THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021), No 4, p. 50-55

BASELINE CHARACTERISTICS, CLINICAL PROFILE AND OUTCOMES OF PATIENTS WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA A SINGLE CENTER EXPERIENCE IN SOUTH INDIA

Karanth S.[1], Karanth S.[2], Rao R.[1*]

[1] Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India
[2] Department of Hematology, A. J Hospital and Research Center, Mangalore, India

Received 15.11.2020; accepted for printing 07.08.2021

Abstract

Paroxysmal nocturnal hemoglobinuria is a rare, nonmalignant, acquired disease that manifests as hemolytic anemia, bone marrow failure and thrombosis that occurs due to a somatic mutation in the PIG-A gene. Here, regardless of treatment, we assessed the baseline characteristics and clinical profile of patients with a confirmed paroxysmal nocturnal hemoglobinuria diagnosis or detectable paroxysmal nocturnal hemoglobinuria clone.

A total of 16 patients, 10 male and 6 females, who presented to our center between April 2016 to March 2020 and diagnosed with paroxysmal nocturnal hemoglobinuria were provided treatment for the management of their condition. Information regarding patients' medical and treatment history, comorbid conditions, paroxysmal nocturnal hemoglobinuria clone size, disease characteristics and outcomes, symptoms, paroxysmal nocturnal hemoglobinuria -specific treatments, paroxysmal nocturnal hemoglobinuria -related events, morbidity, mortality, and quality of life were collected. Data including hemoglobin levels, transfusion requirements, renal dysfunction, thrombotic events and other laboratory data were collected.

Frequently reported symptoms included fatigue (75%), dyspnea (44%), hemoglobinuria (25%), and abdominal pain (44%) with an overall 44% hospitalization rate due to related complications. Median granulocyte PNH clone size was 36.3% (range 14-78 percent). Overall, 37.5% patients had classical paroxysmal nocturnal hemoglobinuria and 62.5% patients had paroxysmal nocturnal hemoglobinuria with secondary bone marrow disorders. Post individualized therapy; the mortality rate was 18.75%. Presently 13 patients are on follow up with either steroids (38.5%), steroids with danazol (23%), cyclosporine (7.7%), thalidomide (7.7%), or intermittent blood product support (23%).

The data from this study can be used to identify the patterns that would indicate the necessity for a diagnosis of paroxysmal nocturnal hemoglobinuria and to identify the diagnostic outcomes.

Keywords: *paroxysmal nocturnal hemoglobinuria, thrombosis, hemolysis, management.*

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired bone marrow disorder that is primarily characterized by hemolytic anemia, thrombosis, peripheral blood cytopenias, and in most cases, a poor quality of life [*Brodsky R, 2014; Schrezenmeier H et al., 2014*]. The incidence and prevalence of PNH is estimated to be approximately 1.3 per million annually and 16 per million, respectively. It usually develops between 30 – 40 years of age, although initiation of physical symptoms can occur at any age [*Hill A, 2006*]. Uncontrolled complement activity in PNH results in systemic complications, mostly due to intravascular hemolysis and platelet activation [*Schrezenmeier*

Address for Correspondence:
Raghavendra Rao
Associate Professor, Department of Medicine, Kasturba Medical College, Manipal Academy of Higher Education, Manipal, India
Tel.: +91 9901731924
E-mail: ragsmanipal1983@gmail.com

H et al., 2014]. Paroxysmal nocturnal hemoglobinuria is a life-threatening disease where the cellular abnormalities develop from an acquired mutation in the phosphatidylinositol glycan class A) gene in a self-renewing hematopoietic stem cell, followed by clonal expansion. The first step in the synthesis of the glycosylphosphatidylinositol (GPI) anchor is mediated by the PIGA protein. The GPI anchor is a glycolipid that links various cell surface proteins to the plasma membrane of hematopoietic cells. The mutation results in a deficiency of glycosylphosphatidylinositol (GPI)-anchored complement regulatory proteins, including CD55 and CD59, on the surface of blood cells that causes complement□mediated intravascular hemolysis, promotion of inflammatory mediators, and systemic hemoglobin release [*Parker C et al., 2005; Hill A et al., 2013;Schrezenmeier H et al., 2014;*]. A marked increase in the risk of thromboembolism is observed in patients with chronic hemolysis, that could eventually lead to target organ damage, and ultimately, death [*Parker C et al., 2005*].

