da HPN varia conforme o grau de deficiência da âncora GPI, sendo mais intensa em células tipo III. Fatores como infecções, inflamação e cirurgias podem acentuar a ativação do complemento e a hemólise. A inflamação sistêmica e o risco trombótico reforçam a importância de terapias que inibem o complemento, como os bloqueadores de C5. A HPN é um modelo clássico de doença decorrente da falha na regulação do complemento, ocasionada pela mutação no gene PIGA e ausência de CD55/CD59. A compreensão dos mecanismos desse desequilíbrio fisiopatológico, que apresenta implicações clínicas e imunológicas, reforça o uso de terapias-alvo específicas.

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FROM CLONAL SELECTION TO COMPLEMENT BLOCKADE: EVOLVING CONCEPTS IN PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

AP De Azambuja [a], MM Oliveira [b], YC Schluga [a], RA Marchesini [a], RA Pasquini [a]

[a] *Hospital de Clínicas da Universidade Federal do Paraná (UFPR), Curitiba, PR, Brazil*
[b] *CIONC, Curitiba, PR, Brazil*

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, acquired clonal disorder of hematopoietic stem cells caused by somatic mutations in the X-linked PIGA gene. These mutations impair glycosylphosphatidylinositol (GPI) anchor biosynthesis, leading to the absence of GPI-anchored complement regulators such as CD55 and CD59 on blood cells, which become highly susceptible to complement-mediated destruction. The clinical spectrum ranges from subclinical clones to severe hemolytic disease with thrombosis and/or bone marrow failure. Clonal expansion of PIGA-mutant cells may occur via extrinsic immune selection—frequently associated with aplastic anaemia—or intrinsic clonal evolution involving additional genetic alterations. **Objectives:** To perform a comprehensive review of paroxysmal nocturnal hemoglobinuria (PNH) by integrating a narrative synthesis of the literature with a retrospective analysis of 180 patients diagnosed and followed at a single reference center. The study aims to describe clinical and laboratory features, clonal distribution, classification subtypes, treatment patterns, and outcomes, while contextualizing real-world cohort data within current knowledge on PNH pathophysiology, clonal dynamics, diagnostic strategies, and therapeutic advances in complement inhibition. **Material e methods:** We conducted a narrative review of the literature, incorporating historical and contemporary studies on PNH pathophysiology, clonal dynamics, diagnosis, and treatment. Key topics included immune-mediated mechanisms of clonal selection, disease classification systems, diagnostic approaches using high-sensitivity flow cytometry, and the evolving landscape of complement inhibition therapies. In parallel, we retrospectively reviewed the medical records of 180 consecutive patients with confirmed PNH diagnosed between 2000 and 2025 at Hospital de Clínicas da Universidade Federal do Paraná, collecting demographic, clinical, laboratory, and therapeutic data. Clonal distribution, disease subtype classification, treatment patterns, and outcomes were analysed, with particular focus on associations between clonal size, clinical presentation, and prognosis. Flow cytometry with monoclonal antibodies and/or FLAER remains the gold standard for PNH diagnosis, allowing high-sensitivity detection of GPI- deficient cells across hematopoietic lineages. Complement inhibition with eculizumab and ravulizumab, both C5 monoclonal antibodies, has markedly reduced intravascular hemolysis, thrombotic risk, and improved quality of life, although residual extravascular hemolysis from C3-mediated opsonization persists. Novel proximal complement inhibitors—such as pegcetacoplan (C3 inhibitor) and oral alternative pathway inhibitors targeting factor B (Iptacopan) or factor D (Danicopan)—offer broader complement blockade and more flexible dosing options. Allogeneic hematopoietic stem cell transplantation (HSCT) remains the only curative therapy but is limited by high treatment-related risks. Despite these advances, access to complement inhibitors remains uneven worldwide. **Discussion and conclusion:** PNH exemplifies the link between clonal hematopoiesis, immune-mediated bone marrow failure, and complement dysregulation. Understanding its biology is essential for early diagnosis, risk stratification, and personalized care. New complement inhibitors may lessen disease burden. Continued research is needed to optimize therapeutic sequencing, improve accessibility, and clarify the molecular drivers of clonal evolution.

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GENETIC VARIANTS AND LEVELS OF INFLAMMATORY CYTOKINES FROM SICKLE CELL ANEMIA PATIENTS FROM MANAUS, AMAZONAS, BRAZIL

MOOD Nascimento [a,b], MMP Luciano [a,b], RS Leal [c], VBL Lobato [b], NA Fraiji [d], MS Gonçalves [e], RaR masawmy [a], SRL Albuquerque [a,d], AP Alcântara [f], JPM Neto [a,f,g]

[a] *Programa de Pós-Graduação em Imunologia Básica e Aplicada (PPGIBA), Universidade Federal do Amazonas (UFAM), Manaus, AM, Brazil*
[b] *Programa de Pós-Graduação em Ciências Farmacêuticas (PPGCF), Universidade Federal do Amazonas (UFAM), Manaus, AM, Brazil*
[c] *Pós-Graduação em Farmácia (PPGFAR), Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil*
[d] *Fundação Hospitalar de Hematologia e Hemoterapia do Amazonas (HEMOAM), Manaus, AM, Brazil*

[e] *Instituto Oswaldo Cruz (IOC/FIOCRUZ), Salvador, BA, Brazil*
[f] *Programa de Pós-Graduação em Ciências Aplicadas à Hematologia (PPGH), Universidade do Estado do Amazonas (UEA), Manuas, AM, Brazil*
[g] *Universidade Federal de Juiz de Fora (UFJF), Juiz de Fora, MG, Brazil*

