Two new cases with Pearson syndrome and review of Hacettepe experience

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Pearson syndrome (PS) is a mitochondrial disease and clinical presentation is rather varied. These patients are often subjected to extensive biochemical and clinical work-up for diagnosis. We report two new cases and review our experience with PS in Hacettepe University. The first case had large deletion of mitochondrial DNA (mtDNA) and presented with severe metabolic acidosis and anemia associated with hemophagocytosis in bone marrow. He also had liver involvement and tubulopathy. The second case, who had the 4997 bp common deletion, presented with anemia at 8 weeks of age followed by an uneventful 4 years. She developed very severe acidosis and renal Fanconi syndrome at the age of 4.5 years. Our cases revealed once more the clinical diversity of the disease and no correlation between the size and site of mtDNA deletion and clinical presentation. We encourage physicians to look for PS in children with early sideroblastic anemia and multiple organ system involvement.

Key words: Pearson marrow syndrome, mtDNA deletion, refractory anemia, sideroblastic anemia, renal tubulopathy, hemophagocytosis.

Pearson syndrome (PS) is a multisystem disorder consisting of refractory sideroblastic anemia in childhood with vacuolization of marrow precursors and exocrine pancreatic dysfunction. This syndrome is a rare, often fatal, disorder of infancy[1,2]. Severe, transfusion-dependent, macrocytic anemia begins in early infancy and is associated with a variable degree of neutropenia and thrombocytopenia[1,2]. Defects in the mitochondrial respiratory chain affect various organs such as liver and kidney. Generally patients have lactic acidosis and high lactate/pyruvate molar ratios in their plasma[3,4]. Proximal renal tubular acidosis (pRTA) has been shown to have an association with renal involvement in these patients. pRTA typically manifests as part of a generalized defect of proximal tubule function and renal Fanconi syndrome with glucosuria, low molecular weight proteinuria, amino aciduria, urinary phosphate wasting, hypophosphatemia, and hypouricemia[5]. It is a multisystem disease and prone to many complications related to the affected systems. Here we report two cases of Pearson syndrome, one presenting with severe hematological involvement and hemophagocytosis in bone marrow and the other with mild hematological involvement but intractable proximal RTA. In this report, in addition to presenting the two new cases, we also review the previous cases seen at our center.

Case Reports

Case 1

A seven-month-old boy was admitted to a local health center with a two-week history of fever, cough, vomiting, and diarrhea. The patient was the first child of healthy, unrelated parents. Pancytopenia, increased activated partial thromboplastin time (aPTT) and international normalized ratio (INR) and acidosis were

detected at a local health care center, and the patient was referred to our hospital with the diagnosis of metabolic disorder. Physical examination revealed toxic appearance, lethargy, paleness, and hepatomegaly 4 cm below the right costal margin. Hemoglobin level was 7.4 g/dl, platelet $93x10^9$/L, white blood cells $7.4x10^9$/L, and mean corpuscular volume (MCV) 91.3 fl. Peripheral blood smears showed burr cell, schistocyte, and acanthocytes. Results of the laboratory examinations were as follows: alanine aminotransferase (ALT) 237 U/L, aspartate aminotransferase (AST) 506 U/L, blood pH 7.28, bicarbonate 7 mEq/L, serum sodium 127 mEq/L, potassium 3.0 mEq/L, chloride 95 mEq/L, calcium 13.2 mg/dl, phosphorus 2.0 mg/dl, lactic acid 69.4 mg/dl (10-14 mg/dl), pyruvic acid 2.18 mg/dl (0.5-1.0 mg/dl), ferritin 2886 ng/ml, triglyceride 414 mg/dl, and fibrinogen 111 mg/dl. Urine analysis revealed proteinuria 150 mg/dl, glucosuria 50 mg/dl, and generalized aminoaciduria, along with hypophosphatemia and hypokalemia, suggesting proximal renal tubular involvement. Bone marrow aspiration smear showed vacuolization of hematopoietic precursors, especially erythroblasts, and hemophagocytosis. The presence of severe metabolic acidosis, elevated levels of lactate and pyruvate and hematopoietic precursors in the bone marrow aspiration smear led to the diagnosis of PS. Furthermore, urine organic acid test result was suggestive of a mitochondrial disorder (PS). This was confirmed by the presence of a large (90%) deletion of mitochondrial DNA (mtDNA). Fresh frozen plasma and mitochondrial cocktail were commenced and peritoneal dialysis was performed for severe acidosis. During the follow-up, mechanical ventilation was instituted due to respiratory depression. The patient died two days after admitting to our hospital and partial autopsy was performed. Postmortem examination of the pancreas showed prominent fatty infiltration, mild fibrosis and focal microcystic acinar dilatation. There was prominent macrovesicular steatosis of the liver, accompanied by mild hemosiderosis around the portal areas. Fibrosis was not present. Cytochrome-c-oxidase (COX) staining of the frozen liver tissue showed significant reduction in hepatocytes. Examination of skeletal muscle revealed faint staining of COX with few COX-negative fibers. Oil-red-O stain showed mild increase in lipid content in some fibers. No pathological finding was detected in heart muscle. There were cystic dilatations of the proximal tubules in the renal cortex and vacuolar changes in the tubule epithelium, which supports the renal tubular involvement. Hemophagocytosis was not present in other organs.

