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Case Report

The Phenotypic Spectrum of Pearson Syndrome is Still Expanding

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Abstract

Pearson syndrome is a rare, sporadic multiorgan disorder that continues to evolve. It is caused by a deletion in the Mitochondrial DNA (mtDNA). Single large-scale Mitochondrial DNA (mtDNA) deletion syndromes (SLSMDS) include three syndromes with overlapping phenotypes: 1. Pearson Syndrome (PS), 2. Kearns-Sayre syndrome (KSS), 3. Chronic Progressive External Ophthalmoplegia (CPEO). PS is characterized by three cardinal clinical features: macrocytic sideroblastic anemia, exocrine pancreatic insufficiency, and lactic acidosis. We report a new patient with Pearson Syndrome with a unique clinical presentation. Fanconi syndrome, adrenal insufficiency, and hypoglycemia were some of our patient's clinical manifestations suggestive of "Pearson like" phenotype. This case report aims to focus on the large still expanding clinical spectrum of PS overtime. This phenomenon is due to heteroplasmy; i.e. coexistence of copies of Mutated DNA (Δ-mtDNA) in the same cell with Wild-Type DNA (wtDNA). As proven by our patient's case, whole-exome sequencing of blood, testing both mitochondrial and nuclear DNA led to the diagnosis.

Introduction

Pearson syndrome (bone marrow-pancreas syndrome), first described in 1979 by Pearson [1] and categorized ten years later to the group of mitochondriopathies by Rötig [2], is a sporadic multiorgan disorder that continues to evolve. Only a very few cases have been described so far, and the incidence is estimated to be nearly one case per million[3]. Mitochondriopathies are a heterogeneous group of disorders. An impairment of the mitochondrial respiratory chain enzymes account for these disorders [4]. Pearson Syndrome (PS) is caused by a deletion in the mitochondrial DNA (mtDNA) and belongs explicitly to the group of single large-scale mitochondrial DNA (mtDNA) deletion syndromes (SLSMDS).

Single large-scale mitochondrial DNA (mtDNA) deletion syndromes (SLSMDS) include in total three syndromes with overlapping phenotypes:

1. Pearson Syndrome (PS, refractory sideroblastic anemia associated with pancreatic insufficiency),
2. Kearns-Sayre Syndrome (KSS, ptosis/ophthalmoparesis associated with pigmentary retinopathy and other specific diagnostic criteria)
3. Chronic Progressive External Ophthalmoplegia (CPEO, primarily affecting the ocular muscles) [4].

Three main clinical features characterize PS: macrocytic sideroblastic anemia, exocrine pancreatic insufficiency, and lactic acidosis. The anemia is transfusion-dependent in infancy, and pancytopenia can also occur. Vacuolization in hematopoietic progenitors, hypocellularity, and ringed sideroblasts are typically observed in the bone marrow (BM) [3]. Pancreatic dysfunction is a specific feature of PS, but it is not needed for the diagnosis [5]. It occurs secondary to pancreas fibrosis ultimately leading to fatty diarrhea and failure to thrive due to malabsorption [1]. Lactic acidosis is due to a rise in anaerobic metabolism caused by defective oxidative phosphorylation and decreased ATP production from the mutated mitochondria [6]. A ¨common deletion¨ of about 5 Kb (4977 bp) is found in about one-third of affected patients [7]. PS as a multiorgan dysfunction can also lead to other manifestations, including renal tubulopathy, liver cholestasis and fibrosis, adrenal insufficiency, diabetes mellitus, cardiomegaly, and cardiac conduction defects [8,9] .Children who survive PS may develop Kearns–Sayre syndrome or Leigh syndrome later in life [3,10].

