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Paroxysmal nocturnal haemoglobinuria in pregnancy

Abstract

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal pluripotent hematopoietic stem cell disorder, resulting due to a mutation of the phosphatidylinositol glycan A (PIG-A) gene. A variety of symptoms are observed in the PNH patients including anemia, thrombosis, and cytopenias. The disease is markedly contradicting with chronic symptoms thereby requiring supportive therapy including folic acid and iron replacement, periodical transfusions, and glucocorticoids, and anticoagulation therapy. A new treatment strategy including inhibition of the terminal complement cascade with a monoclonal antibody (eculizumab) has also been discussed. The researches in the past reveal that antibody eculizumab tends to decrease the complement-mediated intravascular hemolytic and need for periodical transfusion. It also enhances the quality of life in patients with this rare disorder. Although there rare chances of incidence of PNH during pregnancy, it can lead to major maternofetal complications. Although only a few studies have been done on pregnant patients with PNH, these findings depict significant breakthroughs in guiding safe pregnancy and lowering the amount of risk involved earlier.

Keywords: paroxysmal nocturnal haemoglobinuria, hemolytic, complement, pregnancy, eculizumab

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Abbreviations: AA, aplastic anemia; BM, bone marrow; CD55, complement decay-accelerating factor; CRPs, complement regulatory proteins; PNH, paroxysmal nocturnal haemoglobinuria; GPI anchor, glycosyl phosphatidylinositol anchor; MAC, membrane attack complex; PI, phosphatidylinositol

Introduction

Paroxysmal nocturnal haemoglobinuria (PNH) is a rare hematological disease with an incidence of 1:100 000 to 1:500 000per year. It is presented with triad of anemia, bone marrow (BM) failure, and thromboses.[1,2] There can be a noted variation in the PNH symptoms in different individuals. Sometimes, PNH can be quite asymptomatic and therefore it is important to rule out the presence of this disorder in uncertain cases of hemolytic, thrombosis or cytopenia. [3]

An increased occurrence of PNH is reported in some regions such as, Thailand and some Asian countries. These regions also have a higher incidence of Aplastic anemia (AA).[5] PNH primarily affects adults including women of reproductive age.[6–7] Although the disease includes chronic symptoms, spontaneous remissions are known to happen in certain cases as well. The average survival time in PNH is 10-15years from the time of diagnosis. Either thrombocytopenia associated hemorrhage or thrombosis are the most common causes of death among PNH patients.[8]

The destruction of glycosyl phosphatidylinositol anchor (GPI anchor) causes deficiency or complete absence of GPI anchored surface proteins.[9–10] The absence of GPI-anchored proteins namely complement decay-accelerating factor (CD55) and MAC-inhibitory protein (CD59) that primarily function as complement regulatory proteins (CRPs) results in complement-mediated hemolytic, which is a characteristic of PNH.[11,12]

Despite the multiple research studies on this disorder, the existing mode of treatment still comprises of only supportive, erythrocyte and platelet transfusions, and long-term anticoagulation therapy.[8,13] However, some recent developments in the treatment of PNH suggest bone marrow (BM) transplantation as the recommended procedure for the PNH patients with bone marrow failure.[14] In addition, the induction of Eculizumab, a humanized monoclonal antibody that binds complement protein C5, has resulted in significant advancements in the long-term management of PNH.[15–17]

Discussion

GPI-anchored proteins

The majority of eukaryotic cell membrane proteins have hydrophobic amino acids stretches that consists of a transmembrane polypeptide chain, which embeds the proteins into phospholipids double layer of the membrane.[18] GPI anchored proteins are membrane bound proteins. Several proteins are linked to the outer cell membrane leaflet by GPI anchor. This structure involves three key elements: a core containing a phosphatidylinositol (PI) moiety, one glucosamine and three mannose molecules and one ethanolamine phosphate unit.[19] a peptide bond links the C-terminus of the protein polypeptide to the last moiety. The GPI-anchor is created in the endoplasmic reticulum and attached to the polypeptide post-translational by a transaminase enzyme. [20–21]