Paroxysmal nocturnal hemoglobinuria has been classified into three subcategories, such as classic PNH where the patients have clinical evidence of intravascular hemolysis, but have no evidence of another defined bone marrow abnormality, PNH in the setting of another specified bone marrow disorder where the patients have clinical and laboratory evidence of hemolysis but also have concomitantly, or have had a history of, a defined underlying marrow abnormality (e.g., PNH/aplastic anemia or PNH/refractory anemia- myelodysplastic syndrome), and subclinical PNH (PNH-sc) where the patients have no clinical or laboratory evidence of hemolysis [*Parker C et al., 2005*].

Thrombosis, which occurs in up to 40% of patients, is responsible for the greatest number of deaths in PNH, inspite of its rare symptomatic presentation. Thromboembolism accounts for nearly 40% to 67% of the deaths due to PNH. The frequency of occurrence of one thromboembolic event during the course of this disease is 29% to 44%, although the reasons behind the sudden thrombotic event remain an enigma [*Hill A et al., 2013; Schrezenmeier H et al., 2014*]. The most frequent symptom in patients with PNH is fatigue; the other symptoms include abdominal pain, headache, shortness of breath (dyspnea), dysphagia, and erectile dysfunction. These symptoms can be debilitating and significantly reduce the quality of life (QoL) of patients with PNH. Another risk associated with PNH is chronic renal tubular damage caused by microvascular thrombosis and accumulation of iron deposits.

Although allogeneic bone marrow transplantation is the only potentially curative therapy for PNH, it is offered for refractory PNH, secondary PNH patients with profound cytopenias or malignant transformation. This therapy is association with considerable morbidity and mortality [*Schrezenmeier H et al., 2014*]. Supportive measures such as blood transfusions and anticoagulation therapy have been the favored therapies for the management of PNH; however, prophylactic anticoagulation has been associated with an increased risk of bleeding complications [*Schrezenmeier H et al., 2014*]. Since complement-mediated cytolysis results in hemolysis, PNH therapy should involve inhibition of the complement. The complement inhibitor eculizumab, a humanized monoclonal antibody against complement C5, is a widely effective therapy for patients with classical PNH. Eculizumab has been shown to effectively control the signs and symptoms of hemolysis and markedly improved the quality of life of PNH patients. Notably, significant adverse events with eculizumab have not been reported. Moreover, corticosteroids have reportedly improved hemoglobin levels and reduced hemolysis in some PNH patients.

In the current study, we assessed the baseline characteristics and clinical profile of patients with a confirmed paroxysmal nocturnal hemoglobinuria diagnosis or detectable paroxysmal nocturnal hemoglobinuria clone and initiated individualized treatment based on their symptoms and associated risk factors.

To overcome it
is possible, due to the
uniting the knowledge and
will of all doctors in the world

MATERIALS AND METHODS

Patient Population

The study was conducted between April 2016 to March 2020 at our centre after obtaining permission from Institutional Ethics Committee (IEC: 613/2016). The work was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Informed consent was obtained from all the participants. A total of 16 patients, 10 males and 6 females, aged 14 – 66 years, were included in the study. Inclusion criteria involved a clinical diagnosis of PNH or detection of ≥5% PNH clone. A paroxysmal nocturnal hemoglobinuria clone was defined as a population of granulocytes and/or erythrocytes deficient in GPI. Informed consent was obtained from all the participants.

