

Pearson syndrome, a rare mitochondriopathy - case report**Síndrome de Pearson, uma mitocondriopatia rara - relato de caso**

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Kariny Louize Lopes

Undergraduate student in Biomedicine at the Centro Universitário de Formiga - UNIFOR-MG

Endereço: Rua Dr. Arnaldo Sena, 328, Água Vermelha, Formiga-MG, CEP: 35570-000

E-mail: lopes.uniformg@gmail.com

Lilia Rosário Ribeiro

PhD in Genetics and Plant Improvement from the Federal University of Lavras – UFLA

Full Professor at Centro Universitário de Formiga - UNIFOR-MG

Endereço: Rua Dr. Arnaldo Sena, 328, Água Vermelha, Formiga-MG, CEP: 35570-000

E-mail: lilia@uniformg.edu.br

Hesley Machado Silva

Doctor in Education

Full Professor at Centro Universitário de Formiga - UNIFOR-MG

Endereço: Rua Dr. Arnaldo Sena, 328, Água Vermelha, Formiga-MG, CEP: 35570-000

E-mail: hesley@uniformg.edu.br

Robert A. Michaels

PhD, CEP

President of RAM TRAC Corporation (Schenectady, New York, USA), consulting in toxicology and health risk assessment Schenectady, NY

E-mail: ram@ramtrac.com

ABSTRACT

Pearson's Syndrome (PS) is a rare multisystemic mitochondriopathy caused by deletions and/or duplications in mitochondrial DNA (mtDNA). We describe a girl, age 3 years and 10 months, who was diagnosed with PS. The case highlights two main characteristics of PS: dysfunction in the hematopoietic system, and pancreatic exocrine insufficiency. The PS diagnosis in the present case was confirmed via molecular diagnosis, specifically mtDNA analysis, which revealed the presence of heterozygous deletions in the MT-ND4, MT-ND5, MT-ND6 and MT-TM genes. The patient is dependent on erythropoietin to maintain hemoglobin levels, and pancreatin to manage pancreatic dysfunction. She has surpassed the average longevity of Pearson's Syndrome patients, who usually die before age three. The PS case described here also highlights the importance of molecular diagnosis in patients exhibiting multisystemic symptoms of unknown etiology.

Keywords: Pearson's Syndrome, mitochondriopathy, pancreatic insufficiency, multisystemic.**RESUMO**

A Síndrome de Pearson (PS) é uma mitocondriopatia multisistêmica rara causada por deleções e/ou duplicações no ADN mitocondrial (mtDNA). Descrevemos uma rapariga, com 3 anos e 10 meses de idade, que foi diagnosticada com PS. O caso destaca duas características principais da PS: disfunção no sistema hematopoiético, e insuficiência pancreática exócrina. O diagnóstico de PS no presente

caso foi confirmado através de diagnóstico molecular, especificamente análise mtDNA, que revelou a presença de deleções de heterozigose nos genes MT-ND4, MT-ND5, MT-ND6 e MT-TM. O paciente depende da eritropoietina para manter os níveis de hemoglobina, e da pancreatina para gerir a disfunção pancreática. Ela ultrapassou a longevidade média dos doentes com Síndrome de Pearson, que normalmente morrem antes dos três anos de idade. O caso de PS aqui descrito também realça a importância do diagnóstico molecular em pacientes com sintomas multissistêmicos de etiologia desconhecida.

Palavras-chave: Síndrome de Pearson, mitocondriopatia, insuficiência pancreática, multissistêmica.

1 INTRODUCTION

Pearson's Syndrome (PS) is a mitochondrial cytopathy, usually fatal in early childhood, caused by deletions and/or duplications in mitochondrial DNA (mtDNA). These mutations predominantly occur spontaneously in the ovocyte, but rarely may also occur via maternal inheritance (FARRUGGIA; DI MARCO; DUFOUR, 2018; KHASAWNEH et al., 2018; SHANSKE et al., 2002). PS is extremely rare, having been being reported in fewer than 150 cases worldwide (FARRUGGIA; DI MARCO; DUFOUR, 2018).

