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Epidemiological estimates of paroxysmal nocturnal hemoglobinuria in Bulgaria

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SUMMARY Paroxysmal nocturnal hemoglobinuria is a rare clonal hematopoietic stem cell disorder with debilitating health consequences if untreated. Although cases have been described globally, precise epidemiological distribution is difficult to assess due to geographical underrepresentation in disease reporting. Evaluation of the burden of paroxysmal nocturnal hemoglobinuria in Bulgaria is currently missing. To provide epidemiological estimates, a systematic literature search for publications in the Bulgarian language or by Bulgarian authors was performed for a ten-year period (2013-2022), and clinically relevant information on case presentation was collected. Additionally, data was retrieved from the National Health Insurance Fund and National Statistical Institute on the count of registered cases with ICD-10 code "D59.5" and census for the same period. The estimated prevalence of paroxysmal nocturnal hemoglobinuria is relatively lower in the Bulgarian population than in other countries, and it is estimated to be 2.77 cases per 1,000,000 patient years. The treatment pattern mainly shows conventional blood product support use and is consistent with the pre-complement inhibition era. Underdiagnosis, lack of a reliable disease reporting system, and, until recently, restricted access to complement inhibitor therapy are significant impediments to the management of paroxysmal nocturnal hemoglobinuria in Bulgaria.

Keywords anemia, intravascular hemolysis, complement inactivating agents, health resources

1. Introduction

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic multi-system, progressive, and life-threatening disorder characterized by intravascular hemolysis, thrombotic incidents, severe infections, and bone marrow failure (*1*). PNH arises due to clonal expansion of hematopoietic stem cells deficient in membrane expression of glycosyl-phosphatidyl inositol (GPI) linked proteins (*2*). GPI deficiency is caused by somatic mutations in the PIG-A gene (phosphatidyl-inositol glycan class A gene) of stem cells, as this gene codes for an enzyme necessary for GPI anchor biosynthesis (*2*). The GPI deficiency affects the membrane expression of two complement regulatory proteins: CD55 – decay accelerating factor, and CD59 – an inhibitor of the membrane attacking complex (*3*). Decreased or lacking membrane expression of CD55 and CD59 renders PNH blood cells increasingly susceptible to complement-mediated lysis (*4*). As a result of enhanced complement activation, the hallmark clinical features are intravascular hemolysis, cytopenia, and thrombosis, particularly unusual site thrombosis.

There is variation in reporting of PNH occurrence globally. According to an updated analysis from the International PNH registry, 68% of cases are reported from Europe, 14% - from the US, and only 18% from the rest of the world (*5*). Inconsistency of representation is most probably related to poor registration and disease reporting, either due to a lack of accessible diagnostic facilities or the inability to maintain data repositories. Previously, PNH distribution in Bulgaria has not been assessed and epidemiological estimates are currently unknown. Therefore, this report aims to summarize data on PNH cases in Bulgaria from publicly available sources and provide estimates of its occurrence in the country.

2. Systematic review of published cases

Literature was searched in a systematic manner for publications in Bulgarian language or by Bulgarian authors from 2013-2022. The following search strategy was applied: for publications in Bulgarian language the repository of the Central Medical Library, Medical

University-Sofia (*www.cml.mu-sofia.bg*) and Google Scholar were searched with text "пароксизмална нощна хемоглобинурия" (Bulgarian translation of "paroxysmal nocturnal hemoglobinuria"); Scopus was searched with item ["paroxysmal" AND "nocturnal" AND "hemoglobinuria"] within All fields with subsequent language filter for Bulgarian. For publications by Bulgarian authors, PubMed was searched with strategy ["paroxysmal nocturnal hemoglobinuria"] AND "Bulgaria" as all fields query and Scopus with "paroxysmal nocturnal hemoglobinuria" with filter "Bulgaria" by Country/Territory.

In total, 19 records were identified through database search. After removing duplicates, seven publications (five case reports and two original articles, 9 PNH cases; Supplemental Figure S1, *http://www.irdrjournal.com/action/getSupplementalData.php?ID=204*) were selected as containing relevant data on PNH cases in Bulgaria (*6-12*). Items were excluded if they were reviews, not by Bulgarian authors, or other documents that did not report relevant information. Clinical characteristics of reported cases and sources are presented in Table 1.

