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Pearson syndrome: Unique endocrine manifestations including Neonatal Diabetes and adrenal insufficiency

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ABSTRACT

Purpose: Pearson syndrome is a very rare metabolic disorder that is usually present in infancy with transfusion dependent macrocytic anemia and multiorgan involvement including exocrine pancreas, liver and renal tubular defects. The disease is secondary to a mitochondrial DNA deletion that is variable in size and location. Endocrine abnormalities can develop, but are usually not part of the initial presentation. We report two patients who presented with unusual endocrine manifestations, neonatal diabetes and adrenal insufficiency, who were both later diagnosed with Pearson syndrome.
Methods: Medical records were reviewed. Confirmatory testing included: mitochondrial DNA deletion testing and sequencing of the breakpoints, muscle biopsy, and bone marrow studies.
Results: Case 1 presented with hyperglycemia requiring insulin at birth. She had several episodes of ketoacidosis triggered by stress and labile blood glucose control. Workup for genetic causes of neonatal diabetes was negative. She had transfusion dependent anemia and died at 24 months due to multisystem organ failure. Case 2 presented with adrenal insufficiency and anemia during inturcurrent illness, requiring steroid replacement since 37 months of age. He is currently 4 years old and has mild anemia. Mitochondrial DNA studies confirmed a 4.9 kb deletion in patient 1 and a 5.1 kb deletion in patient 2.
Conclusion: The patients reported highlight the importance of considering mitochondrial DNA disorders in patients with early onset endocrine dysfunction, and expand the knowledge about this rare mitochondrial disease.

1. Introduction

Pearson marrow-pancreas syndrome was originally described in 1979 [1]. The disease is usually present in infancy with transfusion dependent macrocytic anemia, variable neutropenia and thrombocytopenia, with multiorgan involvement including exocrine pancreas, liver and renal tubular defects [2]. The cause of Pearson syndrome is a mitochondrial DNA deletion that is variable in size and location, but similar to the mtDNA deletion found in Kearns–Sayre syndrome [3], a disorder characterized by progressive external ophthalmoplegia, atypical retinal pigmentation and cardiac conduction defects before the age of 20 years [4]. Patients with Pearson syndrome can have fatal outcomes early in life, and those that survive past the age of 3 years develop symptoms consistent with Kearns–Sayre [3].

Endocrine abnormalities have been reported in some patients with confirmed diagnosis of Pearson syndrome [5–12]. However, endocrine disorders are rarely part of the initial clinical presentation. We report two patients whose initial clinical presentation included neonatal diabetes and adrenal insufficiency, and were later diagnosed as having Pearson syndrome.

2. Materials and methods

2.1 Genetic Sequencing for ABCC8, KCNJ11 and Insulin genes was performed at Ambry Genetics using their proprietary methods.
2.2 Muscle Biopsy for Case 1 was analyzed at UC Irvine Medical Center Department of Pathology and Laboratory Medicine (Orange, CA). Standard methods for histochemistry and electron microscopy were utilized.
2.3 Mitochondrial DNA testing
Testing for common mtDNA point mutations (A3243G, T3271C, G3460A, A8344G, T8356C, T8993G, T8993C, G11778A) and the common Pearson deletion were performed using standard PCR amplification and restriction enzyme digestion at the Genetics Center (Orange, CA).
Case 2 was also analyzed by Southern Blot at Mitomed Diagnostic Laboratory UC Irvine (Irvine, CA) using PvuII, BamH I, Hind III, and SnaB I restriction enzymes.

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Deletions were confirmed by sequencing the surrounding breakpoints at Baylor College of Medicine Medical Genetics Laboratory (Houston, TX).

2.4 Bone marrow Standard bone marrow evaluation was performed using H&E staining and Perl's staining for iron.

2.5 Retrospective chart review of the patients' clinical course and laboratory test results was performed after exempt status was granted from CHOC Childrens' IRB.

3. Results

3.1. Patient 1

Patient 1 was the 3rd full term child of unrelated healthy parents weighing 2351 g (5th%). At birth she was pale with a hemoglobin of 3.1 g/dL (10.2–15.4 g/dL), hematocrit of 8.6% (32.1–40.9%) and reticulocyte count of 3% (0.5–2.5%). She also had hyperglycemia with persistent blood glucose levels at 180–190 mg/dL (65–110 mg/dL) requiring an IV insulin drip at 0.48 units/kg/day for the first 2 weeks of life. She was transitioned to subcutaneous Regular insulin requiring 0.5–1.5 units of insulin per day with maximum blood glucose of 310 mg/dL. By one month of age blood glucose levels ranged from 94 to 235 mg/dL without insulin treatment. Insulin levels were measured 3 times while off insulin and found to be inappropriately low at 1.7, 2.3, and 2.9 mcu/mL (0–13 mcu/mL) during times of hyperglycemia. Genetic testing for neonatal diabetes was negative, including ABCC8, KCNJ11 and Insulin genes. Thyroid function, parathyroid hormone, ACTH, IGF-BP3, and somatomedin C were all within normal limits.

Since birth, the patient also had transfusion dependent macrocytic, normochromic anemia requiring red blood cell transfusions for hemoglobin <8 mg/dL every 3–4 weeks on average. Bone marrow aspiration and biopsy were performed at 2 months of age showing granulated red cell precursors consistent with ringed sideroblasts and increased iron stores.

