Paroxysmal nocturnal haemoglobinuria and its various manifestations

A Woolhead, H Deepak, M Patel, S Vaidiyanathan

Citation

A Woolhead, H Deepak, M Patel, S Vaidiyanathan. *Paroxysmal nocturnal haemoglobinuria and its various manifestations*. The Internet Journal of Anesthesiology. 2007 Volume 16 Number 1.

Abstract

Paroxysmal nocturnal hemoglobinuria also called as Marchiafava-Micheli Syndrome is a rare disorder characterized by intravascular hemolysis and hemoglobinuria, the latter accentuated during sleep. Leukopenia, thrombocytopenia, and episodic crises are common. Manifestations can vary and could be often misleading. Severe infections can occure due to aplastic bone marrow and splenic thrombosis. Diagnosis requires flow cytometry, although the acid hemolysis test [Ham test] is still valid. Treatment is mainly supportive. We report one such case that presented in the Emergency Unit with purpura fulminans, haemolysis, DIC , acute renal failure and thrombocytopenia. This case highlights the problems encountered in acute crisis in patients with PNH which was made worse by superimposed infection.

INTRODUCTION

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder resulting from a somatic mutation in the hematopoietic stem cell. It is characterized by intravascular hemolysis, cytopenias, frequent infections, bone marrow hypoplasia, and a high incidence of life-threatening venous thrombosis. An absent glycosylphosphatidylinositol (GPI)-anchored receptor prevents several proteins from binding to the erythrocyte membrane. These include the complement-regulatory proteins, CD55 and CD59, whose absence results in enhanced complement-mediated lysis. Patients present with anemia and hemoglobinuria.

CASE REPORT

A 24 year old Caucasian male was brought to the A &E with altered consciousness. He was feeling unwell for the past few days as per his girl friend. Background history showed a history of paroxysmal nocturnal haemoglobinuria [PNH] for which he was on treatment with warfarin folic acid, iron supplements and steroids for the past 1 year. History of thrombosis in mesenteric veins was present. He also had Budd Chiari syndrome had undergone TIPPS procedure and have a venous filter in his inferior venacava. On examination there was generalized purpura. He had low oxygen saturation, was hypotensive, tachypneic and tachycardic. The patient started desaturating and had to be intubated. Monitoring was done with pulse oxymeter, arterial BP, CVP and renal output monitoring. Hypotension was present which did not respond to fluids, so was started on Noradrenaline infusion. There was no renal output .CVP was low and did not increase with colloid infusions. Cyanosis started setting in even after ventilation with 100 % oxygen. ABG showed severe metabolic acidosis.

Lab reports showed severe thrombocytopenia, anemia, increased INR, hyperkalemia, hypocalcaemia and increased D-Dimers. Based on his previous history it was concluded that he was having a severe episode of haemolysis superimposed on severe infection.The clinical picture pointed towards meningococcal septicemia with waterhouse-friderichsen syndrome .The patient was given platelet infusions and hydrocortisone. Inspite of all the supportive measures, the patient died after 3 hours.

DISCUSSION

Paroxysmal nocturnal haemoglobinuria (PNH) is an acquired clonal chronic haemolytic anaemia in which intravascular haemolysis resulting from an intrinsic defect in the membrane of red cells which makes the red cells highly susceptible to complement. In the 1930's Ham in the USA [1] and Dacie in the UK [2] developed the acidified serum test, which became the defining diagnostic test for PNH.

In contrast to all other haemolytic anemias due to an intrinsic red cell abnormality, PNH is an acquired rather than an inherited disorder. This fact, together with the finding that

normal cells co-exist in the patient' blood with those that are hypersensitive to complement, led some 35 years ago to the working hypothesis that PNH arises through a somatic mutation in a haemopoietic cell [3]

This disease has been referred to as the great impersonator because of the variety of symptoms observed during the initial manifestation and course of the disease. The clinical syndrome can present in 3 types of symptoms including (1) an acquired intracorpuscular hemolytic anemia due to the abnormal susceptibility of the red cell membrane to the hemolytic activity of complement; (2) thromboses in large vessels, such as hepatic, abdominal, cerebral, and subdermal veins;[4] and (3) a deficiency in hematopoiesis that may be mild or severe, such as pancytopenia in aplastic anemia state. The triad of hemolytic anemia, pancytopenia, and thrombosis makes PNH a truly unique clinical syndrome.