Although some cases lack full demographic description, it is notable to mention that female cases were more prevalent (5/9 cases), and presenting features of the majority of them were late pregnancy complications. Additionally, two-thirds of the cases with available age data were younger than 40 years (4/6 cases), and nearly half of the cases (4/9 cases) were PNH clones in association with other hematologic disorders. Generally for all reported cases is the severe morbidity associated with the condition: transfusion dependency, pregnancy complications, intrauterine growth retardation, cardio-vascular co-morbidity, hemorrhagic diathesis, and severe Grade 4 thrombocytopenia. All required prolonged treatment and intensive blood product support.

3. Epidemiological data

Data was retrieved from the National Health Insurance Fund (NHIF) through an official query (№19-243/01.08.2023) under the Access to Public Information Act. Information was gathered on the number of registered patients with ICD-10 code "D59.5" among all hospitalized patients nationwide for the period 2013-2022 and on the number of patients registered with ICD-10 "D59.5" in the outpatient setting. Demographic statistics from the Bulgarian population census for 2013-2022 were downloaded from the National Statistical Institute (*www.nsi.bg*), and patient years were calculated. Count data on the distribution of hospitalized and outpatient cases with ICD code "D59.5" is presented in Table 2. The prevalence of PNH based on the number of patient-years for the ten years 2013-2022 is estimated at 2.77 cases per 1,000,000 patient-years (194 cases reported by NHIF for the studied period divided by 69,908,268 patient-years). However, these are only registered cases by ICD-10 code. As there is no available associated clinical data, it is difficult to clarify what proportion of these cases are strictly diagnosed based on flow cytometry testing and what proportion have been registered with the PNH ICD-10 code based on clinical features only. A prerequisite to this discrepancy is that the hospital registration system does not explicitly require the presence of flow cytometry results for the ICD-10 code "D59.5" but depends on the treating physician's discretion. Thus, this number may be an overestimation, and the PNH cases diagnosed by the gold standard with flow cytometry may be lower.

4. Discussion

Although PNH is a condition reported globally, precise epidemiological data on incidence and prevalence are still scarce. According to data from the 2022 Orphanet report on the prevalence of rare diseases, the prevalence of PNH in the European population is estimated at 2/100,000 (*13*). The report does not present data on incidence. A retrospective population-based study from the UK estimates yearly PNH incidence at 3.5 new cases per 1,000,000 population or around 220 newly diagnosed cases (*14*). In the same survey, the estimated annual prevalence is calculated at 3.81 /100,000 or 2,400 prevalent cases. Another retrospective study on Medicare data estimated the incidence to be 5.7/1,000,000 patient-years for three years (2015-2018) or 257 new cases yearly, with a prevalence of 12-13/1,000,000 patient-years (*15*). Both sexes are nearly equally affected (*16*). Some studies report a median age at diagnosis of around 50 years and a range of 5-91 years, while other studies reported a median age of around 30 years with an age range of 9-80 years (*17*).

The estimated prevalence of PNH in Bulgaria based on NHIF data seems lower than that reported for other countries. As NHIF data does not contain demographic characteristics such as sex and age, distribution by those parameters cannot be estimated. Assumptions could only be made from the systematic literature search that predominantly females are affected and subjects are of a younger age. The estimation of lower PNH prevalence in Bulgaria may be due to several reasons. On the one hand, this may indicate a lower predisposition of the Bulgarian population to PNH. It is more likely, however, to mirror underdiagnosis due to lower clinical suspicion for PNH and a lower referral rate for PNH screening by flow cytometry.

The treatment pattern that emerges from the case reports in Bulgaria reflects the difficulties in accessing complement inhibitor therapy in countries with limited resources (*18*). The current treatment strategy of PNH relies on complement inhibition by anti-C5 monoclonal antibodies (terminal complement inhibition) or small molecule C3 inhibitors (proximal complement inhibition) (*19*). Complement blockade is the only pathogenetically oriented treatment that achieves

