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Screening and diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) in Greece: Consensus recommendations from a multi-specialty expert panel

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KEY FINDINGS & CONCLUSIONS

- The findings of this study led to a proposed PNH screening and diagnostic algorithm in Greece, designed to provide guidance for the timely and accurate diagnosis across medical specialties.
- This algorithm serves as an evidence-based tool offering clinical recommendations to reinforce diagnostic practices for PNH, a rare disease, within the Greek medical community.

OBJECTIVE

- To develop clinically relevant, consensus-driven recommendations for the timely and accurate identification of patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) in Greece, from different medical specialties, who are likely to be involved in the diagnosis and coordination of PNH patient care.

INTRODUCTION

- PNH is a rare, life-threatening, acquired blood disorder characterized by hemolytic anemia, thrombosis, and bone marrow failure[1-3].
- The heterogeneous clinical presentation and disease limited awareness among physicians often delay the diagnosis, compromising patient clinical outcomes[4].

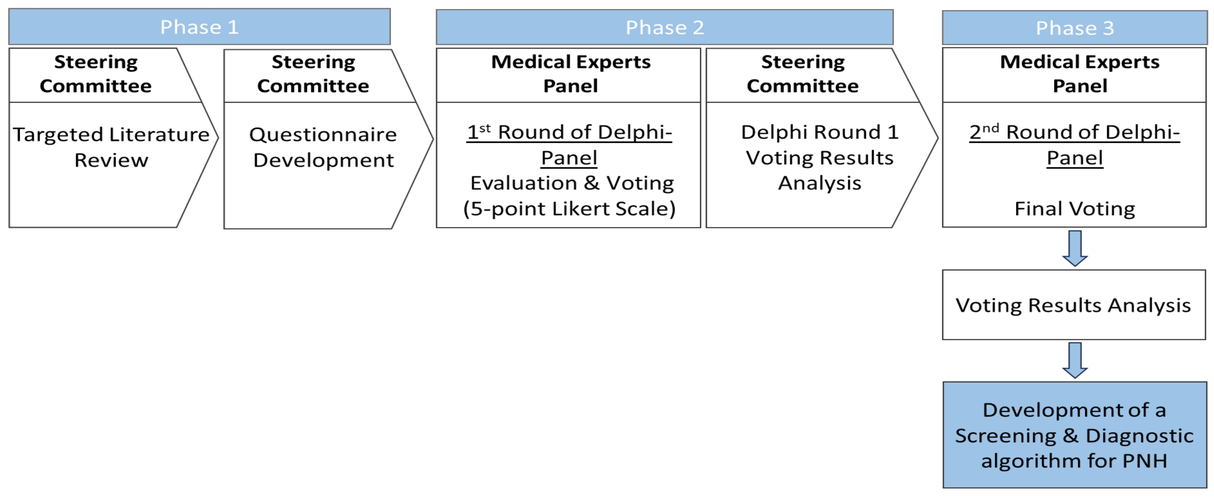
METHODS

- The study was divided into three phases (**Figure 1**).
- In phase 1, a Steering Committee based on a targeted literature review, prepared a questionnaire with i) a list of evidence-based statements on PNH symptoms, diagnosis, and monitoring, along with ii) 6 hypothetical patient cases of common signs, symptoms and potential confounding factors to capture the differential diagnosis.
- A 10-member expert panel, comprising of 4 hematologists and 6 clinicians from different specialties (internist, nephrologist, gastroenterologist, hepatologist, urologist, and cardiologist), participated in a Delphi- panel process.
- All panelists rated the evidence-based statements on a five-point scale (from “strongly disagree” to “strongly agree”) in two Delphi rounds and suggested diagnostic, monitoring tests and specialist referrals for the patient cases.
- Consensus and strength were determined using predefined criteria[5,6]:

a) ≥70% of respondents with a positive rating (i.e., 4 or 5) for consensus or median score is ≥4 or ≥70% of respondents with a negative rating (i.e., 1 or 2) for consensus or median score is ≤2.

b) The strength of the consensus was defined as “very strong” (≥90% agreement), “strong” (80–89% agreement), “moderate” (70%–79% agreement) and “no consensus” (<70% agreement).