There are varying reports regarding the onset of symptoms. The range varies from 2 to 80 years,but it now understood that the median age is around 40 years. Men and women are affected equally, and no familial tendencies exist.A study done shows that white American patients were younger with significantly more classic symptoms of PNH including thrombosis, hemoglobinuria, and infection, while Asian patients were older with more marrow aplasia and a smaller PNH clone.[5] There is an increased risk of infections in patients with PNH due to aplastic bone marrow. The generalized pancytopenia and splenic vein thrombosis put the patient to an increased risk of capsulated organisms like pneumococci,meningococci and other encapsulated bacteria.

There have been case reports suggesting that cerebral thrombosis might be the first manifestation of PNH [6 7] Transjugular intrahepatic portosystemic shunt is done for patients who come with Budd chiari syndrome which is a very common occurrence in patients with PNH [8] .There are an increased risk of thrombosis in mesenteric veins and also the subdermal veins.Splenomegaly can be manifested by splenic vein thrombosis and papilledema can be found in cerebral thrombosis.

The intravascular haemolysis manifests as dark cola-colored urine that is a manifestation of hemoglobinuria. The latter may be confused with hematuria, and erroneous treatment could be given for urosepsis. Hemosiderin nearly always is present in the urine sediment and can accumulate in the kidneys, which shows up on MRI or CT scans. Elevated reticulocyte count and serum lactic acid dehydrogenase (LDH) with a low serum haptoglobin in the absence of hepatosplenomegaly are the hallmarks of intravascular hemolysis. Bone marrow usually is markedly erythroid, with decreased or absent iron stores, depending on how long the patient has been losing iron in urine. Acute renal failure has been documented in PNH [9] .Though rare purpura fulminans is also seen [10]

Lab diagnosis involves demonstration of the presence of RBCs that are exceptionally sensitive to the hemolytic action of complement. The state-of-the-art laboratory test is to send the patient's blood for flow cytometry to detect CD59 (MIRL), a glycoprotein, and CD55 (DAF) in regulation of complement action. Absence or reduced expression of both CD59 and CD55 on PNH red cells is diagnostic [11]. A recent study identified a novel autosomal recessively inherited form of GPI-deficiency involving a mutation in a promotor component of the pig-m gene and characterized by a thrombotic tendency and seizures. In both these developments, flow cytometry played a critical role. In the first instance, in monitoring direct response to a new therapeutic agent; second, in demonstrating the phenotypic/genotypic link in a new form of GPI deficiency [12]

Hepatic vein thrombosis is detected with a routine technetium Tc 99m colloid scan of the liver and spleen. This often reveals diminished function in all portions of the liver except the caudate lobe, which is spared because it is drained by the inferior vena cava rather than the hepatic vein. An MRI or ultrasound can demonstrate the cessation of flow through the hepatic vein or by injecting or using a dye to demonstrate thrombus in the vein. MRI with contrast may demonstrate sagittal vein thrombosis [13]

Treatment includes folic acid 5mg/day in view of increased rate of erythropoiesis.

Assess iron stores using transferrin saturation index (TSI): Give oral ferrous sulfate if <20%. (Ferritin is acute-phase reactant and can be misleading.). Determine steady state Hb levels after correction for iron deficiency. Transfuse packed RBC (WBC depleted by filter) when appropriate. Washing red cells is no longer necessary, and irradiated blood products is recommended for future.

Modulation of complement is controlled poorly by high doses of glucocorticoids. The usual adult dose of prednisone is 20-40 mg/d (0.3-0.6 mg/kg/d) given daily during hemolysis and changed to alternate days during remission. A new anticomplement agent, eculizumab, is a humanized monoclonal antibody against terminal protein C5; it has

recently been shown to be highly effective in reducing intravascular hemolysis.[14] [15] Stimulation of erythropoiesis using androgenic hormones has been successful in patients with moderate decrease in red cell production. This has been replaced mainly by using recombinant erythropoietin therapy.

If bone marrow transplantation can be done it is the treatment of choice for cases of aplastic anaemias.

In our case the patient presented with purpura fulminans with symptoms and signs of intravascular haemolysis, thrombocytopenia,DIC and signs of sepis. Purpura fulminans is a manifestation of severe infections like meningococcal infections, toxic shock syndrome and drug reactions [16] [17] . There is an increased incidence of infections in patients with PNH [18] .Because of overlap of many of the symptoms,it might be differentiate the primary cause of purpura fulminans. We concluded that the patient had meningococcal infection leading to picture of DIC, resistant hypotension superimposed on PNH, which was later established by laboratory results. New studies have been done regarding the use of activated protein C in treatment of purpura fulminans due to infections [19] but its use is not fully conclusive. No studies have proved conclusively the use of haemodialysis in treatment of acute episodes of PNH. This case highlights the different manifestations of a patient with PNH due to decreased immunity.

