Clinical and Laboratory Features of Paroxymal Nocturnal Hemoglobinuria and its Therapeutic Options in the Developing World

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ABSTRACT

BACKGROUND: Paroxymal nocturnal hemoglobinuria is a rare non malignant clonal blood disorder that manifests with intravascular hemolytic anemia, bone marrow failure, hemoglobinuria and thrombosis.

METHOD: This is a prospectively designed study of the patient diagnosed PNH during the period of January 2008 to January 2009 in hematology unit of National academy of medical science, Bir hospital. Clinical and laboratory features along with treatment response to anabolic steroid, corticosteroids and cyclosporine were studied.

RESULTS: There were total of 12 PNH patients. To diagnose twelve PNH patients in a single institution in a one year period is not very common. Ten (83.3%) patients were diagnosed by Hams test and two (16.7%) were diagnosed by analysis of CD 55 and CD 59 via flow cytometry. All were male patients. All patients presented with anemia. Mean age at presentation was 41.5 years of age. Mean hemoglobin was 6.27g/dl. Mean platelet count was 153000/ul. Mean LDH was 2280U/L. Seven patients (58%) presented with hemoglobinuria. Three Patients (25%) had hypocellular marrow. One patient (8.3%) had thrombotic episode. Eighty percent of patients with very severe anemia had hemoglobinuria. Eight patients (66%) had repeated episodes of hemoglobinuria during regular followup.

CONCLUSION: Coomb’s negative hemolytic anemia is the hall mark of PNH. High suspicion is needed to diagnose PNH. Most of the patients respond to corticosteroid and anabolic steroid. While allogenic BMT is potentially curative, the benefits must be weighted against the significant morbidity and mortality associated with the procedure. Recently Eculizimab is found to be very effective in the treatment of PNH. Guidelines for management of PNH should be made in a country like ours where we don’t have bone marrow transplantation facilities.

Key words: clonal blood disorder, flow cytometry, hemoglobinuria

INTRODUCTION

Paroxymal nocturnal hemoglobinuria (PNH) is a complex hematologic disorder characterized by non malignant clonal expansion of one or several hemopoetic stem cells that have acquired a somatic mutation of PIGA (a gene located on X chromosome that is required for synthesis of the glycosylphosphatidylinositol anchor moiety). Deficiency of the GPI anchored complement regulatory proteins CD55 and CD59 accounts for the intravascular hemolysis that is clinical manifestation of disease. PNH is characterized by, in the classic case, by attacks of intravascular hemolysis and hemoglobinuria that occur chiefly at night while the patient is asleep. In many patient however, the classic pattern is absent at diagnosis. These patient manifest chronic, low grade intravascular hemomolysis punctuated by occasional episodes of hemoglobinuria usually in association with infection and unusual stress. Thrombocytopenia, leucopenia, and thrombosis involving unusual sites are other notable clinical characteristics of PNH. A close association exists between PNH and certain bone

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marrow failure syndromes particularly aplastic anemia, although the fundamental basis of this association is incompletely understood.

MATERIALS & METHODS

This is the prospectively designed study of the patient diagnosed PNH in the hematology unit of National academy of medical science, Bir hospital, a tertiary referral center in kathmandu, Nepal from January 2008 to January 2009. Patient visiting hematology unit for evaluation of hemolytic anemia were studied. Detail history and physical examination were carried out in all study cases. Careful review of peripheral smear to rule out hereditary hemolytic anemia was done. Other laboratory investigation that aids to rule out other causes of hemolytic anemia like coombs test, osmotic fragility test, G6PD quantitification test and Hb electrophorosis were done. Patient who were found negative in the above mentioned investigation were advised for Hams test or CD55 and CD 59 analysis, which ever is feasible for them explaining the sensitivity and specificity of both test. Bone marrow aspiration and biopsy was done in every diagnosed case of PNH to access the marrow cellularity. All patients were followed up for minimum of six months from the diagnosis after starting treatment with steroids and cyclosporine.

RESULTS

There were total of 12 PNH patients. To diagnose twelve PNH patients in a single institution in a one year period is a great achievement. Ten (83.3%) patients were diagnosed by Hams test and two (16.7%) were diagnosed by analysis of CD 55 and CD 59 via flow cytometry. All were male patients. All patients presented with anemia. Mean age at presentation was 41.5 years of age. Mean hemoglobin was 6.27g/dl. Mean platelet count was 153000/ul. Mean WBC count was 4097/ul. Mean LDH was 2280U/L. Seven patients (58%) presented with hemoglobinuria. Three Patients (25%) had hypocellular marrow. One patient (8.3%) had thrombotic episode. Two cases (16.6%) had splenomegaly. Five cases (41.6%) responded to the danazol. Similarly two cases (16.6%) responded to cyclosporine and rest (41.8%) responded to the corticosteroid. Eighty percent of patients with very severe anemia had hemoglobinuria. Eight patients (66%) presented had repeated episodes hemoglobinuria during follow up.

Table 1. Clinical and laboratory features of PNH patient.

