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Original Article

Distinct clinical characteristics of paroxysmal nocturnal hemoglobinuria in patients in Southern Taiwan: A multicenter investigation

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Abstract Paroxysmal nocturnal hemoglobinuria (PNH) is an extremely rare acquired disorder. The aim of this study was to investigate the demographics, clinical manifestations, and outcomes of PNH patients in southern Taiwan. Data on PNH patients diagnosed over a 30-year period (1985–2015) were retrospectively collected from four tertiary medical centers in southern Taiwan. Blood samples were collected for hematologic panel testing and flow cytometry detection of PNH clones. Radiologic studies were performed to assess the frequency of complications. Twenty-four patients were enrolled in this study. The median duration of disease in the study participants was 10.8 years. The median granulocyte PNH clone size was 92.5% (range, 1.3%–99.8%), and the median lactate dehydrogenase (LDH) level was 2920.2 ± 1462.0 IU/L. The incidence of thromboembolism and impaired renal function was 16.7% and 29.2%, respectively. The primary treatment strategies included steroids (79.2%), androgens (42.0%), eculizumab (33.3%), immunosuppressants (16.7%), and anticoagulants (4.2%).

Conflicts of interest: All authors declare no conflicts of interests.

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In eight patients treated with eculizumab, there was a marked reduction in the LDH levels of 14.89-fold—1.63-fold that of the upper limit of normal; seven patients exhibited decreased transfusion requirements. Twenty-one patients were alive with regular follow-up at the time of publication. Our study demonstrates that PNH patients in southern Taiwan may exhibit different clinical characteristics and outcomes relative to patients in other countries. There was a trend toward a greater PNH granulocyte clone size, which may lead to more hemolysis. In our study, the percentage of patients with impaired renal function, but not the percentage of patients with thrombotic events, was higher than values reported worldwide and in the observational cross-sectional International PNH Registry. More large-scale studies with comprehensive data on the clinical response to different treatments are needed.

Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is an extremely rare clonal abnormality caused by a mutation of the *PIG-A* gene on the X chromosome [1]. The worldwide prevalence of PNH is estimated to be in the range of 1—5 cases per million individuals [2]. The functional somatic *PIG-A* mutation causes impaired biosynthesis of glycosylphosphatidylinositol (GPI), leading to the deficiency or diminished expression of the GPI-anchored complement regulatory proteins CD55 and CD59 on the cell membrane [3].

With respect to the clinical manifestations of PNH, the affected PNH cells exhibit increased sensitivity to complement lysis, leading to pancytopenia, hemolysis, and thrombosis. The conventional treatment options for PNH are limited to the use of supportive measures, such as blood transfusions and anticoagulation therapy. The novel complement inhibitor eculizumab, a humanized monoclonal antibody against complement C5, significantly improves the outcomes of patients with this disease [4,5]. As diagnostic tools improve and ongoing epidemiologic studies are conducted, some geographic and ethnic differences in the incidence of complications have been reported [6]. However, these studies lack the large case series reported in Taiwan.

We conducted a multicenter study on the demographics, clinical manifestations, and outcomes of PNH over the last 30 years in southern Taiwan.

Participants and methods

Data collection of the study population

Between 1985 and 2015, there were 24 PNH cases, including 10 males and 14 females, from four medical centers in southern Taiwan. The collected clinical data included lactate dehydrogenase (LDH) levels, hemoglobin levels, platelet levels, transfusion requirements, thrombotic events (identified using major adverse vascular event categories), physician-reported renal dysfunction, and treatment modalities. Our study received Institutional Review Board approval (IRB number: KMUH-IRB-20140201, VGHKS 15-CT3-05, 105-6702C, B-BR-105-014-T).

Diagnostics of PNH

Before 2010, the diagnosis of PNH was established by clinical presentation, the direct and indirect Coombs test [7], and the Ham test [8] (or sugar water test [9]). After 2010, flow cytometric analysis using antibodies directed against GPI-AP were used for the diagnosis of PNH in Taiwan. For the detection of GPI-deficient granulocytes, a lyse-wash-stain technique was employed. Cells were analyzed in a CYTOMICS FC 500 (CXP Software) instrument (Beckman Coulter, Miami, Florida, USA). In red blood cells (RBC assay), an indirect immunofluorescence test with anti-CD59 FITC, anti-CD55 PE, and anti-CD235a CyChrome monoclonal antibodies was used in eighteen patients [10,11]. In four-color FLAER (Fluorescent Aerolysin) assay for white blood cells (WBCs), the samples from 21 patients were stained with anti-CD15 PC5, anti-CD45 PC7, anti-CD24 PE (Beckman Coulter, Miami, Florida, USA), and FLAER working solution (catalogue number FL2, Victoria, British Columbia, Canada; www.protoxbiotech.com) for 15 min at room temperature [11,12]. The minimum clone size detected was 0.1% for WBCs and 3% for RBCs. The results are expressed as the percentage of granulocytes negative for CD55/CD59 or FLAER/CD24 [13,14]. Previously diagnosed patients also underwent flow cytometric analysis retrospectively and met the minimal essential diagnostic criteria of PNH [5].

All patients received a bone marrow examination for concomitant myelodysplastic syndromes or aplastic anemia. The patient series was classified into three groups according to the clinical expression and PNH clone percentage: classic PNH, PNH in the setting of another specified bone marrow disorder (SBMD), and subclinical PNH, according to the Nakakuma classification as amended by Parker [6,15].

Treatment of PNH

The treatment of PNH included steroids, androgens, and immunosuppressive therapy (including azathioprine, antithymocyte globulin, and cyclosporine). Anticoagulation therapy was used in patients with thrombotic events. Eculizumab (Soliris; Alexion Pharmaceuticals, Inc., Cheshire, CT, USA) was approved in 2013 by the National Health Insurance of Taiwan for the treatment of PNH with >50%