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Case Report - 1

A neonate presenting with lactic acidosis, hypotonia, encephalopathy and tubulopathy: Possible RRM2Brelated encephalomyopathic mitochondrial DNA depletion syndrome.

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Abstract

Mitochondrial disorders (MD) are a group of rare genetic disorders with wide range of phenotypic variations. Mitochondrial DNA depletion syndromes (MDS) are even rarer. The main clinical forms of MDS are myopathic, encephalomyopathic (EM), hepatocerebral and neurogastrointestinal. They are categorized according to clinical features and genetic analysis.

We report the 1st Sri Lankan patient presented during the neonatal period with encephalopathy, hypotonia, neuro developmental delay, tubulopathy, lactic acidosis with elevated methylmalonic acid, ethynylmalonic acid and 3-methyl glutaconic acid in urine. As we were unable to confirm the genetic diagnosis, we categorized our patient according to consensus mitochondrial disease criteria which scored eight and a score between 8-12 is categorized as a definite MD.

The presence of tubulopathy with nephrocalcinosis further narrowed down the differential to MDS though an exact genetic diagnosis is not available. Out of four clinical forms of MDS, EM MDS is the most likely diagnosis.

Background

Mitochondrial disorders (MD) are characterized by multisystem involvement and myriad of phenotypic variations with wide range of severity[1]. Dysfunction in electron transport chain cause depletion of adenosine triphosphate (ATP) production. Lack of ATP will upregulate glycolysis causing increased production of pyruvate. This excess pyruvate is converted to alanine or will be reduced to form lactate[2]. As expected, the effects of MD are heavy on tissues with high energy requirement such as neurons, skeletal muscles and cardiac muscle of which central nervous system involvement is more prominent[3]. Some of these syndromes are associated with renal involvement[4].

Estimated incidence of mitochondrial disorders are in between 1:5000 and 1:10000 live births but the exact incidence of MDS are not known[1].

We report on rare case of neonatal presentation of encephalomyopathic (EM) MDS presenting with tubulopathy and nephrocalcinosis, based on clinical presentation and available investigations in resource poor setting. Documentation of associated clinical features to broaden our understanding about its clinical manifestations.

Case presentation

A four-day baby boy, the second born child to healthy nonconsanguineous parents, admitted due to poor sucking and neonatal convulsions from day one of life. He was born at term with birth weight of 3.4kg following an uncomplicated pregnancy due to abnormal lie.

Examination revealed hypotonia with elicitable reflexes. There was no microcephaly, dysmorphism or organomegaly. During follow up, significant developmental delay was observed in all domains and developmental age was less than six weeks even at five months of age and severe failure to thrive. There were poor antigravity movements in all four limbs. He was extremely poor in fixing and following and couldn't appreciate social smile. Ophthalmologic assessment of extraocular movements and fundoscopic examination were normal. Otoacoustic emission testing was normal as well. Subtle improvement was observed with neurorehabilitation.

The first-born baby boy has had convulsions from neonatal period and severe developmental delay in all domains, failure to thrive with hypotonia and passed away at four months of age, probably following an aspiration. He has not had any investigations performed for aetiology.

During investigations hypoglycaemia and meningitis were excluded in the index patient. Normal anion gap metabolic acidosis was revealed with hypokalaemia, hypercalciuria and nephrocalcinosis with hyposthenuria compatible with distal renal tubular acidosis.

His metabolic acidosis persisted but turned to high anion gap during third week of life. His serum and cerebrospinal fluid lactate levels were high with marginally elevated serum ammonia level.

Electroencephalogram revealed burst suppression suggestive of underlying neonatal encephalopathy.

Marked elevation of lactic acid with mild elevation of methylmalonic acid, ethynylmalonic acid and 3-methyl glutaconic acid were elevated in urine organic acid profile. These are markers of tricarboxylic acid (TCA) cycle which takes plan in mitochondria. In mitochondrial dysfunction intermediate products of TCA cycle are elevated. His liver, renal functions, creatine kinase (CK), triglycerides, cholesterol, uric acid level and serum amino acid profile were normal. There was no evidence of cardiomyopathy. Electromyography (EMG) showed no features of myopathy. There was no detectable structural abnormality in the magnetic resonant imaging of brain.

Discussion

Diagnosis of MD are challenging. It is based on clinical, biochemical, pathological and molecular criterions[3]. Clinically MD have multisystem involvement. MD due to mitochondrial DNA mutations are more easily identifiable in comparison to MD due to nuclear DNA disorders. The latter lack classical clinical/biochemical findings and performing mutation analysis is quite challenging[2].

