sugar level of 2.6 mmol/L (Ref. 2.5 - 4.5) (accompanying random blood sugar - 4.5 mmol/L) with no organisms and

negative bacterial antigen. CSF lactate level was 6.86 mmol/L (Ref. 1.11 - 2.77) with a paired serum lactate of 2.78 mmol/L (Ref. 0.5 - 2.3).

His CSF and blood cultures yielded no growth. His serum ceruloplasmin level was 30 mg/dL (Ref. 14 - 40) and serum Cholesterol was 5.58 mmol/L (Ref. 2.88 - 5.23). Homocysteine level of 6.78 µmol/L (Ref. 5 - 15) and vitamin B12 level of 350 pg/mL (Ref. 200 - 900) were normal. Electrocardiogram and echocardiogram revealed normal cardiac functions.

Electroencephalogram (EEG) findings showed nonspecific encephalopathy with asymmetric involvement. 3T Magnetic Resonance Imaging of brain and spine revealed extensive white matter changes with patchy brain stem changes and subtle thalamic and globus pallidus involvement with changes of long segment cervical and patchy dorsal myelitis with enhancement of cauda acquina nerve roots which was reported as compatible with mitochondrial disease. The nerve conduction test did not reveal any abnormalities. Electromyogram could not be done due to incorporation.

Urine organic acid analysis revealed the presence of 3-hydroxy-N-butyric acid and acetoacetic acid with moderate elevation of lactic acid with mild amount of tricarboxylic acid compounds and 3-methyl glutaconic acid, indicative of primary mitochondrial pathology.

Genetic analysis for mitochondrial encephalo-myopathy, lactic acidosis and stroke-like episodes; MELAS (MT-TL1 pathogenic variant gene sequencing) and Kearns Sayre syndrome (KSS) (m.8470_1344del4977 by PCR) were negative.

The child required intravenous midazolam 0.2 mg/kg bolus (2.4 mg) followed by 12 µg/kg/min infusion to control the status epilepticus followed by intubation and ventilation at intensive care setting for 1 week. Intravenous dextrose was given to maintain euglycaemia. Subsequently he was started on intravenous levetiracetam 40 mg/kg (480 mg) bolus followed by 10 mg/kg twice daily (120 mg) which was later changed to an oral dose of 125 mg twice daily. He was started on oral prednisolone 2 mg/kg which was gradually tailed off and was started on physiotherapy and occupational therapy as well as speech and language therapy. He was also started on multiple supplements including vitamin C, co enzyme Q, creatine monohydrate, carnitine, vitamin K, vitamin E, thiamine, riboflavin, dichloroacetate and omega 3 fatty acids.

He showed good response to initial therapy and was able to wean off ventilation within a week and was seizure free afterwards. Vomiting did not recur. He regained ability to talk, walk and swallow safely and use hand function adequately with interventions. However, he remained emotionally labile and sleepy. Subsequent investigations showed that his blood gases have markedly improved with pH of 7.35 (Ref. 7.32 - 7.43), $PCO_2$ - 25 mmHg (Ref. 40 - 50), $HCO_3^-$ - 16 mEq/L (Ref. 22 - 26) with markedly reduced lactate of 3.7 mmol/L (Ref. 0.5 -2.3). Follow-up EEG showed improvement of encephalopathy. He was discharged from the ward 36 days following the admission.

Unfortunately, 1 month following discharge he again presented with a prolonged refractory afebrile status epilepticus following a brief period of generalized ill health and needed to be put under general anesthesia in intensive care setting for seizure control. Investigations showed severe lactic acidosis. Child was unable to be recovered and succumbed to his illness.

## Discussion

Diagnosis as well as management of mitochondrial diseases is complex and challenging. As the saying goes “any tissue and any signs at any age” is the hall mark of mitochondrial disease (4). Clinical course in children is usually acute and progressive whereas as adults show a chronic slowly progressive course. Clinical spectrum is not limited to the neuromuscular system; indeed, several non-neuromuscular organs may exhibit symptoms and signs, such as the heart, eyes, ears, kidneys, endocrine glands, liver, bone marrow, and the gastrointestinal tract (5).

As seen in our case, lactic acidosis, encephalopathy and retinitis pigmentosa are classic presentations of mitochondrial diseases. Lactic acidosis remains a strong predictor of mitochondrial disease.