Figure 1. Scheme describing the Delphi panel approach for the development of a screening and diagnostic PNH algorithm in Greece



RESULTS

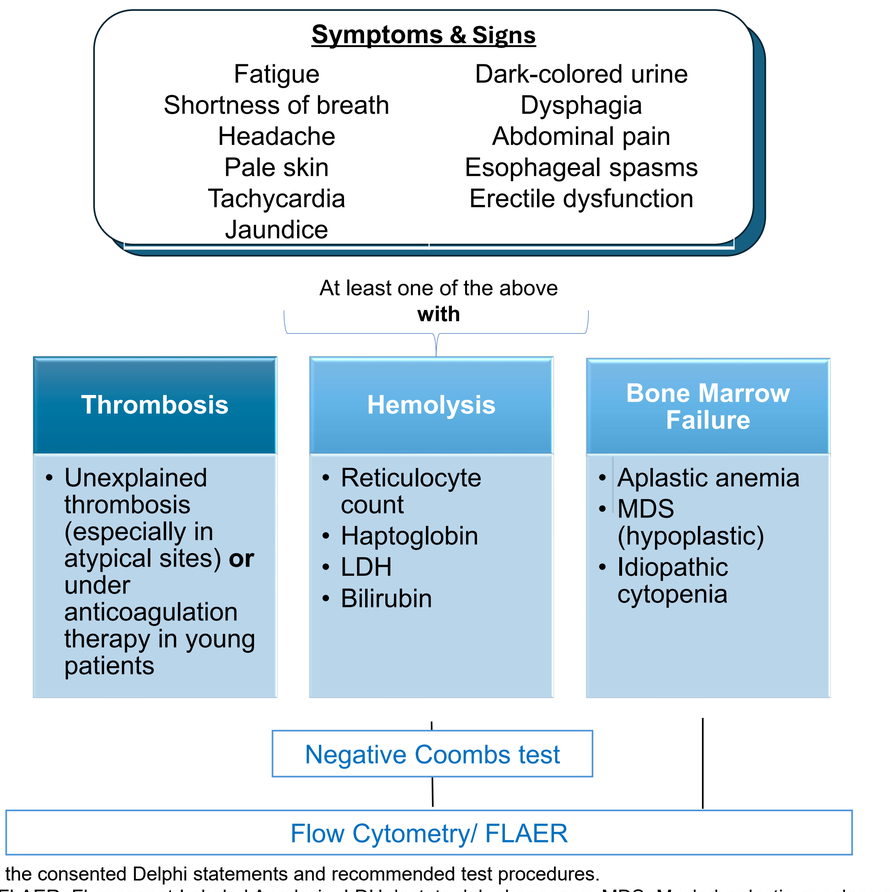
Table 1. Overview of recommended screening and diagnostic tests and specialists’ referrals for the hypothetical patient cases

