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Classic Paroxysmal Nocturnal Haemoglobinuria In Children of 11 Years Old: Case Report

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Abstract

Introduction: Paroxysmal nocturnal haemoglobinuria is a rare disease, and predominantly affects young adults, although pediatric cases have been reported. It is secondary to mutation in the X-linked gene of PIG-A, leading to loss of GPI-anchored membrane proteins, making the cell vulnerable to hemolysis by complement system.

Case report: We report an 11-year-old female patient in follow-up since October 2017, with an initial diagnosis of autoimmune hemolytic anemia despite DAT (direct antiglobulin test) persistently negative and maintaining haemolytic activity despite corticosteroid therapy, with fatigue and mild to moderate thrombocytopenia. She was transferred from hematologic service; a diagnostic review was performed and confirmed classic PNH by immunophenotyping. Due to the underlying thrombocytopenia, an inventory was performed for bone marrow failures. The other differential diagnoses of DAT negative hemolytic anemias (membrane diseases, enzymatic deficiencies and hemoglobinopathies) were investigated and excluded, findings compatible with myelodysplasia were supported by medullary evaluation.

Discussion: PNH is a heterogeneous disease and should be considered in all cases of hemolytic anemia with negative DAT, thrombosis in non-usual sites and in bone marrow failure syndromes. As it is a rare disease and still unknown by most physicians, it is underdiagnosed and several patients are inadvertently given ineffective treatments due to erroneous etiologic diagnoses. The present case is even more relevant given the rarity of the disease in a pediatric context, with some clinical presentation peculiarities in this age group.

Keywords

Paroxysmal Nocturnal Hemoglobinuria; Pediatrics; Hemolysis

Introduction

Paroxysmal Nocturnal Hemoglobinuria is a rare disease, affects 10 per 1 million individuals, both men and women and is more common in young adults although pediatric cases have already been reported with just over 40 well-documented cases reported in literature[1]. Most affected children are aged at least 10 years[2]. It is secondary to mutation in the X-linked gene of PIG-A (phosphatidylinositol glycan-class A) which affects the multipotent hematopoietic progenitor cell, being responsible for anchoring of some proteins in cell membrane.

Absence or functional defects in about fifteen proteins associated with PNH promote cell membrane instability, which becomes vulnerable to activation of complement system. Clinical presentation is varied and non-specific, therefore, all patients with hemolytic anemia negative for direct antiglobulin test (negative direct coombs), medullary failure syndromes, unexplained thromboses in unusual sites, cytopenias and haemolysis should be investigated.

Immunophenotyping by flow cytometry is the test of choice for diagnostic confirmation and uses peripheral blood marked with monoclonal antibodies that bind to the GPI-anchored proteins (glycosylphosphatidylinositol). Diagnosis is confirmed by laboratorial evidence of deficiency of GPI-linked proteins in association with a compatible clinical context.

GPI-bound proteins that can be evaluated include CD55, CD59, CD14, CD15, CD16, CD24, CD45 and CD64. Most laboratories include the evaluation with fluorecolic aerolysin (FLAER), a reagent derived from a bacterial toxin that binds directly to the anchor GPI[3].

PNH is divided according to clinical manifestations in classical PNH, in which predominates hemolytic phenotype, PNH in the context of bone marrow failure syndromes and subclinical PNH, in which the presence of small clones does not promote clinical or laboratory manifestations of hemolysis. There are probably differences in clinical manifestation between children and adults, as, in adults, hemoglobinuria appears to be a common clinical finding while in children, only 9-15% of cases presented such manifestation[4]. In children, the disease rarity associated with more frequent atypical manifestations comparing to adults, makes the diagnosis even more challenging, corroborating the relevance of the present report. A significant difference between children and adults is that, in general, small clones (<10%) are more commonly found in children, which are usually related to medullary failure component, while in adults large clones deficient in GPI (> 50%) are more common, having hemolysis as the predominant clinical

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manifestation[5]. However, the case reported bellow does not follow this pattern.

This case refers to an 11-year-old child with classical PNH, initially treated as an Autoimmune Hemolytic Anemia and with an inadequate response to corticosteroids. As observed in other pediatric reports, there was no evidence of hemoglobinuria.

Case Report

An 11-year-old female patient started hematologic monitoring in October 2017 in the context of severe hemolytic anemia with negative direct antiglobulin test. As first line therapy, the child received oral corticosteroid (Prednisone 1 mg / kg / day), however had a poor response and maintained Hb persistently between 7.0-7.5 g/dl. The use of Rituximab for second line treatment was considered. Since initial presentation, mild to moderate thrombocytopenia (between 50-150 thousand platelets per mm^3) without hemorrhagic phenotype was observed. At first, thrombocytopenia was also attributed to immune activity.