Case Report

Here, we report a new patient with Pearson Syndrome with a unique clinical presentation. This 21-month-old boy is the second child of healthy, unrelated parents. The pregnancy was uneventful except for maternal diabetes. He was born after 38 weeks of gestation with a birth weight of 3.130 g. After the child's birth, his mother was diagnosed with a cystic formation of the brain. He was well until two months of age, when he presented with pallor and fatigue. A Complete Blood Cell Count (CBC) demonstrated anemia with an Hgb of 5.5g/dl. Macrocytic hypochromic anemia with low reticulocyte count and considerable anisocytosis, pyknocytosis, and poikilocytosis was revealed. He was treated with a packed red blood cell transfusion and subsequently discharged at home. A month later, he presented with pancytopenia (WBC:3.260/ µL, Hb: 6.7 g/dl, PLT: 135.000/ µL), prompting a bone marrow aspiration (BMA). Vacuolization of myeloid precursors was observed in his bone marrow and hypocellularity with mild phagocytosis was documented. There were no signs of malignancy. After testing his bone marrow with the rt-PCR method, no virus was detected, including the ParvoB19 virus. Cytogenetic analysis revealed no evidence of Fanconi anemia. Signs of spontaneous bone marrow recovery were seen after his third blood transfusion.At the age of 14 months, his pediatrician referred him to the first Department of Pediatrics due to hypotonia, failure to thrive, delay in reaching milestones, and recurrent episodes of respiratory tract infections. On admission to our institution, he was hypotonic with delayed motor development but without ataxia. He could not walk or sit without support. The tendon reflexes were diminished, but his cranial nerve functions were spared. Although easily fatigued, he was mentally alert.

Up to 14 months, his weight was below the 3rd percentile, and his height and head circumference in the 15th percentile. His peak weight was 10% below the mean at five months but decreased to 30% below the mean by 14months. Between 6 months and 14months, he presented a stunting of weight gain , not gaining any weight during this 9-month period. His initial laboratory work-up revealed a normal CBC (WBC: 6470/ µL, Hb: 12,1 g/dl, Hct: 36,3%, MCV: 92,9 fL, PLT: 160.000/

μL), hyponatremia: 132 mmol/L, elevated blood lactate of 59.8 mg/dL (normal value < 22 mg/dL) with normal liver function tests and normal creatine kinase levels. Interpretation of his Arterial Blood Gas (ABG) showed a metabolic acidosis with an elevated anion gap, partially compensated by respiratory alkalosis.Regarding his metabolic state, he presented low urinary lactate of 8.923 mmol/mol of urine creatinine (normal value 21-38), and high urine pyruvate at 454.5 mmol/mol of urine creatinine (normal value 5.1-28.2). There was also ketonuria due to poor feeding, and metabolites of Krebs cycle were excreted in his urine. Total blood carnitine was low at 20.27 μmol/lit (normal value 25-75 μmol/lit), and the ratio of free carnitine to the total was 60.1% (normal value above 75%).Due to his severe hypotonia, we proceeded to enzyme testing for Pompe disease, which was negative, and brain Magnetic Resonance Imaging (MRI) which depicted no abnormalities. His hearing and ophthalmological examinations were unremarkable. Ultrasound examination of the liver and echocardiography were normal. His kidneys were slightly increased in size with increased echogenicity. Chest X-ray showed interstitial findings. His inpatient stay was complicated with episodes of unexplained vomiting and hyponatremia that persisted or even worsened despite substitutive treatment. Genetic testing for congenital hypoaldosteronism was negative; he was heterozygous for p.V386A variant for CYP11B2 gene. Further workup revealed primary adrenal insufficiency (ACTH>1.250pg/ml, Cortisol 6.7μg/dl) and therefore, hydrocortisone and fludrocortisone were continued. In addition, his physical findings suggested that he was volume-depleted, which was consistent with renal salt wasting. He was also tachypneic, trying to compensate for metabolic acidosis. His laboratory work-up showed persistent hyponatremia (128 mmol/L), hypochloraemia (90mmol/L), hypophosphatemia (2.8 mg/dL), hypomagnesemia (1.3mg/dL) and hypouricaemia (0.5 mg/dL). His urine pH was between 5.0 and 5.5; there was proteinuria (traces to 100mg/dL), glucosuria, natriouria, calciuria, uricosuria, phosphaturia, magnesiuria, and generalized aminoaciduria. These findings indicated tubular dysfunction and, specifically, pointed towards Fanconi syndrome. Bicarbonate, phosphate, magnesium supplementation was administered. Due to his excessive weight loss, an enteral feeding tube was placed.