The pathology was described first in 1979, mainly characterized by pancreatic exocrine insufficiency and dysfunction of the hematopoietic system. Together, these produce sideroblastic anemia (inability to make hemoglobin despite sufficiency of iron), vacuolization of precursor cells (stem cells committed to formation of new blood cells), neutropenia (abnormally low blood neutrophil count), and pancytopenia (deficiency of red blood cells, white blood cells, and blood platelets). PS eventually was recognized as multisystemic following reports of renal and hepatic problems in some carriers (FARRUGGIA et al., 2016; KHASAWNEH et al., 2018). PS affects both sexes, without evident racial predilection (MEDSCAPE, 2019).

Clinical manifestations of PS commonly begin in the first year of life, and most patients die before age three (FARRUGGIA et al., 2016). Due to the multiplicity of symptoms and organs involved, PS diagnosis is difficult, requiring analyses of the mitochondrial genome to confirm cytopathy. So far, available treatments are only palliative, not curative. Most patients depend upon blood transfusions, and some may benefit from pancreatic enzyme replacement (KHASAWNEH et al., 2018).

2 CASE REPORT

We describe a girl, age three years and 10 months, whose birth followed a healthy, uneventful pregnancy. She appeared to be anatomically normal at birth, with weight 3,335 kg and length 50 cm. The patient is the second child of a healthy couple. The family history is reported negative for inbreeding and for genetic and hematological diseases.

The patient's symptoms began at 7 months. They included paleness of skin and mucous membranes, lack of appetite, yellowish eye color, and shortness of breath. The complete blood count (CBC) revealed mild anemia, with hematocrit (Ht) 29.0 percent and hemoglobin (Hb) 9.8 g/dL. In the five subsequent months, both hematocrit and hemoglobin decreased, with Ht = 11.9 percent and Hb = 4.1 g/dL.

At 1 year of age, the patient was referred to the Hospital das Clínicas of the Federal University of Minas Gerais, where she remained hospitalized for eight days due to persistent severe anemia with no apparent cause. The patient presented with neutropenia (0.37×10^3 cells/ μ L), thrombocytopenia (121×10^3 cells/ μ L), macrocytic anemia (Ht = 16.1%, Hb = 5.9 g/dL, VCM = 88.5 fL), and anisocytosis (RDW = 17.5). She required and received blood transfusion. Liver, pancreatic and renal function evaluation tests yielded normal results.

To understand the possible causes of the patient's anemia, several tests were performed: folic acid, lactate dehydrogenase (LDH), vitamin B12, direct Coombs test, serum iron, ferritin, transferrin saturation index, and iron fixation capacity. Results were within applicable reference values, thereby ruling out iron deficiency anemia, hemolytic anemia, and megaloblastic anemia.

A subsequent bone marrow aspiration test was performed using Perls method, in which Prussian blue dye is used as an indicator to quantify levels of iron storage. The test revealed sideroblastic anemia, in which iron accumulates in mitochondria around erythroblast nuclei, imparting a ringed appearance (perinuclear ringed sideroblasts). This diagnosis was indicated by values of 57 percent of sideroblasts and 20 percent of sideroblasts in the ring structure.

A myelogram was done, in which contrast dye is injected into the spinal column prior to x-ray. The test revealed, in the erythrocytic series, the presence of cytoplasmic vacuolization in 76.9 percent of pro-erythroblasts, asynchrony of erythroblast maturation, and erythroblast binucleation. In the granulocytic series, cytoplasmic vacuolization was verified in 74.3 percent of the myeloblasts, and in 23 percent of pro-myelocytes, in addition to asynchrony in neutrophil cell maturation and polysegmented neutrophils. Other abnormal laboratory findings were not observed, other than a slight increase in lactate (3.7 mmol/L).