In April 2018, the child was transferred from service, still in use of corticosteroids (Prednisone 0.3 mg / kg / day) and with evidence of active hemolysis (Hb 7.5 g/dl, LDH 2253 U/L, Indirect Bilirubin 0.8 mg/dl, Reticulocytes 14%) as well as fatigue symptoms. In the context of negative DAT hemolytic anemia, it was decided to proceed with a new investigation, considering the hypothesis of Paroxysmal Nocturnal Hemoglobinuria, in addition to other differential diagnoses, such as hemoglobinopathies, erythrocyte membrane defects, erythrocyte enzyme deficiency and new direct antiglobulin test (persisted negative).

The result of the second investigation confirmed the diagnosis of Paroxysmal Nocturnal Hemoglobinuria through Immunophenotyping (High Sensitivity Flow Cytometry). The markers used in flow cytometry for diagnosis were CD16, CD24 and FLAER in granulocytes, CD14, CD55 and FLAER in monocytes, CD55 and CD59 in erythrocytes, evidencing PNH clone in 88.9% of granulocytic cells, 88.5% of monocytic cells and 94.4% of red cells. In the face of diagnostic modification, corticotherapy was interrupted, immunization against encapsulated germs (especially meningococcus) provided and Eculizumab was requested (still awaiting initiation of treatment). Due to the evidence of associated thrombocytopenia and the association between PNH and bone marrow failure syndromes, a prognostic investigation was conducted with myelogram, bone marrow biopsy and karyotype, suggesting underlying myelodysplasia component (hypercellular bone marrow with dysplastic changes in three cell lines).

Discussion

PNH has a wide spectrum of clinical manifestations, and its investigation should be considered in differential diagnosis of DAT negative hemolytic anemias (negative antiglobulin test), thrombotic events in unusual sites and in association with medullary failure syndromes. It is It is worth emphasizing that the definition of a certain medullary failure syndrome does not exclude the possibility of PNH, and the presence of mutated clones must be investigated periodically due to its expansion capacity over time.

In hemolysis context, other possibilities to be considered involve hemoglobinopathies, erythrocyte membrane defects (as hereditary spherocytosis), enzymatic deficiencies (such as glucose-6-phosphate dehydrogenase deficiency), drug-related hemolysis, cold paroxysmal hemoglobinuria, and immune hemolytic anemia itself (which in some rare cases may also not induce DAT). All these diagnoses were excluded in this case.

It is not uncommon to observe symptoms related to vasospasms or smooth muscle spasms secondary to nitric oxide reduction, which is consumed by free hemoglobin in hemolysis[6]. Among these clinical manifestations, the most frequent are abdominal pain, erectile dysfunction, fatigue and esophageal spasm. The pathophysiological mechanism of thrombotic events has not been fully elucidated. It is believed that some components are involved such as NO (nitric oxide) consumption leading to vasoconstriction, release of procoagulant microparticles by platelets during complement-mediated attack, deficiency of some fibrinolysis proteins that are also anchored by GPI, and the increase in C5a itself, which induces prothrombotic and proinflammatory cytokines such as IL-6, IL-8 and TNF-alpha[7].

This condition adds significant morbidity and mortality; however, since the availability of Eculizumab, which is effective both in controlling hemolysis and reducing thrombotic events, the life quality of patients has improved with a concomitant reduction in mortality. This drug corresponds to an IgG monoclonal antibody inhibitor of C5 complement fraction, which prevents final formation of the membrane attack complex (MAC)[8]. Complement inhibitor treatment is indicated for all symptomatic patients; however, as it does not act on the mutation-initiating event in hematopoietic progenitor cells, it is not a curative option. Evidence demonstrates similar efficacy of Eculizumab in adults and children, also being recommended in pediatric age group[9].

Hematopoietic stem cell transplantation is the only definitive therapeutic alternative, but given relevant short, medium and long term toxicity, it is reserved for the context of medullary failure syndromes and in patients refractory to Eculizumab[10].

For the presented case, ideal treatment associates complement inhibitor and support measures, such as education support regarding additional risk factors that may contribute to thrombotic events (avoiding additional cardiovascular risk, use of hormonal contraceptives or overweight), transfusional support and iron and folic acid replacement. Prophylactic anticoagulation remains controversial.

Conclusion

Given the rarity of the disease and the lack of knowledge by some physicians, Paroxysmal Nocturnal Hemoglobinuria still constitutes an underdiagnosed medical entity. This case emphasizes the need to always consider and investigate this diagnosis in the context of hemolytic anemias with negative direct antiglobulin test, even in children

without hemoglobinuria, thus avoiding the use of several immunosuppressive drugs with adverse effects that add significant morbi-mortality, being costly and ineffective options for PNH.

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