Introduction: Sickle cell anemia Patients (SCA) frequently experience vaso-occlusive crises (VOC) and chronic hemolysis. In Brazil, it is estimated that over 100,000 people are affected, resulting in significant clinical, social, and economic impact. The inflammatory microenvironment characteristic of SCA leads to the release of hemolysis byproducts into the bloodstream, stimulating the production of inflammatory cytokines that exacerbate endothelial activation, cellular recruitment, and chronic pain. Among these cytokines, IL-1β, IL-8, and IL-18 stand out due to their significant roles in modulating clinical severity and systemic inflammation. **Objectives:** We evaluated inflammatory cytokine levels of inflammatory cytokines and genotyped single nucleotide variants (SNVs) in the promoter regions of the IL-1β, IL-8, and IL-18 genes in patients SCA patients and healthy individuals. **Material e methods:** This case-control study involved patients under the care of HEMOAM and healthy blood donors. Cytokine concentrations were analyzed using the BD Symphony S6 flow cytometer. Single nucleotide variants (SNVs) (IL-1B c.-31C>T; IL-8 c.-251A>T; and IL-18 c.-607A>C) were analyzed by real-time PCR. Statistical analyses were conducted using SPSS v19, considering p-values less than 0.05 as significant. **Results:** As expected, cytokine levels were significantly elevated (up to 10 $\times$) in patients compared to controls. Strongly expressive results were observed among patients. Homozygous mutant genotypes for IL-1B (c.-31TT) and IL-8 (c.-607AA) showed significantly elevated levels, whereas the homozygous mutant genotype for IL-8 (c.-251TT) showed significantly reduced levels of their respective interleukins when compared to heterozygous and wild-type genotypes ($p < 0.001$; $p < 0.023$; $p < 0.001$, respectively). Although cytokine concentrations in the control group were considerably lower, significant differences were also observed between genotypes. **Discussion and conclusion:** Our findings confirm previous studies in the literature showing that SCA patients have elevated levels of inflammatory cytokines. The substantial increase in IL-1β among individuals with the c.-31TT genotype reinforces its role in inflammatory activation and VOC episodes. For IL-8, patients with the c.-251AA genotype also exhibited higher levels than control groups. When elevated, this cytokine is associated with more severe clinical manifestations. These findings support the hypothesis that SNVs in IL-8 may intensify inflammation and worsen the clinical condition of patients. In IL-18, elevated levels were identified, especially in individuals with the c.-607AA genotype, suggesting that this cytokine may serve as an indicator of more severe inflammation. Collectively, these results support the notion that SNVs in the promoter regions of IL-1β, IL-8, and IL- 18 influence the magnitude of the inflammatory immune response in SCA. Conclusion: We believe the obtained data obtained may contribute to a better understanding of chronic inflammation in SCA and serve as a foundation for personalized therapeutic strategies. Further studies are necessary to support diagnostic and treatment approaches, particularly for patients in the northern region of Brazil.

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HEMOGLOBINÚRIA PAROXÍSTICA NOTURNA ASSOCIADA À APLASIA MEDULAR: EVOLUÇÃO CLÍNICA E LABORATORIAL COM USO DE ECULIZUMABE – ESTUDO DE CASO (2024)

WS Teles, AP Barreto Prata Silva, FK Fraga Oliveira, CM de Souza Neto, MN Andrade

Centro de Hemoterapia de Sergipe (HEMOSE), Aracaju, SE, Brasil

Introdução: A hemoglobinúria paroxística noturna (HPN) é uma desordem hematológica clonal rara, resultante de mutação somática no gene PIGA, levando à deficiência de proteínas reguladoras do complemento, como CD55 e CD59, na superfície das hemácias. Essa alteração promove hemólise intravascular crônica, risco elevado de eventos tromboembólicos e comprometimento multissistêmico. Estima-se uma incidência de 1 a 5 casos por milhão de habitantes, com impacto significativo na qualidade de vida e sobrevida dos pacientes. **Objetivos:** Relatar um caso de aplasia medular associada à HPN acompanhada em um hemocentro do Nordeste do Brasil, enfatizando evolução clínica, parâmetros laboratoriais e resposta ao tratamento com eculizumabe. **Material e métodos:** Estudo observacional e descritivo baseado na análise retrospectiva de prontuário clínico, exames laboratoriais e evolução terapêutica de paciente diagnosticado com HPN e aplasia medular, atendido em 2024. Paciente masculino, 34 anos, diagnóstico confirmado por citometria de fluxo e biópsia de medula óssea. Iniciou eculizumabe em regime de ataque (600 mg IV semanal por 4 semanas) seguido de manutenção (900 mg IV a cada 14 dias). Foram analisados exames antes e após três meses de tratamento. Antes do início do tratamento com eculizumabe, o paciente apresentava hemoglobina de 6,8 g/dL, LDH de 4.161 U/L, plaquetas em 87.000/mm^3 e leucócitos em 3.000/mm^3. Após três meses de terapia, observou-se elevação da hemoglobina para 8,5 g/dL, redução expressiva do LDH para 620 U/L, aumento das plaquetas para 110.000/mm^3 e dos leucócitos para 4.200/mm^3, evidenciando melhora laboratorial significativa. **Discussão e conclusão:** Os achados laboratoriais demonstram resposta favorável ao eculizumabe, com elevação dos níveis de hemoglobina, redução expressiva do LDH e melhora das citopenias. Essa evolução corrobora estudos recentes (2023-2024) que evidenciam a eficácia do bloqueio do complemento na redução da hemólise e prevenção de eventos trombóticos em pacientes com HPN.O diagnóstico precoce e o início oportuno do eculizumabe são determinantes para otimizar o prognóstico em pacientes com HPN. Este caso demonstra que o tratamento contribui para estabilização clínica, melhora laboratorial e potencial redução de complicações.