The patient was referred to the division of metabolic disorders at 2 months of age. Work up included urine organic acids, that showed moderate increases of lactic, fumaric and malic, with slight increase in pyruvic, 3-OH butyric and 2-OH butyric, and no increase in 3-methylglutaconic acid. Carnitine levels and acylcarnitine profiles were normal. Plasma amino acids showed elevated alanine at 684 umol/L (143–439 umol/L). Serum lactic acid was elevated at 3.6 mmol (<2.2 mmol). Based on the increased lactic acid, alanine and abnormal urine organic acids, a mitochondrial disease was suspected. A muscle biopsy was obtained which showed no evidence of mitochondrial disease. However, mitochondrial DNA testing in blood was positive for the Pearson syndrome common deletion with 50% heteroplasmy. Similar results were obtained in fibroblasts. Sequence analysis confirmed a 4.9 kb deletion spanning from nucleotide 8483–13,459 of the mitochondrial genome (junction nucleotide 8482:13,460). The deletion was flanked by a direct repeat sequence of 13 nucleotides (8470–8482/13,447–13,459). She was treated with coenzyme-Q, riboflavin and carnitine.

The patient remained stable, off insulin, with mild hyperglycemia until 7 months of age when she presented with a blood glucose of 345 mg/dL and hemoglobin A1C of 7.3% (4.6–6.2%). She was restarted on insulin requiring 0.26–0.65 units/kg/day of basal insulin, with correction doses of 0.5–1.0 unit of rapid acting insulin for blood glucose greater than 300 mg/dL.

From 12 to 22 months, she had 5 episodes of acidosis with initial blood ketones 6.6–22.9 mg/dL (0.21–2.8 mg/dL), glucose 274–456 mg/dL and bicarbonate 5.0–13.0 mmol/L (17–29 mmol/L). The ketoacidosis was usually triggered by an acute illness and recovery often took > 24 h despite adequate hydration and IV insulin.

Outside of acute illness, her blood glucose levels were difficult to control, as she was prone to hyperglycemia, but was also extremely sensitive to minimal amounts of insulin. Her hemoglobin A1C ranged from 6.0%–7.6%.

Plasma amino acids were monitored and showed persistently elevated alanine ranging from 684 to 940 μmol/L. Also, serum lactic acid was consistently elevated ranging from 2.3 to 3.6 mmol while stable and 5.0–9.0 mmol when acutely ill.

GI studies were performed due to failure to thrive and to assess for pancreatic insufficiency. Over time, negative GI workup included: periodic monitoring of fecal fat, stool reducing substances, stool trypsin, endoscopy and biopsies of duodenum and esophagus. Amylase and lipase were low until 15 months of age at which time they normalized. At 20 months of age, due to poor growth, poor feeding and failure to thrive, a gastrostomy tube was placed and the patient was started on pancreatic enzymes. However, there was minimal improvement in weight gain.

The patient had severe developmental delay. Interval opthamologic evaluations were normal with the exception of esotropia. A renal tubular defect was evident at 18 months of age when the patient was hospitalized with non-gap acidosis. She was started on citric acid/sodium citrate to treat metabolic acidosis and also required phosphate, calcium carbonate and magnesium oxide supplements. Cardiology evaluations, including EKG and echocardiograms, were normal until the final hospital admission.

At 22 months of age she was admitted due to severe metabolic acidosis with a lactic acid of 15.6 mmol, and septic shock secondary to a central line infection. The patient's clinical status progressively worsened and she became encephalopathic with EEG demonstrating diffuse slowing. Twenty four days after admission, brain MRI, which had been normal at 2 months of age, showed diffuse brain volume loss, abnormal T2 prolongation and abnormal and symmetric restricted diffusion in the basal ganglia, midbrain, pons, medulla and dentate nuclei. Despite all efforts, the patient developed multisystem organ failure. The family elected to minimize medical interventions and she died at 24 months of age.

3.2. Patient 2

Patient 2 was the 2nd full term male of unrelated healthy parents weighing 3494 g (50th%). At 24 months of age he was found to have mild anemia and was started on iron supplementation. After 3 months of iron therapy, the patient was noted to be pale and was admitted for workup. Laboratory results showed low hemoglobin at 4.4 g/dL (10.2–15.4 g/dL) with an MCV of 108 FL (76–91FL), elevated reticulocyte count at 3.1% (0.5–2.5%) with normal Vitamin B12, serum folate and RBC folate levels. A bone marrow biopsy showed hypocellularity for age and vacuolization in all 3-cell lines. He was also found to be positive for RSV and Parvovirus B19. After red blood cell transfusions, the patient was discharged in stable condition and did not require further outpatient transfusions.

At 33 months of age the patient was readmitted due to abdominal pain and emesis and was found to have persistent anemia with hemoglobin of 8.6 g/dL along with metabolic acidosis with elevated anion gap (22 mEq/L, normal 1–15 mEq/L, bicarbonate 7.7 mmol/L normal 21–32 mmol/L), low glucose (52 mg/dL), low sodium (131 mmol/L normal 134–145 mmol/L) and elevated potassium (5.2 mmol/L normal 3.5–5.0 mmol/L). The patient was treated with IV fluids and fully recovered without transfusion. Initial metabolic workup revealed elevated lactic acid at 6.4 mmol and abnormal urine organic acids showing mild increase in lactic, pyruvic, fumaric and 3 OH butyric acids. Initial test for the common Pearson mtDNA deletion in blood was negative using a PCR approach.

At 37 months of age the patient presented in shock with respiratory failure and severe metabolic acidosis (pH 6.98 normal 7.35–7.45, bicarbonate 7 mmol/L, lactic acid 9.6 mmol/L normal 0.5–2.2 mmol/L). He had pancytopenia with WBC 2.6 K/UL (3.9–13.7 K/UL) ANC 234/UL (1400–9100/UL), hemoglobin 8.5 g/dL and platelets 29 K/UL