Molecular genetics background

Until date, all PNH patients have had genetic mutations in an X-linked gene known as PIG-A. [22, 23,9] The PIG-A gene product is initially required in the assembly of GPI anchors.[24] Consequently, a block in GPI anchor biosynthesis by PIG-A gene mutations arises during the synthesis of GPI-anchored proteins Failure to generate a mature GPI anchor causes intracellular degradation of similar proteins including those involved in complement regulation. Subsequently, no GPI-anchored proteins appear on the cell surface.[25]

Unlike the other genes involved in GPI anchor biosynthesis, PIG-A

is located on the X chromosome. Since males and females have only one active X chromosome per cell, it is possible for a single somatic mutation to cause a PNH phenotype.[26, 27]

Complement-mediated haemolysis in pnh

Hemolytic is the most distinctive manifestation of PNH; which affects all patients with clinical PNH. However, the extent to which hemolytic affects PNH patients may vary from one to the other.[28] While the term nocturnal indicates that the hemolytic is initiated only at night, it can occur at any point in time. The complement system is a main component of immunity system and has the ability to identify both exogenous pathogenic microorganisms with injured self-tissues, and amplify adaptive immunity.[29, 30] three pathways can activate the complement system: the classic, the lectins and the alternative pathways.[31] PNH erythrocytes are sensible to complement activation through any of these pathways. However, the alternative pathway of the complement system is in a state of continuous activation, which elucidates why hemolytic can happen at any time in PNH patients.[25]

PNH RBCs are extremely vulnerable to complement-mediated lyses because of the deficiency, or complete absence of two primary GPI-anchored complement regulatory membrane proteins namely CD55 and CD59. CD55 is a glycoprotein with a molecular weight of 68 000, which accelerates the rate of reduction of membrane bound C3 converts.[11] CD59 is a glycoprotein with a molecular weight of 19 000-that directly restrains the membrane attack complex (MAC) from forming a hole in the cell membrane by blocking the aggregation of C9.[12,32] Thus, CD55 reduces the amount of C3 that is cleaved and CD59 reduces the number of MACs that are formed. However, CD59 plays a more vital role in providing protection to the cells from the complement attack.

Thrombosis in pnh

Nearly 40% of the PNH patients succumb to death due to thrombosis, thereby classifying it as the leading cause of death in PNH. Venous thrombosis is quite common in PNH and can occur at any site. However, the propensity of its occurrence in the abdominal veins and cerebral veins is much common[8,33,34] although the accurate cause of thrombotic tendency is still unclear, progressive studies are being conducted to find a reasonable explanation. Past studies have shown that nitric oxide (NO) reduction is associated with increased platelet aggregation, increased platelet adhesion, and faster clot formation.[35] To repair the damage, the platelets undertake exocytosis of the complement attack complex resulting in the formation of micro vesicles lined with phosphatidylserine on their outer surface.[36] Phosphatidylserine is a powerful pro coagulant that is confined to the inner surface of the plasma membrane; subsequently the micro vesicles from PNH platelets activate coagulation and possibly contribute to Thrombophilia in PNH.[37] PNH blood cells lack the GPI-anchored receptor for urokinase-type plasminogen activator thereby disrupting fibrinolysis.[38] Urokinase ordinarily converts plasminogen to plasmid and regulates fibrinolysis. Lastly, tissue factor pathway inhibitor (TFPI), a major inhibitor of the procoagulant tissue factor, requires a GPI-anchored protein as a cofactor.[39]

Bone marrow failure in pnh

Cytopenia is a condition in which the production of certain types of blood cells stops or is greatly reduced. It may take several forms including less RBC, WBC and platelet count resulting in anemia, leucopenia, and thrombocytopenia. Bone marrow (BM) failure is another feature of PNH. Some degree of marrow failure is common or even predictable in PNH patients ranging from mild cytopenias to severe Aplastic anemia (AA).[40–42] In many cases, BM failure becomes evident due to the conditions of neutropenia and thrombocytopenia in addition to Aplastic anemia, which may commonly arise in association with PNH. According to a previous study, BM failure is noted in nearly 30-70% of the PNH patients. According to the French registry, out of 430 or more PNH patients, 26% were presented with normal blood count, 52% were diagnosed with AA/PNH, and the remaining 22% with intermediate PNH.[34]