References

1. Ham TH. Chronic hemolytic anemia with paroxysmal nocturnal haemoglobinuria. A study of the mechanism of hemolysis in relation to acid-base equilibrium. N Engl J Med 1937; 217:915
2. Dacie JV, Israels MCG, Wilkinson JF. Paroxysmal nocturnal haemoglobinuria of the Marchiafava type. Lancet 1938; 1:479.
3. Dacie JV. Paroxysmal nocturnal haemoglobinuria. Proc Roy Soc Med 1963; 56:587
4. Noji H, Shichishima T, Okamoto M, Shichishima-Nakamura A, Matsumoto H, Tajima H, Ogawa K, Maruyama Y. Microvascular thrombosis in the hepatic vein of a patient with paroxysmal nocturnal hemoglobinuria. Int J Hematol. 2007 Oct;86(3):216-21.
5. Araten DJ, Thaler HT, Luzzatto L. High incidence of thrombosis in African-American and Latin-American patients with Paroxysmal Nocturnal Haemoglobinuria. Thromb Haemost. Jan 2005;93(1):88-91
6. Tejada J, Hernández-Echebarría L, Sandoval V, Mostaza JL. Cerebral ischemia as first manifestation of paroxysmal nocturnal hemoglobinuria. Neurologia. 2007 Sep;22(7):471-4.
7. Poulou LS, Vakrinos G, Pomoni A, Michalakis K, Karianakis G, Voulgarelis M, Ziakas PD. Stroke in paroxysmal nocturnal haemoglobinuria: patterns of disease and outcome Thromb Haemost. 2007 Sep;98(3):699-701
8. Chang CY, Singal AK, Ganeshan SV, Schiano TD, Lookstein R, Emre S. Use of splenic artery embolization to relieve tense ascites following liver transplantation in a patient with paroxysmal nocturnal hemoglobinuria Liver Transpl. 2007 Nov;13(11):1532-7.
9. Tsai CW, Wu VC, Lin WC, Huang JW, Wu MS. Acute renal failure in a patient with paroxysmal nocturnal hemoglobinuria. Kidney Int. 2007 Jun;71(11):1187.
10. Watt SG, Winhoven S, Hay CR, Lucas GS. Purpura fulminans in paroxysmal nocturnal haemoglobinuria Br J Haematol. 2007 May;137(4):271
11. Richards SJ, Barnett D. The role of flow cytometry in the diagnosis of paroxysmal nocturnal hemoglobinuria in the clinical laboratory. Clin Lab Med. 2007 Sep;27(3):577-90
12. Richards SJ, Hill A, Hillmen P. Recent advances in the diagnosis, monitoring, and management of patients with paroxysmal nocturnal hemoglobinuria. Cytometry B Clin Cytom. 2007 Sep;72(5):291-8.
13. Socie G, Mary JY, de Gramont A, et al. Paroxysmal nocturnal haemoglobinuria: long-term follow-up and prognostic factors. French Society of Haematology. Lancet. Aug 31 1996;348(9027):573-7
14. Singh J, Malani AK, Pabla M. Eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006 Dec 28;355(26):2786
15. Pride YB.Eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006 Dec 28;355(26):2787
16. McBride WJ, Hanson JP, Miller R, Wenck D. Severe spotted fever group rickettsiosis Emerg Infect Dis. 2007 Nov;13(11):1742-4
17. Numanoglu A, Bickler SW, Rode H, Bosenberg AT. Meningococcal septicaemia complications involving skin and underlying deeper tissues--management considerations and outcome. S Afr J Surg. 2007 Nov;45(4):142-6.
18. Abe R, Shichishima T, Ogawa K, Saitoh Y, Maruyama Y. Neutropenia due to parvovirus B19 infections in patients with paroxysmal nocturnal hemoglobinuria. Blood transfusion and natural infection cases. Acta Haematol. 2006;116(4):245-8.
19. Salinas U, Unzueta J, Vidarte MA, Rodrigo MP, Gómez JJ, Aguilera L. Meningococcal purpura fulminans: treatment with recombinant protein C activator in 3 cases. Rev Esp Anestesiol Reanim. 2007 Oct;54(8):503-6

Author Information

Alan Woolhead, FCARCSI
Consultant Anaesthetist, Department of Anaesthesia and Intensive Care, Our Lady of Lourdes Hospital

HRH Deepak, MD
Senior House officer, Department of Anaesthesia and Intensive Care, Our Lady of Lourdes Hospital

Mansoor Ghyias Patel
Senior House officer, Department of Anaesthesia and Intensive Care, Our Lady of Lourdes Hospital

Sabanayagam Vaidiyanathan, DA
Senior House officer, Department of Anaesthesia and Intensive Care, Our Lady of Lourdes Hospital