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Pearson Syndrome Presenting as Nonimmune Hydrops Fetalis With Severe Pancytopenia in a Premature Neonate: A Case Report

Nasab Abdulsater [1], Maha Annan [1], Hassan Fakherdine [2], Ali Berro [3], Hadeel Jaafar [2]

1. Pediatric Department, Faculty of Medical Sciences, Lebanese University, Beirut, LBN 2. Pediatric Department, Al-Zahraa Hospital University Medical Center, Beirut, LBN 3. Hemato-oncology Department, Al-Zahraa Hospital University Medical Center, Beirut, LBN

Corresponding author: Nasab Abdulsater, nasab.abdulsater83@gmail.com

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Abstract

Pearson syndrome is a rare multisystem mitochondrial disorder caused by deletions in mitochondrial DNA and classically characterized by sideroblastic anemia, bone marrow dysfunction, and pancreatic insufficiency. Neonatal presentation is uncommon and may pose a significant diagnostic challenge. We report the case of a premature female neonate who presented with nonimmune hydrops fetalis, profound anemia, severe neutropenia, recurrent inflammatory episodes, persistent pancytopenia, and transient hyperglycemia requiring insulin therapy. Extensive investigations failed to identify an infectious, hematologic, cardiac, or metabolic cause. Bone marrow aspiration demonstrated findings consistent with bone marrow failure, and whole exome sequencing subsequently confirmed a mitochondrial DNA deletion syndrome consistent with Pearson syndrome. This case highlights the importance of considering mitochondrial disorders in neonates presenting with unexplained hydrops fetalis and persistent cytopenias.

Categories: Hematology, Genetics, Pediatrics
Keywords: genetic disease, hydrops fetalis, mitochondrial cytopathy, pancytopenia, pearson's syndrome

Introduction

Pearson syndrome is a rare mitochondrial disorder first described by Pearson et al. in 1979 [1]. The disease results from large-scale deletions of mitochondrial DNA (mtDNA) and predominantly affects tissues with high metabolic demands. Clinical manifestations commonly include refractory anemia, neutropenia, thrombocytopenia, exocrine pancreatic dysfunction, growth failure, and metabolic abnormalities [1-3]. The presentation is highly variable, often leading to delayed diagnosis [2,3]. Although hematologic abnormalities are well recognized, presentation during the neonatal period with hydrops fetalis is exceptionally rare [4,5]. We describe a premature neonate with severe nonimmune hydrops fetalis and profound cytopenias who was ultimately diagnosed with Pearson syndrome through genetic testing.

Case Presentation

A female neonate was delivered at 31+1 weeks of gestation via cesarean section because of a prenatal diagnosis of hydrops fetalis. She was born to a gravida 3, para 1, abortus 1 (G3P1A1) mother whose pregnancy was remarkable only for maternal anemia treated with oral iron supplementation. Maternal infectious screening, including testing for TORCH (toxoplasmosis, other infections, rubella, cytomegalovirus (CMV), herpes simplex virus) infections and parvovirus, was negative. Both direct and indirect Coombs tests were negative. There was no significant past medical history or parental consanguinity. The patient's older sibling was healthy and developing normally.

At birth, the infant had a birth weight of 2.010 kg and Apgar scores of 6 and 7 at one and five minutes, respectively. Due to respiratory distress and severe hydrops fetalis, she required immediate endotracheal intubation and admission to the neonatal intensive care unit. Physical examination revealed generalized edema consistent with hydrops fetalis. Significant ascites was present and required therapeutic paracentesis. A mild pericardial effusion had been identified prenatally and subsequently resolved spontaneously without specific intervention. Following resolution of the generalized edema and ascites, her weight decreased to 1.200 kg, reflecting the severity of fluid overload at presentation.

Initial laboratory investigations on the first day of life demonstrated severe anemia, with a hemoglobin concentration of 2.5 g/dL, and profound neutropenia, with an absolute neutrophil count (ANC) of 350 cells/µL. The patient received a packed red blood cell transfusion. Empiric antimicrobial therapy with ampicillin, gentamicin, and cefotaxime was initiated. The initial laboratory findings are summarized in Table *1*.

Test	Patient Value	Unit	Reference Range
Hemoglobin	2.5	g/dl	12-16
White blood cell count	1.59	$10^{\wedge 3}/\mu L$	4-11
Absolute neutrophil count	0.35	10^3/µL	1.6-7.2
C-reactive protein	<0.6	mg/L	0-5
Platelets	137	10^3/µL	150-400
Thyroid-stimulating hormone	2.2	uIU/ml	<15uIU/ml

TABLE 1: Initial laboratory investigations during the neonatal period.

Given the presence of nonimmune hydrops fetalis, a broad differential diagnosis was considered, including infectious, hematologic, metabolic, genetic, and cardiac etiologies. Cardiac causes were subsequently excluded following echocardiographic evaluation, which demonstrated only a mild pericardial effusion without structural cardiac abnormalities. Electrocardiography was normal.