Laboratory/ imaging analyses	*Case 1:* Patient with pancytopenia requiring red blood cells and platelet transfusions, fatigue, and shortness of breath	*Case 2:* Patient with pulmonary embolism, history of deep vein thrombosis, and negative thrombophilia tests	*Case 3:* Patient with fatigue, severe abdominal pain, and anemia along with thrombophlebitis and mild* chronic kidney disease	*Case 4:* Patient with headache, shortness of breath, jaundice, tachycardia and thrombosis of the transversal sinus	*Case 5* Patient with hematuria, dark urine episodes, and history of esophageal spasms	*Case 6:* Patient with jaundice, history of erectile dysfunction, recurrent episodes of renal colic, and hematuria
Part A: Initial tests						
Complete blood count (CBC)	✓£	✓£	✓£	✓£	✓£	✓£
Reticulocyte count	✓£	✓§	✓£	✓£	✓£	✓¥
Peripheral blood smear/film	✓£	✓§	✓£	✓£	✓§	✓¥
Ferritin serum	✓£		✓£	✓£	✓£	✓£
Biochemical screening**	✓£	✓£	✓£	✓£	✓£	✓£
Hemostasis screening***	✓£	✓£	✓£	✓£	✓£	✓£
Direct Coombs test	✓§					✓£
Haptoglobin serum	✓§			✓¥	✓¥	✓¥
Urinalysis	✓£		✓£	✓¥	✓£	✓£
Urinary Hemosiderin					✓§	
Bone marrow aspirate	✓§					
Bone marrow biopsy	✓¥					
Serum protein electrophoresis and immunoglobulins			✓§			
Viral serology#	✓£					
Antiphospholipid antibodies$		✓£		✓£		
Thrombophilia screening				✓£		
Electrocardiogram	✓§	✓£		✓§		
Echocardiogram		✓£		✓§		
Upper abdominal ultrasound (+/- doppler)	✓§		✓¥		✓£	✓¥
CT pulmonary angiography		✓£				
Part B: Follow-up tests & specialists’ referrals						
Direct Coombs test	Requested in part A	✓§	✓£	✓£	✓§	Requested in part A
Flow cytometry/FLAER	✓£	✓£	✓£	✓£	✓£	✓£
Specialists’ Referrals	Hematologist£	Hematologist£ and pulmonologist§	Hematologist£	Hematologist£ and neurologist¥	Hematologist£	Hematologist£

✓: Consensus reached; £: Very strong recommendation (≥90% agreement); ¥: Strong recommendation (80–89% agreement); §: Moderate recommendation (70%–79% agreement); *glomerular filtration rate 50 mL/min; **Glu, Ur, Crea, Na, K, Fe, TIBC, TP, ALB, tBIL, iBIL, LDH, CPK, AST, ALT, ALP, γGT, UA, Mg, CRP, NT-pro BNP; ***PT, APTT, INR, FIB, D – dimers , #HbsAg, anti-HBc, anti-HBs, anti-HBe, HBeAg, anti-HBc, anti-HCV, HIV, Parvovirus; $Including lupus anticoagulant and anticardiolipin antibody
Note: Empty cells depict parameters either not requested or consensus was <70%.
Abbreviations; DVT: Deep Vein Thrombosis

- All evidence-based statements and PNH symptoms, diagnosis, and monitoring received a very strong recommendation with ≥90% agreement after two rounds of Delphi voting.
- Consensus (>70% agreement) was achieved for 94.8% of diagnostic tests and 88.8% of medical referrals. (**Table 1**).
- All 6 hypothetical patient cases were appropriately referred to a hematologist (**Table 1**), indicating strong alignment in the recognition of PNH-related clinical features among different specialties.
- The strongly recommended diagnostic tests included complete blood count, reticulocyte count, blood smear, serum ferritin, and biochemical/hemostasis screening (**Table 1**).
- Study results were endorsed by the fact that similar responses were extracted between hematologists and non-hematologists, preserving consensus in a subgroup level.
- The consented Delphi evidence-based statements and recommended test procedures drawn from the patient cases led to the development of a structured, evidence-based screening and diagnostic algorithm for PNH in Greece (**Figure 2**).
- The diagnostic algorithm should be applied to patients who have at least one key sign and symptom of PNH in conjunction with evidence of bone marrow failure, hemolytic conditions, or thrombosis (**Figure 2**).

Figure 2. Proposed PNH screening and diagnostic clinical algorithm in Greece*



*Built based on the consented Delphi statements and recommended test procedures.
Abbreviations: FLAER=Fluorescent-Labeled Aerolysin, LDH=lactate dehydrogenase, MDS=Myelodysplastic neoplasms

Disclosures

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