Data Collection

Information regarding patients' medical and treatment history, comorbid conditions, paroxysmal nocturnal hemoglobinuria clone size, disease characteristics and outcomes, symptoms, paroxysmal nocturnal hemoglobinuria-specific treatments, paroxysmal nocturnal hemoglobinuria-related events, morbidity (including myeloproliferative/ myelodysplasia/aplastic anemia, other malignancies), mortality, and quality of life were collected and recorded.

Data collected from clinical assessments included hemoglobin levels, transfusion requirements, renal dysfunction, thrombotic events (identified using major adverse vascular event categories), and other laboratory data. Data were presented as frequency (%).

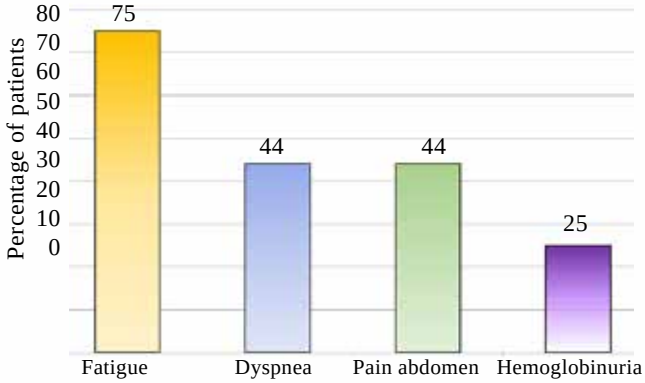

FIGURE 1. Symptoms presented by the patients at their first visit.

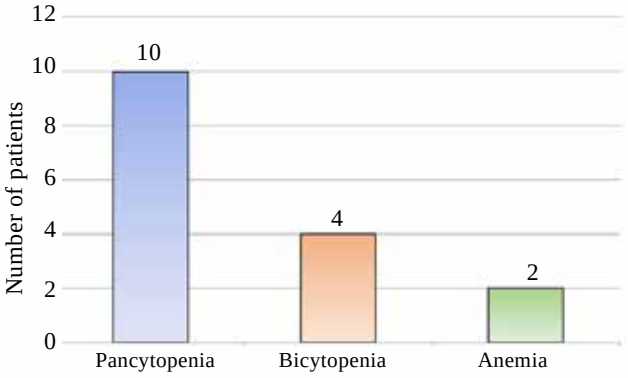

FIGURE 2. Clinical presentations of the patients with paroxysmal nocturnal hemoglobinuria.

Management of Paroxysmal Nocturnal Hemoglobinuria

The therapies for the management of paroxysmal nocturnal hemoglobinuria included anticoagulation, immunosuppression, bone marrow transplant, and intermittent blood product support. The various drugs and their doses are listed in Table 1.

RESULTS

Demographic Characteristics

Here, we report the characteristics of the 16 patients, 10 males and 6 females, diagnosed with paroxysmal nocturnal hemoglobinuria between April 2016 to March 2020 and treated at our centre. The median age of the patients was 39 years. As shown in Figure 1, the patients frequently presented with symptoms, such as fatigue (75%), dyspnea (44%), hemoglobinuria (25%), and abdominal pain (44%). Overall, 44% of the patients had been hospitalized due to paroxysmal nocturnal hemoglobinuria-related complication. Moreover, 6.25% of patients had a history of thrombotic events and 12.5% a history of impaired renal function.

Clinical Diagnosis

Blood analysis at first visit revealed that 37.5% patients had classical paroxysmal nocturnal hemoglobinuria and 62.5% patients had paroxysmal nocturnal hemoglobinuria with secondary bone marrow disorders (BMDs). The patients with secondary bone marrow disorders were diagnosed either with aplastic anemia or hypoplastic anemia (43.75%) and myelodysplastic syndromes (18.75%). As shown in Figure 2, 62.5% of the patients had pancytopenia, 25% had bicytopenia, and 12.5% had anemia.

Flow cytometric analysis of the peripheral blood revealed that the median granulocyte parox-

ysmal nocturnal hemoglobinuria clone size was 36.3% (range 14%-78%). Patients without a history of BMD presented with a larger clone size, the median clone size being significantly larger compared to patients who had at any point been diagnosed with associated BMD (43.3% vs. 32.1%).