After discharge, the parents were advised to return the patient to the hospital every 15 days to monitor her symptoms, evaluate the need for blood transfusion, and perform further tests. Subsequent test results continued the pattern described above. The patient, despite depending on transfusions, remained stable until a new clinical picture was manifested: diarrhea, lack of appetite and weight loss.

At age 1 year and 7 months the patient again was hospitalized. In addition to tests described above, a Fecal Pancreatic Elastase test was performed. This revealed, 112 mcg/g of feces, indicating mild to moderate pancreatic insufficiency. From the compromise of the pancreas, the diagnosis for

PS seemed evident. For the confirmation of the mitochondriopathy, mitochondrial DNA analysis was performed via the Multiplex Ligation Probe-dependent Amplification (MLPA) technique. The results revealed the presence of heterozygous deletions in the genes MT-ND4, MT-ND5, MT-ND6 and MT-TM. This result, associated with hematological and biochemical dysfunctions, confirmed the diagnosis of PS.

After the PS diagnosis, the patient continued to be dependent on blood transfusions for maintenance of hemoglobin values. Pancreatic exocrine dysfunction treatment via pancreatin also was initiated.

At 2 years and 6 months, a ferritin test revealed that the patient's iron reserves were extremely high (905.0 ng/mL). Such elevation might be explained by the patient's numerous blood transfusions, requiring introduction of a chelator to remove iron. To reestablish acceptable ferritin levels, the patient's physicians opted to suspend transfusions, due to its long-term harm and substitution by erythropoietin. After the treatment change, the patient's red blood cell series gradually increased, and is now normal. Despite apparent susceptibility to infections due to neutropenia, at 3 years and 10 months of age, the patient presented only two episodes of infection, requiring hospitalization for 7 days, receiving antibiotic via intravenous, without further complications.

3 DISCUSSION

The mitochondria are organelles that have their own genes, termed mitochondrial DNA (mtDNA), that are able to replicate, transcribe, and translate information (KHASAWNEH et al., 2018; SOLANO et al., 2003). The mtDNA is a circular molecule of double tape composed of 16,695 Kb and 37 genes that encode 13 polypeptide components of the mechanism (LIU et al., 2012). Mutations in mtDNA, therefore, can cause failures in oxidative phosphorylation (CHEN et al., 2011; KHASAWNEH et al., 2018).

Mutations in mtDNA may occur sporadically or due to maternal inheritance. Such mutations may cause PS, among other serious human diseases (TUPPEN et al., 2010). In the PS mitochondriopathy, the preponderance of carriers exhibit bone marrow dysfunction, including sideroblastic anemia, moderate to severe neutropenia, and vacuolization of hematopoietic precursors (ARZANIAN et al., 2010; FARRUGGIA; DI MARCO; DUFOUR, 2018; KHASAWNEH et al., 2018). Pancreatic exocrine insufficiency, although frequently described, is nonexistent in some cases.

Pancreatic endocrine functioning usually remains normal, although some PS patients also may develop diabetes mellitus (ARZANIAN et al., 2010; FARRUGGIA; DI MARCO; DUFOUR, 2018). Metabolic acidosis, as well as low birth weight, also have been reported in several PS patients, whereas renal and hepatic impairment and physical abnormalities have been reported only rarely

(FARRUGGIA; DI MARCO; DUFOUR, 2018; LACBAWAN et al., 2000; TUMINO et al., 2011). Due to the multiplicity of symptoms and organs involved, the diagnosis of PS is difficult, and usually is made based upon biochemical and hematological tests, eventually leading to mtDNA analysis (KHASAWNEH et al., 2018; TADIOTTO et al., 2018).

The patient described herein manifested two of the main symptoms of PS: dysfunction of the hematopoietic system (sideroblastic anemia, vacuolization of the precursors of the marrow and neutropenia) and pancreatic exocrine insufficiency. The hematological disorder manifested at five months, and its subsequent evolution, were similar to other cases reported in medical literature: critical hemoglobin and hematocrit values, elevated VCM, leukopenia and marked neutropenia.