In patients with primary mitochondrial disease, truly elevated lactate levels have sensitivity between 34 and 62% and specificity between 83 and 100% (7). Elevated CSF lactate can be a helpful marker of mitochondrial disease in patients with associated neurologic symptoms. This patient had elevations in both serum and CSF lactate. Urine organic acid show changes in mitochondrial disease including mild-to-moderate 3-methylglutaconic acid (3MG) elevation and dicarboxylic aciduria (7) which was positive in this case as well.

Stroke-like lesions in a nonvascular distribution, diffuse white matter disease, and bilateral involvement of deep gray matter nuclei in the basal ganglia, mid-brain, or brainstem are all known classic neuroimaging findings in syndromic mitochondrial disease. These "classical" changes are selectively also observed in no- syndromic mitochondrial diseases, however they are neither sensitive nor specific enough to allow for a primary mitochondrial disease diagnosis without the presence of other abnormalities (7, 8). Most of these changes were noted in our patient as well.

DNA analysis by means of next-generation sequencing (NGS) is the new gold standard for mtDNA analysis because they allow significantly improved reliability and sensitivity of mtDNA genome analyses for point mutations, low-level heteroplasmy, and deletions and provide a single test to accurately diagnose mtDNA disorders (7, 9). With more than 1,400 genes involved in mitochondrial function, it is difficult to analyse all genes. In our case we analysed for classical KSS and MELAS mutations which came as negative; however, the possibility of large deletions or duplications were not excluded.

Since we were unable to achieve a genetic diagnosis, we used the mitochondrial disease criteria which was proposed in 2006 and reevaluated in 2017 and found to be having a sensitivity of 72.5% with a positive predictive value of 69.5% to diagnose mitochondrial disease (10, 11). It categorizes patients to 4 criteria including mitochondrial disease unlikely, possible, probable and definite: using a scoring system (Table 1).

**Table 1:** Mitochondrial disease criteria (simplified version for bedside use*) (10, 11)

| **Clinical signs and symptoms 1 point /symptom (maximum 4 points)** | | | **Metabolic/ imaging studies (max. 4 points)** | **Morphology (max. 4 points)** |
|---|---|---|---|---|
| **Muscular presentation (max. 2 points)** | **CNS presentation (max. 2 points)** | **Multisystem disease (max. 3 points)** | | |
| Ophthalmoplegia# | Developmental delay | Haemopoietic | Elevated lactate# | Ragged red/ blue fibres** |
| Facies myopathica | Loss of skills | Gastrointestinal tract | Elevated L/P ratio | COX-negative fibres** |
| Exercise intolerance | Stroke-like episode | Endocrine/growth | Elevated alanine# | Reduced COX staining** |
| Muscle weakness | Migraine | Heart | Elevated CSF lactate# | Reduced SDH staining |
| Rhabdomyolysis | Seizures | Kidney | Elevated CSF protein | SDH-positive blood vessels# |
| Abnormal EMG | Myoclonus | Vision | Elevated CSF alanine# | Abnormal mitochondria/EM# |
| | Cortical blindness | Hearing | Urinary TA excretion# | |
| | Pyramidal signs | Neuropathy | Ethylmalonic aciduria | |
| | Extrapyramidal signs | Recurrent/familial | Stroke-like picture/MRI | |
| | Brainstem involvement | | Leigh syndrome/MRI# | |
| | | | Elevated lactate/MRS | |

**Score 1: Mitochondrial disorder unlikely; scores 2 to 4: possible mitochondrial disorder; scores 5 to 7: probable mitochondr ial disorder; scores 8 to 12: definite mitochondrial disorder; #This specific symptom scores 2 points; **This symptom in a higher percentage scores 4 points;*

*L/P: lactate/pyruvate, COX: cytochrome c oxidase, SDH: succinate dehydrogenase, EM: electron microscopy, EMG: electromyography, TR; Tricarbon acid*

Our patient had muscle weakness and exercise intolerance (2 marks), CNS involvement with developmental regression and seizures (2 marks), metabolic and imaging abnormalities including elevated serum and CSF lactate and MRI changes (4 marks), no morphological muscle findings (0 marks), and multisystem involvement with retinitis pigmentosa and kidney disease (2 marks), giving a total of 10 marks (definite mitochondrial disease). EMG and advanced morphological testing could not be performed due to resource constraints and practical limitations, which may have further increased the score if they had been performed.