Efficacy of the Therapies for Paroxysmal Nocturnal Hemoglobinuria

Table 2 lists the therapies provided to the patients based on their clinical diagnosis. Anticoagulation therapy was provided to (6.25% of the patients, immunosuppressive therapy to 66.25% patients, bone marrow transplant to 18.75% patients, and intermittent blood product support to 18.75% of the patients. However, unfortunately three patients died even after the therapy. Presently, the remaining 13 patients are on follow up therapy either with steroids (38.5%;5/13), steroids along with danazol (23%;3/13), cyclosporine (7.7%;1/13), thalidomide (7.7%;1/13), and intermittent blood product support (23%; 3/13).

Discusion

The current clinical investigation evaluated the base-line characteristics of the patients who reported to our centre with symptoms of paroxysmal nocturnal hemoglobinuria. Our patient population had a high morbidity rate at enrollment; 43.75% of patients had aplastic anemia or hypoplastic anemia, 18.75% had myelodysplastic syndromes, 12.5% had a history of impaired renal function, and 6.25% of the patients had experienced at least one thrombotic event. Three patients died inspite of therapy while in the remaining 13 patients; therapeutic support was continued either with immunosuppressive drugs or blood transfusion. Paroxysmal nocturnal hemoglobinuria occurs in both men and women equally. Although it is usually diagnosed in young adulthood, it can occur at any age. The symptoms could be many or just a few, the most frequently reported symptom being fatigue. The severity of the condition depends on the number of faulty blood cells in the patients' body. In our study, therapy was individualized depending on the severity of the patients' condition and the presence of other risk factors.

At present, allogeneic bone marrow transplantation is the only curative therapy for the eradication of paroxysmal nocturnal hemoglobinuria clone in patients with classical PNH and aplastic anemia /PNH. However, it is less popular due to its association with considerable morbidity and mortality. Till date, a substantially small proportion of patients have availed this therapy [Brodsky R, 2010]. Importantly, Human leukocyte antigen (HLA)-identical sibling bone marrow transplantation is an effective therapeutic option for PNH, which is effective even in the hemolytic phase of the disease. Bone marrow transplant is recommended when patients have significant risk factors, such as thrombosis, pancytopenia, myelodysplastic syndromes or acute leukemia, thrombocytopenia, or a marked need for transfusions [*Raiola A et al., 2000*]. Three of the sixteen patients only qualified for bone marrow transplant.

Supportive measures, such as anticoagulation therapy and blood transfusions are the oldest management therapies for PNH; however, anticoagulation therapy has been reported to increase the risk of thromboembolism in patients with PNH, and is associated with an increased risk of bleeding complications. Therefore, anticoagulation therapy is justified for PNH patients with thrombotic episodes who are not associated with contraindications like severe thrombocytopenia. Low molecular weight heparin has been recommended for cases without contraindication to full anticoagulation [*Brodsky R, 2009*]. It has been reported that primary prophylaxis with warfarin prevents thrombosis with acceptable risks in PNH patients. Anticoagulation therapy may thus improve survival and reduce mortality in PNH patients [*Hall C et al., 2003*]. Here, we used enoxaparin injection (1 *mg/kg*) for anticoagulation therapy, which was administered only to one patient. Treatment of anemia, the most common PNH problem is best done by blood transfusions. In our study, blood transfusions were performed in 3 patients. In a blood transfusion, whole blood, or parts of blood from a donor are put right into the patients' bloodstream. Two types of transfusions are available for PNH patients; they are red blood cell transfusion and platelet transfusion [*Schrezenmeier H et al., 2010*]. Blood transfusions have been also indicated in life-threatening cases like acute paroxysm. Transfusion of red blood cell is essential both in the steady state and at the time of chronic hemolytic anemia aggravation. However, the blood transfu-

sion regime is best tailored to the individual patient taking into account the rate of fall in hemoglobin since the last count, the objective clinical assessment, and the subjective state of the patient, also in relationship to physical exertion [*Olutogun T et al., 2015*].