Over the following days, the patient's edema gradually improved, with resolution of ascites following paracentesis. She was successfully extubated, and enteral feeding was initiated. During her hospital course, the infant experienced recurrent episodes of elevated C-reactive protein (CRP) without an identifiable infectious source. Multiple blood and urine cultures remained negative except for a single episode of bloodstream infection caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*, which was treated with meropenem. Despite appropriate antimicrobial therapy, intermittent inflammatory episodes characterized by recurrent CRP elevation continued to occur, leading to repeated courses of broad-spectrum antibiotics, including meropenem, vancomycin, and amikacin.

During the episode of ESBL-producing *E. coli* bloodstream infection, the infant developed transient hyperglycemia lasting several days. The hyperglycemia required treatment with an intravenous insulin infusion. Following appropriate antimicrobial therapy with meropenem and resolution of the infection, glycemic control was achieved, and insulin therapy was successfully discontinued without recurrence.

The patient continued to exhibit persistent cytopenias requiring multiple packed red blood cell and platelet transfusions. Owing to ongoing neutropenia, granulocyte colony-stimulating factor (G-CSF) therapy was initiated. Extensive diagnostic investigations were performed. Thyroid function tests, glucose-6-phosphate dehydrogenase (G6PD) enzyme activity, hemoglobin electrophoresis, TORCH screening, amino acid profile, autoimmune workup, and karyotype analysis were all normal. The patient's blood group was O positive. CMV immunoglobulin G (IgG) and parvovirus IgG antibodies were positive, while urine CMV polymerase chain reaction (PCR) and blood parvovirus PCR were negative. Urine organic acid analysis demonstrated mild elevations of lactic acid, 3-hydroxybutyric acid, and 4-hydroxyphenyllactic acid. The reticulocyte count was low. Bone marrow aspiration revealed findings consistent with bone marrow failure.

Molecular genetic testing was subsequently performed. Next-generation sequencing (NGS)-based copy-number variant (CNV) analysis detected a large pathogenic deletion in the mitochondrial genome of approximately 5 kb (chrM:8483-13446), present in a heteroplasmic state in approximately 71% of reads. This finding was consistent with a mtDNA deletion syndrome. No further clinically relevant variants related to the described phenotype were detected. In the context of the patient's severe neonatal cytopenias, bone marrow failure, metabolic abnormalities, and unexplained nonimmune hydrops fetalis, the genetic findings supported a diagnosis of Pearson syndrome.

The patient was discharged home at corrected gestational age of 38 +3 weeks, and weight of 2 kg, in stable condition with a plan for close outpatient follow-up. Weekly laboratory monitoring, including complete blood counts, was planned, with supportive transfusion therapy using packed red blood cells and platelets administered as clinically indicated, in addition to daily G-CSF. Given the persistent bone marrow failure, the patient will continue follow-up with the hematology and metabolic teams for consideration of hematopoietic stem cell transplantation.

Discussion

Pearson syndrome is a rare multisystem mitochondrial disorder presenting in 1 per 1,000,000 cases, caused by large-scale deletions of mtDNA [1]. First described by Pearson et al. in 1979, the syndrome is classically characterized by refractory sideroblastic anemia, vacuolization of bone marrow precursors, exocrine pancreatic dysfunction, growth failure, and metabolic abnormalities [1,2]. The clinical presentation is highly

heterogeneous, ranging from severe neonatal disease to milder forms presenting later in infancy or childhood [2,3]. Because of its rarity and broad phenotypic spectrum, diagnosis is often delayed [3].

The present case is notable for several reasons. First, our patient presented prenatally with nonimmune hydrops fetalis, a rare and unusual manifestation of Pearson syndrome [4,5]. Hydrops fetalis has a broad differential diagnosis, including cardiovascular disorders, chromosomal abnormalities, congenital infections, hematologic diseases, metabolic disorders, and genetic syndromes. In our patient, extensive evaluation failed to identify a conventional cause of hydrops. The severe anemia observed at birth, with a hemoglobin concentration of 2.5 g/dL, likely contributed significantly to the development of hydrops through impaired tissue oxygen delivery and possible high-output cardiac physiology. Previous reports of neonatal-onset Pearson syndrome have described severe hematologic manifestations and variable presentations, supporting consideration of mitochondrial disorders in neonates with unexplained hydrops and cytopenias [4,5].

A second remarkable feature was the profound hematologic involvement. Severe anemia and neutropenia were evident from the first day of life, followed by persistent cytopenias requiring repeated blood product transfusions. Hematologic abnormalities represent one of the hallmarks of Pearson syndrome and are associated with mitochondrial dysfunction affecting hematopoietic progenitors [2,3,6]. Bone marrow failure may manifest as anemia, neutropenia, thrombocytopenia, or pancytopenia and may result in transfusion dependence [5-7]. The low reticulocyte count observed in our patient further supported impaired bone marrow production rather than peripheral destruction. The persistence of cytopenias despite supportive measures including regular blood, fresh frozen plasma, and platelet transfusions prompted further diagnostic investigations, ultimately leading to genetic confirmation of Pearson syndrome [6,7].