In general, PS carriers are very susceptible to infections. According to Farruggia, di Marco and Dufour (2018), about 80 percent of children acquire severe infections during the course of the disease. However, the patient reported here manifested only two episodes of infections, which were well controlled via intravenous antibiotic therapy. The pancreatic exocrine insufficiency became manifest at age one year and seven months, necessitating pharmacological intervention.

Another common manifestation among patients with PS is lactic acidosis, and together with infections, it is a frequent cause of death among PS patients (FARRUGGIA et al., 2016; TUMINO et al., 2011). Although the patient's serum lactate oscillated between normality and values marginally above the reference value, the pH of the patient's blood never revealed acidosis. Alanine in blood and organic acids in urine also were undetected. The absence of lactic acidosis probably indicates a normal flow of NAD⁺ and NADH, with no interruption of the Krebs cycle (FARRUGGIA et al., 2016; FARRUGGIA; DI MARCO; DUFOUR, 2018).

Most cases exhibit prominent impairment of the hematopoietic system of the bone marrow, with consequent susceptibility to infection. The PS phenotype, however, is variable and multisystemic, and may include a series of clinical manifestations. This occurs because the severity of the mitochondriopathy, and the variety of dysfunctions presented by the patients, together depend upon two main factors: amount of mutant mtDNA molecules in each cell (heteroplasmy), and tissue distribution of mutant mtDNAs (KHASAWNEH et al., 2018; TADIOTTO et al., 2018). Therefore, the degree of heteroplasmy present in each organ involved is fundamental to determining the clinical severity (KNERR et al., 2003). Moreover, evolution of the disease may feature phenotypic transition, that is, changes in the amount and the tissue distribution of mutant mtDNA, causing some PS patients to recover from some problems, but manifest other, new problems. Some PS patients, for example, survived and recovered from hematological dysfunction in childhood, but later developed the rare metabolic Kearns-Sayre Syndrome (FARRUGGIA; DI MARCO; DUFOUR, 2018; KHASAWNEH et al., 2018; KNERR et al., 2003).

No curative therapy is available for PS. Available treatments are only symptomatic. Anemia often requires red blood cell transfusion therapy, and erythropoetin is used in some cases to cease or reduce reliance on blood transfusions (COHEN, 2016; FARRUGGIA; DI MARCO; DUFOUR, 2018). The patient described herein was transfusion-dependent from age seven months to age two years and 10 months. Since then she has benefitted from erythropoetin, eliminating the need for transfusion. Hematocrit and hemoglobin evolved with time to normal values.

PS patients who suffer from recurrent infections due to severe neutropenia can benefit from the granulocytic colony stimulating factor (G-CSF). Patients who have pancreatic exocrine insufficiency may benefit from pancreatic enzymatic replacement. In some cases, supplementation with liposoluble vitamins (A, D, E and K) also is necessary (COHEN, 2016; FARRUGGIA; DI MARCO; DUFOUR, 2018).

Hematopoietic stem cell transplantation has been tried in treating in some patients. PS is a multisystemic disease, however, and transplantation can only correct the hematological abnormalities. The risks and benefits of hematopoietic stem cell transplantation therapy therefore must be evaluated carefully (COHEN, 2016; FARRUGGIA; DI MARCO; DUFOUR, 2018).

4 CONCLUSION

The PS case described here highlights the importance of considering mitochondrial diseases as a possible diagnosis in patients with anemia of unknown etiology and with multisystemic clinical manifestations. It also reinforces the importance of early molecular diagnosis of PS, to enable the medical team to develop a treatment to minimize infectious and metabolic complications resulting. In the absence of curative treatment availability, the goal ultimately must be to give the patient greater life expectancy while maximizing the fraction of high quality in remaining life.

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