Another method used for the treatment of PNH is the immunosuppressive therapy, which was used in most of the patients during the study as well as in the follow-up period. It lowers the immune response of the patient and prevents it from attacking the bone marrow. It is mostly appropriate for PNH patients with aplastic anemia. A standard approach for treating acquired aplastic anemia includes immunosuppressive therapy comprising of anti-thymocyte globulin along with cyclosporine [*Sugimori C et al., 2015*]. Although the remission rate in patients is significantly high, it might become harmful in cases with an increased risk of opportunistic infections, particularly in the absence of any remission and also if aplastic anemia is associated with significant PNH clone, then use of ATG is not appropriate from treatment perspective [*Sugimori C et al., 2015*]. Corticosteroids, such as prednisolone, either alone or in combination with an androgen like danazol have also been used for the treatment of PNH. Despite a paucity of randomized trials affirming the effectiveness of oral steroids in hemolysis reduction in PNH, they have been used for the management of acute episodes because of their immediate effects. A continued use of high dosages of corticosteroids has reportedly been associated with substantial side effects; therefore, the International PNH Interest Group has recommended pulse doses [*Ghosh K et al., 2013*]. The mode of action of steroids for preventing hemolysis involves the inhibition of complement activation by an alternate pathway or the dampening inflammation that stimulates activation of complement [*Parker C et al., 2005; Ghosh K et al., 2013*]. According to a study by Issaragrisil et al., the administration of prednisolone in patients with a short disease interval increases the chances of treatment response. They recommended the continuation of treatment for at least 3 months before assessing the outcome, although a longer follow-up period is needed to ascertain the toxicity and infectious complications of the therapy [*Issaragrisil S et al., 1987*]. Similar to prednisolone, the mechanism of PNH amelioration by danazol is also through complement inhibition by resisting osmotic lysis. Another immunosuppressant used in our study was thalidomide, which mediates its biological effects through its immunomodulatory, anti-inflammatory, and anti-angiogenic properties [*Strupp C et al., 2002*]. It has been shown to decrease the T-helper (CD4): T-suppressor (CD8) cells ratio [*Hassan I et al., 2015*].

Currently, novel complement inhibitors are being developed. The assessment of thrombotic risk is of paramount importance; hence, identification of new markers for thrombotic risk is warranted to achieve a better risk-based prophylactic antithrombotic management [*Devos T et al., 2018*].

CONCLUSION

This study was undertaken to investigate the baseline characteristics, clinical behavior, and outcome in patients with paroxysmal nocturnal hemoglobinuria. Since all treatment modalities have their positive outcomes and adverse effects, individualization of therapy based on the discretion of the treating personnel and the clinical presentations of the patient is the best approach for the treatment of PNH. The data from this study can be used to identify the patterns that would indicate the necessity for a diagnosis of PNH and to identify the diagnostic outcomes. Information about PNH is insufficient, and this study could be useful in the diagnosis of other patients with PNH and ultimately improve their medical outcomes.

ACKNOWLEDGMENTS: *Shubhada Karanth contributed to the background literature review, data acquisition and manuscript preparation. Suresh Karanth contributed to manuscript preparation, design of the study and data analysis. Raghavendra Rao contributed to the conception and design of the study, background literature review, statistical analysis and revision of the manuscript.*