Another notable aspect of this case was the occurrence of transient hyperglycemia requiring intravenous insulin infusion during an episode of bloodstream infection caused by ESBL-producing *E. coli*. The hyperglycemia resolved completely following treatment of the infection and did not recur after discontinuation of insulin therapy. Although endocrine pancreatic dysfunction and diabetes mellitus have been reported in patients with Pearson syndrome, particularly during the later course of mitochondrial disease, the temporal association with sepsis and the transient nature of the hyperglycemia in our patient suggest that it was more likely a stress-related metabolic response to severe infection rather than a manifestation of underlying pancreatic dysfunction [1,2,8]. Nevertheless, given the known multisystem nature of Pearson syndrome, ongoing metabolic and endocrine surveillance remains warranted [3,8].

The patient's recurrent inflammatory episodes represented an additional diagnostic challenge. Despite repeated elevations in CRP, microbiological investigations were largely unrevealing, with only a single documented episode of ESBL-producing *E. coli* bacteremia. Patients with Pearson syndrome are particularly vulnerable to infections because of severe neutropenia and bone marrow dysfunction [5,6]. Distinguishing infectious from noninfectious inflammatory episodes can therefore be difficult in patients with severe mitochondrial disease and may result in repeated courses of antimicrobial therapy [9].

Metabolic investigations in our patient demonstrated mild elevations of lactic acid and other metabolites on urine organic acid analysis. These findings may be compatible with impaired oxidative phosphorylation associated with mtDNA deletions [2,3,9]. Mitochondrial dysfunction can impair aerobic energy production and lead to accumulation of lactate and other intermediary metabolites. Although these abnormalities are not specific for Pearson syndrome, they may provide important clues supporting the diagnosis in the appropriate clinical context [3,9].

The diagnosis of Pearson syndrome remains challenging because no single clinical feature is pathognomonic. Patients often undergo extensive evaluations for infectious, hematologic, immunologic, and metabolic disorders before the underlying mitochondrial disease is recognized [3,4,9]. In our patient, numerous investigations, including TORCH screening, hemoglobin electrophoresis, thyroid studies, autoimmune testing, Coombs testing, karyotyping, and metabolic analyses, failed to establish a diagnosis. Definitive diagnosis was achieved through molecular genetic testing, emphasizing the importance of mtDNA analysis in neonates with unexplained multisystem disease and persistent cytopenias [3,4,9].

The prognosis of Pearson syndrome is generally poor during infancy because of recurrent infections, progressive bone marrow failure, metabolic decompensation, and multisystem organ involvement [2-5]. Survivors may later develop other phenotypes associated with single large-scale mtDNA deletions, including Kearns-Sayre syndrome and progressive external ophthalmoplegia [4,10,11]. The identification of identical mtDNA deletions in individuals with different clinical phenotypes further illustrates the marked phenotypic variability of these disorders [10,11]. Early recognition is therefore essential for prognostic counseling, surveillance for systemic complications, and optimization of supportive care [3,5].

This case expands the recognized clinical spectrum of Pearson syndrome by highlighting a presentation characterized by nonimmune hydrops fetalis, profound neonatal cytopenias, and recurrent inflammatory episodes. The combination of unexplained hydrops fetalis and severe cytopenias in the neonatal period should prompt consideration of mitochondrial disorders and early genetic evaluation when routine

investigations are unrevealing [4,9].

Conclusions

Pearson syndrome should be considered in neonates presenting with unexplained nonimmune hydrops fetalis, severe cytopenias, recurrent transfusion requirements, metabolic abnormalities, and transient hyperglycemia. This case expands the recognized spectrum of neonatal presentations of Pearson syndrome and underscores the value of comprehensive molecular genetic testing in establishing the diagnosis of rare mitochondrial disorders. Early recognition may facilitate appropriate supportive management, genetic counseling, and surveillance for multisystem complications

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Nasab Abdulsater, Maha Annan, Hassan Fakherdine, Ali Berro, Hadeel Jaafar

Acquisition, analysis, or interpretation of data: Nasab Abdulsater, Maha Annan, Hassan Fakherdine, Ali Berro, Hadeel Jaafar

Drafting of the manuscript: Nasab Abdulsater, Maha Annan, Hassan Fakherdine, Ali Berro, Hadeel Jaafar

Critical review of the manuscript for important intellectual content: Nasab Abdulsater, Maha Annan, Hassan Fakherdine, Ali Berro, Hadeel Jaafar

Supervision: Nasab Abdulsater, Maha Annan, Hassan Fakherdine, Ali Berro, Hadeel Jaafar

Disclosures

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