According to the diagnostic criteria of Morava *et al.* (2006) (figure 1), a mitochondrial disorder was suspected. Therefore, a testing for nuclear (nDNA) and mitochondrial DNA (mtDNA) was sent since approximately 75% of mitochondriopathies are linked to mutations in nDNA, with the remaining 25% being linked to mutations in mtDNA [12].The WES study (Whole-exome sequencing) for nuclear DNA identified a potentially pathogenic variant (NM_000495.5: c.212C> T) in the COL4A5 gene associated with ALPORT 1 syndrome (MIM # 301050). Molecular testing for mitochondrial DNA (mtDNA) deletions detected an mtDNA deletion of 6 kb on peripheral blood leukocytes with the Long-Range PCR method. This deletion is consistent with Pearson Syndrome and Kearns-Sayre Syndrome. The deletion in Pearson Syndrome is similar to the mtDNA deletion found in Kearns–Sayre syndrome [13]. Therefore, the diagnosis of PS could be confirmed. At 21 months, the patient remains on a regular outpatient follow-up with normal blood count (Hb 10.9 g/L, mean corpuscular volume 85.8 fL, platelets 200 x 109/L), normal electrolytes, serum bicarbonate 18–24 mmol/L, blood lactate 47.9 mg/dL. An episode of severe hypoglycemia, which has occurred, has been secondary to overall inefficient ATP production as his adrenal gland is unable to increase cortisol production in response to stress. This episode brought him back to the hospital for stabilization. Additionally, after normalizing his pH and serum bicarbonate levels, his tachypnea continues along with fine crackles on auscultation. Reduced lung clearance due to his muscle weakness and possible aspirations could justify his lungs' pathological findings. He managed to gain weight, and now his weight is in the 50th percentile. Fecal elastase is normal up to now. Renal dysfunction has progressed, and therefore, the bicarbonate regimen is being decreased. Because of his poor general condition and his disease's multisystemic nature, the patient is monitored once per month by a multidisciplinary team.

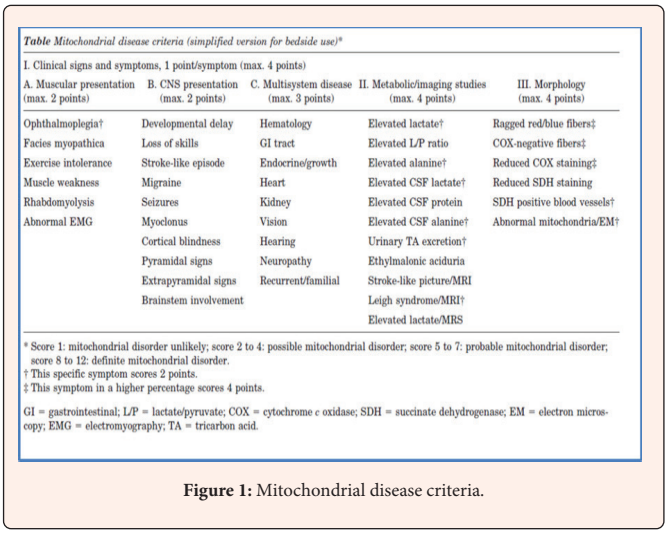

*Table Mitochondrial disease criteria (simplified version for bedside use)**

I. Clinical signs and symptoms, 1 point/symptom (max. 4 points)

A. Muscular presentation (max. 2 points)	B. CNS presentation (max. 2 points)	C. Multisystem disease (max. 3 points)	II. Metabolic/imaging studies (max. 4 points)	III. Morphology (max. 4 points)
Ophthalmoplegia†	Developmental delay	Hematology	Elevated lactate†	Ragged red/blue fibers‡
Facies myopathica	Loss of skills	GI tract	Elevated L/P ratio	COX-negative fibers‡
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; score 2 to 4: possible mitochondrial disorder; score 5 to 7: probable mitochondrial disorder; score 8 to 12: definite mitochondrial disorder.
† This specific symptom scores 2 points.
‡ This symptom in a higher percentage scores 4 points.

GI = gastrointestinal; L/P = lactate/pyruvate; COX = cytochrome *c* oxidase; SDH = succinate dehydrogenase; EM = electron microscopy; EMG = electromyography; TA = tricarbon acid.

Figure 1: Mitochondrial disease criteria.