Case 2

This two-month-old girl was born at 38 weeks gestation by cesarean section to healthy unrelated parents. Birth weight was 4000 g. She presented to a medical center with anorexia, vomiting, diarrhea, weakness, and increased pallor at 8 weeks. She was the only child, and there were no blood group incompatibilities between mother and infant; Coombs test was negative. Family history was negative for hematological diseases. Blood counts of parents were normal. On the physical examination she was pale. Her physical and psychomotor development was apparently normal at 8 weeks. Hemoglobin level was low (6.8 g/dl), with mild macrocytosis (MCV 97.9 fl), anisocytosis and poikilocytosis and reticulocyte count of 3.7%. Platelet count was low at 123 x 10^9/L. Red blood cell transfusions were given twice. Liver function tests were elevated (AST 87 U/L, ALT 65 U/L). Plasma and cerebrospinal fluid (CSF) lactate were significantly elevated at 5 mmol/L and 3.5 mmol/L, respectively (normal 0.5-2.5 mmol/L). Plasma and CSF pyruvate were slightly elevated at 0.27 mmol/L and 0.2 mmol/L, respectively (normal 0.05-0.10 mmol/L). Lactate pyruvate molar ratio in plasma was high. The results of other laboratory tests, including blood glucose, electrolytes, creatinine, creatinine kinase, lactate dehydrogenase, pH, HCO_3^-, coagulation, hemoglobin electrophoresis, and levels of zinc, copper, ceruloplasmin, phenylalanine and vitamin B_{12}, were within the normal range. A bone marrow aspirate demonstrated a reduced cell content, but also vacuolated erythroblasts, myelocytes and promyelocytes. Sideroblasts were also seen. Because of these morphologic features, the diagnosis of PS was clinically considered. Treatment with oral vitamin B_6 and folate was started. During the four-year follow-up, no blood transfusion was needed and a spontaneous remission of the anemia with decreased counts of reticulocytes, stable hemoglobin, mild neutropenia and increasing counts of thrombocytes were found.

At the age of 4 years, she was in a stable clinical and metabolic condition. Her physical development was at the 10th to 25th percentile. Her psychomotor development was normal.

At the age of 4.5 years, due to diarrhea and vomiting, the girl was referred to our hospital for the first time. On admission, she had normal complete blood count (Hb 12.6 g/dl, WBC 9.9x10^9/L, thrombocytes 333x10^9/L, MCV 84 fl) but progressive severe metabolic acidosis, and high plasma lactate (38.1 mg/dl) and plasma pyruvate (1.4 mg/dl). Further investigations showed a complete renal Fanconi syndrome with tubular proteinuria (88 mg/dl), glucosuria (1000 mg/dl), defective bicarbonate reabsorption in the proximal tubule, aminoaciduria, hypokalemia (1.49 mEq/L), and hypophosphatemia (1 mEq/L). The bone marrow examination showed rare vacuolization of both myeloid and erythroid precursors.

In the urinary organic acid profile, an elevated excretion of lactate, pyruvate, 3-hydroxybutyrate, pyroglutamic acid and succinic acid was found. Her metabolic acidosis was very severe and despite HCO_3 infusion and potassium and phosphate supplementation, it progressed and she was put on hemodialysis for acidosis. Acidosis was controlled to some extent with hemodialysis and massive HCO_3 supplementation. Mitochondrial cocktail was commenced.

Changes in skeletal muscle fiber diameters, atrophic fibers and degenerated fibers with vacuolated sarcoplasm were seen with hematoxylin-eosin staining and high level of fat droplets with Oil-red-O staining. Histochemical staining for COX on skeletal muscle biopsy revealed that the COX activity in some of the skeletal muscle fibers was negative, as a characteristic feature of mitochondrial myopathy. mtDNA analysis revealed that she presented the common 4977 bp deletion. Later she had pneumonia, Gram-negative sepsis and impaired diastolic right ventricular function. She died four weeks later despite intensive supportive care.

Discussion

The clinical and biochemical features of PS, a rare and frequently fatal disease in early infancy, were originally described by Pearson et al. in 1979[1]. Twenty years later, Rötig et al.[3,4] showed that the mtDNA deletion, of which the most commonly seen is a 4977 bp deletion located between nt 8488 and nt 13460, caused this syndrome. Since the first report in 1989[3], many other deletions have been detected, among them 4977 bp deletion has been identified in more than 80% of the children diagnosed with PS. In our center, we have diagnosed and followed five infants with PS including these two new cases. Two of our five Cases (Case 2 and the previously reported Case 3) presented the 4977 bp common deletion. The other patients had mtDNA deletions of various sizes (Table I).

