Proximal renal tubular acidosis due to mitochondrial cytopathy: A case report

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ABSTRACT

Proximal renal tubular acidosis (P-RTA) occurs in multiple inherited metabolic conditions; one of them is Mitochondrial disorder. Pearson syndrome, a type of mitochondrial cytopathy, presents with multi system involvement in the form of progressive external ophthalmoplegia, proximal myopathy, seizures, ataxia, stroke, renal tubular dysfunction, hepatic, endocrine failure and sideroblastic anemia. Clinical features are variable due to heteroplasmy. L;iterature search shows that fewer than hundred cases have been reported so far. This case is being reported because of its rarity wherein even though the genetic study was not possible, the clinical features and investigations were suggestive of mitrochondrial cytopathy - Pearson syndrome changing to Kearn Sayre Syndrome (KSS).

Key words: RTA, kidney, Pearson Syndrome, short stature, rickets

INTRODUCTION

Proximal renal tubular acidosis (p-RTA) is type II RTA, characterized by impairment of absorption of bicarbonate with Fanconi syndrome. It may be either due to primary or secondary causes. Primary causes are either sporadic or due to inherited conditions. Mitochondrial disorders can present with proximal RTA. In mitochondrial disorders, Pearson syndrome, Kearns-Sayre Syndrome, and mitochondrial encephalopathy, lactic acidosis may present with tubular dysfunctions.[1] This case was pointing to Pearson syndrome.

CASE REPORT

A 6- year old girl, born of non-consanguineous marriage, presented with complaints of inability to walk independently since 2-3 months and drooping of eyelids since 20 days following high-grade fever. The febrile illness lasted for 9-10 days along with vomiting and one episode of generalized tonic-clonic seizure for which she was diagnosed as acute demyelinating encephalomyelitis with proximal renal tubular acidosis. She was referred to this centre for further treatment. She did not have any sensory or hearing impairment; blurring of vision or diplopia; swallowing difficulties; bladder or bowel involvement. She had a significant past history of repeated hospitalization for blood transfusion between the age of 1-2 years and had received 12 blood transfusions for the diagnosed condition of sideroblastic anemia. She was relatively asymptomatic between 2- 6 years of age. Family, perinatal, development history was not contributing to the present illness.

On examination, her height was 93 cms and weight of 8.6 kg(below -3S Das per WHO 2006 growth charts). She had bilateral ptosis, corneal opacity & post axial polydactyly on left hand. She had hypotonia, hyporeflexia and grade IV power in all four limbs. Other general and systemic examinations were normal.

Investigations showed her Hb: 12.2gm%, TC-7600 and platelets- 88000/cumm. Serum sodium was 125 mEq/L; potassium-3.9mEq/L, Chloride of 103mEq/L and bicarbonate was 8mEq/L. Arterial Blood Gas was suggestive of metabolic acidosis with normal anion gap. Serum Ca^{++} was 9.1mg%, Phosphorous - 1.5 mg% and alkaline phosphatase was 104 IU/L. X-ray wrist was suggestive of rickets. USG abdomen showed increased renal parenchymal

echogenicity. Her 25 hydroxy vit D_3 was 11.8 ng/ml, & Serum Parathyroid hormone was 34.1pg/ml. Her serum ferritin was 1444 ng/dl & Serum amylase was normal.

urine examination revealed: pH - 5; glycosuria (3+); Urine Protein: Creatinine – 1.1; urine calcium: creatinine – 0.2; Urinary phosphorus 896mg/dl (normal-600-800); Fractional phosphorus excretion 38.5 %(normal <5%); findings were suggestive of p-RTA with fanconi sydrome giving to hypophosphatemic rickets.MRI brain showed demyelination at multiple sites of brain and spinal cord.CSF report showed protein of 100mg/dl, normal cells and sugar. ECG was showing left anterior hemi block.

After excluding other secondary causes, and due to its multisystem involvement, in the form of bilateral ptosis, corneal opacity, motor regression, sideroblastic anemia, involvement of white matter of brain and spinal cord and cardiac conduction defect; a provisional diagnosis of proximal RTA due to mitochondrial cytopathy "Pearson Syndrome" was considered and she was subjected to further investigations.

Her investigations were showing Serum. Lactate- 2.8mM/L (mildly elevated), serum Pyruvate-0.39mg/dl (N-0.36-0.59) with elevated lactate: pyruvate ratio. Urine Gas Chromatography/Mass Spectrometry shows grossly elevated lactate, pyruvate, fumarate and ketones suggesting mitochondriopathy. Serum amino acid profile showed grossly elevated Alanine 1120 µmol/L (N-120-600), Carnitine/Acyl carnitine profile showed low free carnitine 4.9uM/L (normal -24.7-66.6), low Free /Acyl carnitine ratio 0.36(N->2.0) findings were consistent with mitochondriopathy. DNA studies could not be done due economic constraint.

DISCUSSION

Pearson syndrome is a multi-organ disorder with a variable clinical presentation mainly consisting of refractory sideroblastic anaemia, exocrine pancreatic dysfunction and marked lactic acidosis.[2] Less than 100 cases have been reported worldwide.[3] The syndrome is due to defective oxidative phosphorylation due to mitochondrial DNA deletions of variable size and location and in some cases additional rearrangements and duplications. Pearson syndrome mostly inherited sporadically affecting both sexes equally.[4] Children with Pearson's syndrome present in early infancy with pallor, pancytopenia, failure to thrive, chronic diarrhoea and marked lactic acidemia. Other manifestations include progressive external ophthalmoplegia, proximal myopathy, neurologic disturbances (seizures, ataxia, stroke), renal (proximal tubulopathy), hepatic failure and endocrine failure.[5,6] Presence of marked metabolic acidosis, complex organic aciduria and cytoplasmic vacuolization of bone marrow precursor cells, strongly suggests Pearson's syndrome and consistent with a underlying defect in the mitochondrial respiratory chain function.[7] Most patients die during infancy or early childhood, often due to unremitting metabolic acidosis, infection, or liver failure. Those few individuals who can be medically supported through infancy may experience a full recovery of marrow and pancreatic function. However, they eventually undergo a phenotypic transformation to Kearns-Sayre syndrome, a mitochondriopathy characterized by progressive external

opthalmoplegia, weakness of skeletal muscle, incoordination, mental retardation, episodic coma, atypical retinal pigmentation, cardiac conduction defects and hearing loss.[6,8] Concept of 'heteroplasmy' can explain such a varied clinical picture, in terms of the extent of organ involvement and "phenotypic switch" to a different syndrome. Rotig et al in 1991 has reported five unrelated patients having a single large (4978 bp) deletion within mitochondrial DNA.[9] No specific therapy is available for Pearson syndrome. Management of intermittent metabolic crises, correction of electrolyte abnormalities, acidosis, and infection may minimize morbidity. Blood transfusions are often needed to manage the sideroblastic anaemia, and patients may be transfusion dependent. Pancreatic enzyme replacement and supplementation with fat-soluble vitamins are needed for patients with malabsorption. Chronic bicarbonate supplementation has been used to treat persistent metabolic acidosis. Although without controlled evidence of benefit, many clinicians supplement coenzyme Q, carnitine and riboflavin.

Other inherited causes of P-RTA were ruled out and Pearson syndrome changing to Kearn Sayre Syndrome as a probable diagnosis was concluded.

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