Table 1. Clinical characteristics of published PNH cases in Bulgaria

Case No.	*Reference*	Publication year	Sex	Age, years	Main diagnosis/condition	Complications	Therapy	Outcome
1	Trayanov *et al.* (*6*)	2014	F	37	Pregnancy 31 g. w.	Grade 4 thrombocytopenia, Preeclampsia, IUGR, Oligohydramnion	PRBC, platelet transfusion, corticosteroids	Labor induction in 31 g.w., alive newborn baby, second grade prematurity
2	Popov *et al.* (*7*)	2015	F	73	Waldenstrom Macroglobulinemia	Hemolytic anemia	PRBC, Rituximab	Clinical improvement, control of hemolysis
3	Kosterizova *et al.* (*8*)	2015	F	37	Pregnancy, 34 g.w.	Hemolytic anemia, Bleeding diathesis, Grade 3 thrombocytopenia, IUGR, Oligohydramnion	Corticosteroids, Dycinone, Folic acid, Mg supplements, Enoxaparin, platelet transfusions (72 units in total)	Labor induction in 35 g.w., alive newborn baby, second grade prematurity
4	Nedkova *et al.* (*9*)	2019	M	49	Coronary artery bypass surgery	Hemolytic anemia, Atrial fibrillation, history of multiple myocardial infarctions	Corticosteroids, Rivaroxaban, iron supplements	Hemoglobin normalization, control of hemolysis
5	Atanasoska *et al.* (*10*)	2022	M	38	Hereditary spherocytosis, type 4	Hemolytic crisis with Hgb drop to 60 g/l, PNH clones in RBC, granulocytes and monocytes	NA	NA
6	Atanasoska *et al.* (*10*)	2022	F	-	Mother of the proband (case №5)	PNH clones in RBC, granulocytes and monocytes	NA	NA
7	Jordanova *et al.* (*11*)	2022	F	34	Aplastic anemia with PNH clones	HELLP syndrome during second pregnancy	Corticosteroid, Eculizumab	NA
8	Wong *et al.* (Ignatova, K) (*12*)	2022	-	-	PALOMINO clinical trial	-	Pegcetacoplan	Transfusion independency and no thrombotic complication in none of the participants
9	Wong *et al.* (Amine, I) (*12*)	2022	-	-	PALOMINO clinical trial	-	Pegcetacoplan	

g.w. – gestational week, IUGR – intrauterine growth retardation, PRBC -packed red blood cells, NA – not applicable

Table 2. Count data from NHIF on the distribution of PNH in Bulgaria*

Year	Diagnosis	Inpatient	Outpatient	Census by Infostat
2013	D59.5	17	8	7,245,677
2014	D59.5	29	4	7,202,198
2015	D59.5	23	8	7,153,784
2016	D59.5	12	8	7,101,859
2017	D59.5	12	7	7,050,034
2018	D59.5	27	7	7,000,039
2019	D59.5	4	9	6,951,482
2020	D59.5	1	5	6,916,548
2021	D59.5	2	6	6,838,937
2022	D59.5	0	5	6,447,710
Total		127	67	69,908,268

*Counts are uniquely identified cases by ID, not the number of hospital admissions or outpatient registrations.

hemolysis control, decreases thrombotic complications, improves the quality of life, and prolongs the survival of PNH patients (*20*). Regulatory approved complement inhibitors are the anti-C5 monoclonal antibodies eculizumab and ravulizumab and the C3 inhibitor, the cyclic peptide, Pegcetacoplan. However, due to their high costs, complement inhibitors are not available in many countries worldwide. In countries without access to complement inhibitor therapy, PNH treatment is based on conventional blood product support. Only one case (№7) was treated with a C5 complement inhibitor – eculizumab. Two other cases (№8 and №9) were treated with a C3 inhibitor – pegcetacoplan within the PALOMINO clinical trial. Although the majority of reported cases would have been indicated for complement inhibition therapy, the fact that only one case was treated with eculizumab outside of a clinical trial is indicative of limited access to the specific treatment due to the associated catastrophic health expenditure (*18*). The European Medicines Agency approved eculizumab for the treatment of PNH in 2007. However, in Bulgaria, it was granted reimbursement approval for the first time in April 2021 and only within the framework of a specific governmental regulation that would fund costs for eculizumab treatment only for patients younger than 18. It was not until the beginning of 2024 that both C5 inhibitors (eculizumab and ravulizumab) and the C3 inhibitor pegcetacoplan were incorporated into the public healthcare system and received full reimbursement status after undergoing health technology assessment procedures several times.

The rarity of PNH makes its epidemiological estimation difficult in real-world settings, particularly in the absence of reliable registration systems. Lack of reliable epidemiological data and insufficient clinical information are obstacles to assessing the exact disease burden in the Bulgarian population. Correct diagnosis highly relies on the access and referral rate to diagnostic testing, the latter being dependent on subjective factors such as clinical expertise and reluctance to screen potential cases. Further, the lack of public funding for the specific treatment until recently has additionally impeded the management of PNH cases. Gaps in epidemiological knowledge may be overcome through collaboration between centers and legislative efforts to support reliable disease reporting.

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