REFERENCES

1. *Brodsky RA.* How I treat paroxysmal nocturnal hemoglobinuria. Blood. 2009; 113: 6522-27.
2. *Brodsky RA.* Paroxysmal nocturnal hemoglobinuria. Blood. 2014; 124: 2804-11.
3. *Brodsky RA.* Stem cell transplantation for paroxysmal nocturnal hemoglobinuria. Haematologica. 2010; 95: 855.
4. *Devos T, Meers S, Boeckx N., et al.* Diagnosis and management of PNH: review and recommendations from a Belgian expert panel. Eur J Haematol. 2018; 101: 737-49.
5. *Ghosh K, Madkaikar M, Gupta M, Jijina F.* Evaluation of danazol, cyclosporine, and prednisolone as single agent or in combination for paroxysmal nocturnal hemoglobinuria. Turk J Haematol. 2013; 30: 366.
6. *Hall C, Richards S, Hillmen P.* Primary prophylaxis with warfarin prevents thrombosis in paroxysmal nocturnal hemoglobinuria (PNH). Blood. 2003; 102: 3587-91.
7. *Hassan I, Dorjay K, Anwar P*. Thalidomide in dermatology: revisited. Indian J Dermatol. 2015; 60: 213.
8. *Hill A, Kelly RJ, Hillmen P.* Thrombosis in paroxysmal nocturnal hemoglobinuria. Blood. 2013; 121: 4985-96.
9. *Hill A, Platts PJ, Smith A., et al.* The incidence and prevalence of paroxysmal nocturnal hemoglobinuria (PNH) and survival of patients in Yorkshire. Blood. 2006; 108: 985.
10. *Issaragrisil S, Piankijagum A, Tang□naitrisorana Y.* Corticosteroids therapy in paroxysmal nocturnal hemoglobinuria. Am J Hematol. 1987; 25: 77-83.
11. *Olutogun T, Cutini I, Notaro R, Luzzatto L.* Complement-mediated haemolysis and the role of blood transfusion in paroxysmal nocturnal haemoglobinuria. Blood Transfusion. 2015; 13: 363.
12. *Parker C, Omine M, Richards S., et al.* Diagnosis and management of paroxysmal nocturnal hemoglobinuria. Blood. 2005; 106: 3699-709.
13. *Raiola AM, Van Lint MT, Lamparelli T., et al.* Bone marrow transplantation for paroxysmal nocturnal hemoglobinuria. Haematologica. 2000; 85: 59-62.
14. *Schrezenmeier H, Brodsky RA, Muus P., et al.* Use of Blood Transfusions In Paroxysmal Nocturnal Hemoglobinuria Patients with and without Aplastic Anemia Enrolled In the Global PNH Registry. Blood. 2010; 116: 2241.
15. *Schrezenmeier H, Muus P, Socié G.s, et al.* Baseline characteristics and disease burden in patients in the International Paroxysmal Nocturnal Hemoglobinuria Registry. Haematologica. 2014; 99: 922-29.
16. *Strupp C, Germing U, Aivado M, Misgeld E, Haas R, Gattermann N.* Thalidomide for the treatment of patients with myelodysplastic syndromes. Leukemia. 2002; 16: 1-6.
17. *Sugimori C, Chuhjo T, Feng X., et al.* Minor population of CD55-CD59-blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia. Blood 2006; 107: 1308-14

THE NEW ARMENIAN MEDICAL JOURNAL
Vol.15 (2021). No 4

CONTENTS

The Journal is founded by
Yerevan State Medical
University after M. Heratsi.

Address for correspondence:

Yerevan State Medical University
2 Koryun Street, Yerevan 0025,
Republic of Armenia

Phones:

(+37410) 582532 YSMU
(+37410) 580840 Editor-in-Chief
Fax: (+37410) 582532
E-mail: namj.ysmu@gmail.com, ysmiu@mail.ru
URL: http//www.ysmu.am

Our journal is registered in the databases of Scopus, EBSCO and Thomson Reuters (in the registration process)

SCOPUS EBSCO THOMSON REUTERS

Copy editor: Tatevik R. Movsisyan

Printed in "collage" LTD
Director: A. Muradyan
Armenia, 0002, Yerevan,
Saryan St., 4 Building, Area 2
Phone: (+374 10) 52 02 17,
E-mail: collageltd@gmail.com

OFFICIAL PUBLICATION OF THE YEREVAN STATE MEDICAL UNIVERSITY