Pregnancy and pnh

PNH in pregnant women may result in increased risks leading to complications for both mother and fetus with higher chances of maternal and fetal mortality rates.[43] As such, the high incidence of thrombotic complications in addition to the difficulty in diagnosing PNH during pregnancy makes the management of PNH in pregnant women much of a crisis situatio[44] of the majority of the pregnancy cases, three-quarter of cases, which is around 10%, are associated with maternal complications while 40% accounts to fetal loss.[45] Thrombosis and haemolysis are the most common cause of fetomaternal morbidity and mortality.[46] Maternal mortality associated with Thromboembolism ranges from 5.8-20.8%, thereby making it the leading cause in this case.[47] According to a study conducted by Fieni et al.[48] in nearly 30.2% of cases, thrombosis affected the pregnant women during the post-partum period while the cases affected during the antenatal or intrapartum period accounted for 16.2%. With the high incidence during the post-partum period, the Budd-Chiari syndrome (also known as hepatic vein thrombosis) is considered as the common thrombotic complication associated with pregnancy.[49]

Anemia is more severe in PNH pregnant woman than in the non-pregnant woman with increased transfusion requirements throughout the pregnancy.[50] Moreover, thrombocytopenia is another common complication resulting in the reduction of platelet count to $<50x10^9/l$.[46] In addition to Warfarin medication, certain low molecular weight heparins (LMWH) at different therapeutic ranges are advised by the physicians during this period. Some physicians even consider the addition of anti-platelet agents. In majority of the cases, the physicians start with heparin, and subsequently shift to Warfarin. Although extended prophylaxis is offered to the patients, the reappearance of thrombosis is common and affects the survival factor.[36]

Due to the lack of GP-anchored effectors molecules in granulocytes and monocytes, the rate of infection in PNH patients is quite high.[18–45] Again, the deposition of hemosiderin in the kidney tubular cells of the PNH patients may result in acute renal failure. While the deposition of hemosiderin normal conditions is mildly toxic, deposition occurring during the conditions of low circulating blood volume and academia may result in acute renal failure.[52]

The proper management of PNH patients during pregnancy necessitates supportive treatment to control the main clinical manifestations of the disease.[44] However, not many specialized options are available to control hemolytic during pregnancy. Despite long-term toxicity of chronic steroidal therapy arising due to the continuous use of steroids, they were widely used for acute hemolytic crises.[28] RBC transfusion in pregnant women with PNH is encouraged to maintain the hemoglobin level above 8g/dL. Transfusions not only elevate the hemoglobin level, but also suppress marrow production of complement sensitive RBCs during an episode of continued haemoglobinuria.[28]

Taking into consideration the massive loss of iron through urine, iron overload is usually not a transfusion-related complication in patients with PNH.[53] Some of the recent studies have noted successful pregnancy results using eculizumab therapy (h5G1.1-mAb, Soliris®, Alexison Pharmaceuticals) in patients with PNH. Clinical trails in PNH patients have shown that eculizumab reduces the transfusion requirement and improves the quality of life.[16,17,54] The first open-label experimental study conducted to evaluate the safety and efficiency of eculizumab involved 11 patients and proved that blocking C5 may lead to the reduction in hemolytic in PNH patients.[17,55] Later, the definitive evidence of efficacy was presented by two large multi-center trails, the shephered[16] and the triumph.[17] Patriquin and Leber[56] conducted a study which presents the first Canadian PNH patient on eculizumab taken through a pregnancy. The application for eculizumab was continued without any interruption in the ante partum period. However, increased dosing and frequency of infusions was necessary for the proper management of pregnancy in such condition. The outcomes were in consensus with the previous studies. And no adverse fetal outcomes were noted with eculizumab exposure.

Conclusion

Although PNH is a rare hematologic disease, it can cause significant fetomaternal morbidity and mortality. For the proper management of pregnancy in PNH patients, it is required that the obstetricians and hematologists should closely monitor such cases. The introduction of eculizumab has definitely led to significant advancement in the long-term management of PNH. The well monitored dosage of eculizumab can prevent adverse clinical manifestations of PNH and minimize the rate of maternal and fetal complications. The data on the administration and outcomes of eculizumab during pregnancy can be used to develop guidelines for improving the pregnancy care in PNH patients.

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Conflict of interest

Author declares that there is no conflict of interest.

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