Lactic acidosis is a well-recognized surrogate marker of MD; however, normal lactate will not exclude the disease[2]. High lactate predicts MD with 34-62%sensitivity and 83-100% specificity[5]. In our patient serum and CSF lactate both were high. Other conditions with elevated lactate include glycogen storage disorders, organic acidaemias, fatty acid oxidation disorders, disorders of pyruvate metabolism and disorders of gluconeogenesis[6]. The clinical features and investigation findings in our patient were not in favour of these differential diagnosis.

Pathological hallmark in muscle biopsy in MD is light microscopic finding of subsarcolemmel accumulation of mitochondria. However, it is known that in early stages of disease, muscle microscopy may be normal[2]. As a result of this and the small size of body we deferred muscle biopsy to a later time in our patient.

Out of MD, mitochondrial myopathy, encephalopathy, lactic acidosis, stroke like syndrome (MELAS), Kearns Sayre syndrome (KSS), Leigh syndrome and MDS are known to develop renal manifestations[4]. Proximal renal tubular acidosis is the commonest renal manifestation[7]. Bartter like syndrome, tubular interstitial nephritis, nephrotic syndrome and focal segmental glomerulonephritis are other reported renal associations. Nephrocalcinosis is mainly documented in MDS and KSS[4]. In our patient there were no features in favor of KSS such as retinitis pigmentosa, ptosis, heart block and cardiomyopathy, indicating a possible diagnosis of MDS.

As we were unable to confirm the genetic diagnosis, we used consensus mitochondrial disease criteria, which was very useful to categorize patients in to four groups: MD unlikely, possible MD, probable MD and definite MD, according to the scoring system. Criteria were classified under clinical signs and symptoms (maximal score: four points), metabolic/imaging studies (maximal score: four points) and muscle biopsy morphology (maximal score: four point)[8]. Out of maximal score of 12 our patient scored eight despite excluding muscle biopsy morphology. A score between8-12 was considered as definite mitochondrial disorder[8].

MDS are an autosomal recessive disorder of nuclear DNA mutations with quantitative reduction in mitochondrial DNA. The main clinical forms of MDS are myopathic, encephalomyopathic (EM), hepato-cerebral and neuro-gastrointestinal. They are categorized according to clinical features and genetic analysis[1,3].

Two possible MDS are myopathic MDS and EM MDS. Myopathic MDS consists of muscle weakness, elevated CPK, encephalopathy, myopathy, renal tubulopathy and CNS manifestations[1,3]. Hypotonia, lactic acidosis, psychomotor delay, epilepsy, feeding difficulties, urinary methylmalonicaciduria, tubulopathy are features of EM MDS, which present during early infancy[1,3]. Out of the above two, EM MDS is more likely as our patient is having almost all the features of EM MDS and having normal CK level and EMG.

SUCLA2 (beta-subunit of the adenosine diphosphate-forming succinyl-CoA-ligase), SUCLG1 (alpha-subunit of GDP-forming succinyl-CoA-ligase) and RRM2B (p53-dependent ribonucleotide reductase) are known mutated genes responsible for EM MDS. Renal tubulopathy had been found in patients with RRM2B gene mutation which is more likely in our patient[3,9]. Among patients with SUCLA2 and SUCLG1 related EM MDS tubulopathy is not recognized but elevated methylmalonic acid in urine is a feature that our patient is also sharing[9].

For many decades muscle biopsy was considered as the investigation of choice to diagnose mitochondrial disorders. With advancement of science currently molecular testing is considered as the gold standard. First line genetic testing commonly used in current practice is clinically based whole exome sequencing with mitochondrial DNA sequencing in both patient and parents. However mitochondrial depletion may only be detected in biopsy specimens of symptomatic high energy demand tissues, such as muscle or liver[10]. We are unable to confirm the diagnosis in our patient in spite of the high likelihood based on clinical and biochemical findings.

Treatment options for our patient are neurorehabilitation with the help of a multidisciplinary team particularly renal support. The role of co factors such as coenzyme Q, levocarnitine, creatine monohydrate and vitamin B, C, E are not substantial[9].

Conclusion

This neonate with neonatal encephalopathy and hypotonia with lactic acidosis with a positive family history with supportive urinary organic acid profile supports underlying mitochondrial disease. The presence of tubulopathy with nephrocalcinosis further narrowed down the differential to MDS though exact genetic diagnosis is not available. Out of four clinical forms of MDS, EM MDS is the most likely diagnosis.

Declarations

Consent for publication – Informed written consent taken from the patient's mother.
Competing interests – The authors declare that they have no competing interests
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Author's contribution –
TS was the major contributor in writing the manuscript.
CW contributed in drafting the work and writing the manuscript.
JW was involved in writing, supervising and editing the manuscript.
All authors read and approved the final manuscript.

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