Management of mitochondrial disease during the acute decompensation stage includes evaluation of routine chemistries, glucose, transaminases, lactate, cardiac and neurologic decompensation. Acute management includes dextrose containing intravenous fluids, stopping exposure to trigger factors/ medications (valproate, statins, metformin etc.), correction of metabolic derangements. Repeat neuroimaging is considered in case of acute neurologic changes.

Despite findings of a Cochrane review of mitochondrial therapies which found little evidence supporting the use of any vitamin or cofactor intervention (12), it is still being used. Consensus recommendations include supplementation with co-Enzyme Q, α-lipoic acid, riboflavin, L-carnitine and folinic acid in case of central nervous system manifestations and replacing other deficient vitamins (7). We have managed our patient according to consensus guidelines.

## Conclusions

Presentation of mitochondrial disease is complex and nonspecific. However, features like lactic acidosis, encephalopathy and retinitis pigmentosa are suggestive and imaging of the involved systems, urine organic acid profile and elevated CSF lactate can be used investigate further. Genetic analysis is confirmatory of mitochondrial disease but in the absence of genetic evidence, mitochondrial disease scoring criteria can be used to classify the presentation according to the probability of mitochondrial disease being the underlying pathology. Consensus management of mitochondrial disease includes symptomatic management, correction of metabolic and electrolyte abnormalities and micronutrient supplementation with proper rehabilitation with physiotherapy and occupational therapy.

Informed consent has been obtained to publish this case report. The authors declare that they have no competing interests.

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## References

1. Hettiarachchi D, Lakmal K. and Dissanayake VHW. Mitochondrial diseases in South Asia - A systematic review. *Mitochondrion*. 2022; 62: 24-30. DOI: 10.1016/j.mito.2021.10.007.
2. Elliott HR, Samuels DC, Eden JA, Relton CL, Chinnery PF. Pathogenic mitochondrial DNA mutations are common in the general population. *Am J Hum Genet.* 2008; **83**(2): 254-260.
3. Gorman G, Chinnery P, DiMauro S. *et al.* Mitochondrial diseases. *Nat Rev Dis Primers* 2, 16080 (2016). DOI: 10.1038/nrdp.2016.80.
4. Chi CS. Diagnostic Approach in Infants and Children with Mitochondrial Diseases. *Pediatrics and Neonatology.* 2015; **56**: 7-18.
5. Chi CS, Lee H. F Tsai CR, Lee HJ, Chen LH. Clinical manifestations in children with mitochondrial diseases. *Paediatr Neurol.* 2010; **43**: 183-189.
6. Falk MJ. Mitochondrial disease diagnosis. In: Kliegman RM, St Geme JW III, Blum NJ, Shah SS, Tasker RC, Wilson KM, editors. *Nelson Textbook of Pediatrics*. 21st ed. Philadelphia: Elsevier; 2019: p.807-810.
7. Parikh S, Goldstein A, Koenig MK, Scaglia, *et al*. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genetics in Medicine, 2015; **17**(9), 689-701. DOI: 10.1038/gim.2014.177.
8. Saneto RP, Friedman SD, Shaw DW. Neuroimaging of mitochondrial disease. *Mitochondrion*, 2008; **8**(5-6), 396-413.

9. McCormick E, Place E. Falk MJ. Molecular genetic testing for mitochondrial disease: from one generation to the next. *Neurotherapeutics*, 2013; **10**: 251-261.

10. Morava É, Van Den Heuvel L, Hol F, De Vries MC, Hogeveen M, Rodenburg RJ, Smeitink JA. Mitochondrial disease criteria: Diagnostic applications in children. *Neurology*. 2006; **67**(10): 1823-1826. DOI: 10.1212/01.wnl.0000244435.27645.54.

11. Witters P, Saada A, Honzik T. *et al.* Revisiting mitochondrial diagnostic criteria in the new era of genomics. *Genet Med.* 2018; **20:** 444-451. DOI: 10.1038/gim.2017.125.

12. Pfeffer G, Majamaa K, Turnbull DM, Thorburn D, Chinnery PF. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev.* 2012; **4**: CD004426.