Results and Discussion

This article describes a case report of Pearson Syndrome with a unique clinical presentation (Table 1) and aims to highlight the wide spectrum of PS clinical manifestations over time, which is indicated by the improvement of our patient's renal tubular acidosis during this short period of monitoring. The transfusion-dependent infantile anemia of classic PS [10] that improves over time follows the same pattern in our patient whose bone marrow spontaneously recovered after three blood transfusions in early infancy. This impressive phenomenon is caused by heteroplasmy. In mitochondriopathies caused by mtDNA mutations, copies of mutated mitochondrial DNA (Δ-mtDNA) co-exist in the same cell with wild-type DNA (wtDNA). Coexistence creates heteroplasmy inside the cell (Farruggia, Di Marco and, Dufour, 2018).Heteroplasmy, tissue distribution of mutant mtDNAs, and vulnerability of each tissue to impaired oxidative phosphorylation (threshold effect) all account for the wide range of clinical presentation [3,15].High expressivity is a characteristic of PS; although PS has classically been thought of as a homogenous entity with bone marrow failure and exocrine dysfunction, however, based on our experience with the current patient, we conclude that PS's phenotypic spectrum still evolves. Pancreatic dysfunction is not a clinical feature of our patient until now, but lactic acidosis was severe due to anaerobic metabolism. His mtDNA deletion of 6kb, is not the "common deletion" of about 5 kb. Adrenal insufficiency and resulting severe hyponatremia and hypoglycemia are other clinical manifestations inour patient. Primary adrenal insufficiency has not been reported so far in patients with a typical 4.9 kb deletion [9]. However, patients with "Pearson-like" phenotype and various mtDNA deletions have been described with functional adrenal abnormalities, as in our patient.The genetic basis of inheritance is sporadic. De novo mutations in the oocyte or during early embryogenesis are the leading cause [16,17]. Since a low possibility of maternal inheritance exists (a case of a woman with ocular myopathy giving birth to a boy with Pearson syndrome has been reported [18]), maternal testing was performed in our patient, which was negative.

PS is a severe metabolic disorder with few previously reported cases. The identification of our patient's mtDNA deletion set the definitive diagnosis of PS as, until

Table 1: Patient characteristics

Age of diagnosis	Pancreas Involvement (Yes/No)	Presenting feature	Bone Marrow	Lactate (mg/dL)	Bicarb (mmol/L)	Renal tubular acidosis	Development	Hypoglycemia (Yes/No)	Adrenal insufficiency (Yes/No)
19m	No	Anemia with pallor and fatigue HgB	Hypocellularity	59.8	12.4	Yes	Gross motor delay	Yes	Yes
		(5.5g/d)	Vacuolization				Speech delay		

then, there were only clinical indications suggestive of this diagnosis. Without a genetic diagnosis, in-depth genetic counseling would not have been possible, and a plausible option for participating in clinical trials and understanding the underlying mechanisms or avoiding further complications would not have been offered. Given improved testing techniques, it is essential to emphasize that the mtDNA deletion was detected via blood sample and not muscle biopsy. As proven by our patient's case, whole-exome sequencing of blood, testing both mitochondrial and nuclear DNA led to the diagnosis and significantly improved the overall diagnosis score. Therefore, analyzing both nuclear and mitochondrial DNA represents the best diagnostic option [19]. The prognosis remains poor, and therapy is purely supportive. Recent ongoing clinical trials in Israel aim to reduce PS symptoms by a process called mitochondrial augmentation therapy. MNV-BM-BLD (autologous CD34+ cells enriched with blood-derived mitochondria) is a therapeutic process for enriching a patient's peripheral hematopoietic stem cells with healthy mitochondria derived from donor blood cells. In conclusion, we suggest using long-read sequencing (third-generation sequencing) in a single test when we suspect a mitochondrial disease. If it is not possible, genetic testing of peripheral blood to search for mtDNA deletions with long-range PCR should be considered. Setting diagnosis in mitochondriopathies is a real challenge for the physician since the patient's phenotype is unpredictable and differs among different patients and within the same patient during the course of the disease itself due to heteroplasmy. Pearson syndrome (bone marrow-pancreas syndrome) -despite its name-, does not require pancreatic insufficiency for the diagnosis. Nevertheless, this diagnosis should be considered in any patient with macrocytic anemia of early infancy, especially when accompanied with pancytopenia.

The detailed description of every single patient may help unravel the whole spectrum of clinical phenotype of PS.

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