Case 3 and Case 4 presented with severe refractory anemia, one with common deletion and one with a smaller deletion, and died before age two with severe anemia[6]. Case 5 with heteroplasmic mitochondrial DNA deletion of 3.5 kb had very severe anemia with renal cortical cysts and died at the age of 41 days due to hepatic involvement and massive bleeding with prolonged prothrombin time (PT) and aPTT (Table I)[7].

Age at presentation and diagnosis of our patients varied between 16 days and 7 months, and there was no correlation between the age at presentation and the size of deletion.

It is well known that in this syndrome, severe, transfusion-dependent, macrocytic anemia begins in early infancy and is associated with a variable degree of neutropenia and thrombocytopenia. Case 2 had not required a transfusion for a period of four years other than two units applied in early infancy. She had been supplemented only with folic acid and B_6 and did not have any complications for a four-year period was promising. A sudden gastroenteritis caused deterioration in the child's progress. On the other hand, Case 3, with the same common deletion, needed very frequent blood transfusions. Although there is no correlation of phenotype to size and site of the mtDNA deletion, this discrepancy may be explained by the varying percentage of deleted mitochondria in the hematopoietic system[8,9].

Renal involvement was confirmed in this case by proximal tubular insufficiency, Fanconi syndrome, and intractable metabolic acidosis[5,10]. Case 2 had a number of remarkable features. After the neonatal period, she had an uneventful four years with no refractory anemia and near normal mental motor development. Even when

Table I. Main Clinical and Laboratory Features of the Patients

Features	Case 1	Case 2	Case 3 (ref 6)	Case 4 (ref 6)	Case 5 (ref 7)
Birth weight (g)	3000	4000	3200	3500	2800
Age at diagnosis	7 months	2 months	4 months	2 months	16 days
Consanguinity	Absent	Absent	Absent	Absent	Absent
Growth retardation	Present	Present	Present	Present	Present
Age at death	7 months	54 months	19 months	13 months	41 days
Transfusion requirement	Died in two days	Very rare	Frequent	Frequent	Died at early age
System involvement	Hematopoietic, Hepatic renal cysts*	Mild hematopoietic Renal Fanconi	Hematopoietic	Hematopoietic	Hematopoietic, Hepatic, renal cysts*
Leukopenia	Absent	Mild	Severe	Severe	Severe
Thrombocytopenia		Mild	Severe	Severe	Severe
MCV (fl)	91.3	97.9	107	96	98
Hyperlactatemia	+	+	+	+	+
Serum iron, µg/dl		310	212	280	260
Ringed sideroblast	+	+	+	+	+
Vacuolization of marrow precursor	+	+	+	+	+
Hb F % (N 2%)	NA	21.8	6.8	10.9	NA
DNA mutation	Grand heteroplasmic deletion	4977 bp common heteroplasmic deletion	4977 bp common heteroplasmic deletion	4.5 kb mtDNA heteroplasmic deletion	3.5 kb mtDNA heteroplasmic deletion
Origin of DNA	Blood	Blood	Blood	Blood	Blood
Treatment	Mitochondrial cocktail	B_6 Folic acid	Biotin	B12 MPZ Multivitamin	Carnitine Biotin Thiamine B_6

*Found at autopsy.
MCV: Mean corpuscular volume.

she developed severe metabolic acidosis and renal Fanconi syndrome, her complete blood count was close to normal.

Case 1 presented with severe metabolic acidosis, anemia and cytopenia, and hemophagocytosis was seen in bone marrow. Furthermore, he had lethargy and increased liver enzymes and bilirubin levels. Proximal renal tubulopathy was suspected based on laboratory findings. He died in two days due to terminal hepatic failure despite the dynamic supportive treatment. Due to fever, hepatomegaly, hypofibrinogenemia, hypertriglyceridemia, Hyperferritinemia, bicytopenia, and hemophagocytosis in bone marrow, clinically secondary hemophagocytic lymphohistiocytosis (HLH) is considered[11]. Although secondary HLH has been documented in association with many different infections, malignant neoplasms, rheumatoid disorders, metabolic disorders, and prolonged intravenous nutrition, it was not confirmed in the post-mortem examination in our patient[12-17]. Liver and muscle were found to be the more seriously affected organ systems, and cystic dilatation of proximal tubules that could be consistent with proximal renal tubular involvement was observed.

In our experience, proximal renal tubular involvement with renal Fanconi syndrome seems to be one of the major manifestations in both the very young ones who died from hepatic failure and the one who had longer survival.

Although Case 1 had a larger mtDNA deletion and more deleterious course than Case 2, according to our experience and the previously reported cases, the size and percentage of the deletion may not be good predictors of the clinical course or severity of the disease. Phenotype expression of mtDNA mutation necessitates the influence of nuclear modifier genes, environmental factors or maybe the presence of polymorphisms. Our cases confirmed once again the clinical diversity of the disease and illustrated the symptomatic and asymptomatic kidney involvement associated with hematopoietic diseases. Even though the diagnosis of PS remains difficult, we encourage physicians to look for PS in children with early sideroblastic anemia, complete or incomplete renal Fanconi syndrome of unidentified cause and multiple organ system involvement.

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