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<tr>
<th>Age</th>
<th>Hb (g/dl)</th>
<th>Platelets (u/dl)</th>
<th>WBC count (u/dl)</th>
<th>Reticulocytes (%)</th>
<th>Treatment</th>
<th>LDH (u/dl)</th>
<th>HbH (g/dl)</th>
<th>Bone marrow</th>
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D* danazol  C** prednisolone  C# hypercellular  H## hypocellular
DISCUSSION

PNH usually begins insidiously with abrupt onset of clinically apparent hemoglobinuria being the presenting symptoms in only 25% of the cases1. The course is chronic with generally stable clinical patterns in a given individual. The diagnosis is usually made in forth and fifth decade2,3, but PNH is also encountered in childhood4 and in old age3. Both genders are affected with perhaps a slight female preponderance. The disease has no familial tendency. Most commonly patients initially complain of weakness, yellowish discoloration of skin and other symptoms of chronic hemolysis, but a history of hemoglobinuria is a part of initial presentation in only 25% of cases. Because PNH may not be considered in such patients, the correct diagnosis is often delayed by months to years. In our study all the cases we have enrolled were referred from the local hospital because of diagnostic dilemma. All were male patients. Patients were symptomatic from months to years before the accurate diagnosis was made. Seven (58%) patients had hemoglobinuria. Most patients (66%) experienced irregular and recurrent exacerbation of hemolysis and hemoglobinuria. Paroxysm was precipitated by wide variety of events including infection, surgery, transfusion, iron supplementation, and vaccination. Because many patients with PNH/aplastic anemia have only a small proportion of complement sensitive test5, few of the changes usually associated with hemolysis are obvious. Therefore, PNH/aplastic anemia syndrome is probably misdiagnosed. In our study three patients had hypocellular marrow on repeated aspiration and they were diagnosed as PNH/aplastic anemia. Most of our patients (83%) were diagnosed PNH by Hams test. Hams test was preferred because most of our patients couldn’t afford flow cytometer analysis of CD 55 and CD 59. We usually don’t perform Hams test or CD55 and CD 59 analysis on diagnosed case of aplastic anemia until and unless a stigma of hemolysis is detected on routine examination. With very sensitive flow cytometry some study had detected PNH clone in sixty percentage of aplastic anemia. In one series of eighty European patients with PNH, aplastic anemia was the first diagnosis in 23 cases1. In some instances, the diagnosis of hemolysis is made first, and pancytopenia develops subsequently2. PNH is associated with striking predisposition towards intravascular thrombosis, especially with the venous circulation2,3. Thrombotic disease account for about 50% of all deaths in patient with PNH. Both acute and chronic renal insufficiency occurs in patients with PNH6. One of our patient developed chronic renal failure and he died of ischemic stroke. Male impotence is common in patients with PNH and is worse during hemolytic exacerbation. In our study only 30% gave a history of impotence. All patients were anemic and in many anemia was severe. The red blood cells are normocytic, but MCV varied considerably in patients. Leucopenia is often detected and may be marked3. Thrombocytopenia of moderate to mild is common3. Six patients (50%) had leukopenia and similar number of patient had thrombocytopenia. When pancytopenia is evident, hypoplastic marrow may be observed, although in many patients bone marrow is hypercellular. Approximately one third to one half of patients appear to respond to androgen therapy with increase in hemoglobin concentration, a reduction in transfusion requirement or both, however attempting to identify the responders is advance problem. The mechanism by which androgen adrogenic steroids ameliorate the PNH is not understood7. The adverse effect of androgen therapy can be substantial, ranging from virilizing effect in female patients and acne in both sexes to serious liver disease, including peliosis hepatitis and hepatocellular carcinoma. We usually taper the dose of androgen once hemoglobin has reached 10g/dl. In our study five patients (41.6%) responded to danazol. Similarly five patients (41.6%) patients responded to corticosteroids. The steroid act rapidly and response can be expected within 24 hours8. However prolonged use of steroid can lead to long term toxicities. We prefer danazol instead of corticosteroid if marrow is hypocellular. Responses to immunosuppressive therapy with cyclosporin and anti thymocyte globulin have been reported9. We have treated two patients with cyclosporine because they didn’t respond to corticosteroid and danazol. As the hemolysis of PNH is a consequence of complement mediated cytolysis, inhibition of complement is a logical approach to therapy. Recently , the results of phase II10 and phase III11 studies using a humanized monoclonal antibody (eculizumab) against complement CD5 to treat patients with PNH is reported. Bone marrow transplantation has been used in the treatment of PNH for more than thirty years12. While allogenic BMT is potentially curative, the benefits must be weighted against the significant morbidity and mortality associated with the procedure. We have to depend upon steroids and cyclosporine until and unless...
Eculizumab and bone marrow transplantation service is available in Nepal.

**CONCLUSION**

Coombs’s negative hemolytic anemia is the hallmark of PNH, but because the disease usually arises in the setting of an underlying abnormality of the bone marrow, hemolysis may account for only part of a patient anemia. High suspicion is required to diagnose PNH. Most of the patients respond to corticosteroid, anabolic steroid and cyclosporine. While allogenic BMT is potentially curative, the benefits must be weighted against the significant morbidity and mortality associated with the procedure. Recently eculizumab is found to be very effective in the treatment of PNH. Our study is limited to small number of patient but to diagnose twelve PNH patients in a single year in one institution is not a small number. Guidelines for management of PNH should be made in a country like ours where we don’t have bone marrow transplantation facilities.

**REFERENCES**