Mini Review
Volume 8:4, 2023

Journal of Forensic Medicine

ISSN: 2472-1026 Open Access

Understanding the Basis for Blocking MCPggaac Haplotype Complement Activity after Atypical Hemolytic Uremic Syndrome Incidence in Three Countries of Southeastern Europe

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Abstract

We present a series of cases involving individuals with the homozygous MCPggaac haplotype, a genetic configuration associated with an increased likelihood and severity of atypical hemolytic uremic syndrome (aHUS), particularly when combined with other high-risk aHUS mutations. Complement blockade therapy was administered at a median age of 92 months (with an interquartile range of 36 to 252 months). Prior to initiating CBT (Eculizumab), patients experienced a median of two disease relapses. These relapses transpired within an average span of 22.16 months (median of 17.5, ranging from a minimum of 8 months to a maximum of 48 months) following the initial subsequent disease onset (observed in 6 out of 8 patients). Treatment encompassed plasmapheresis/intravenous plasma exchange (PI/PEX), occasionally supplemented by renal replacement therapy (RRT). Upon the implementation of complement blockade, the occurrence of disease relapses ceased in the pediatric population. For children possessing the MCPggaac haplotype, with or without additional genetic mutations, achieving remission was feasible through renal replacement therapy, without an immediate imperative for complement blockade. However, in cases where aHUS relapse manifested shortly after disease onset or when relapses transpired recurrently, sustained complement blockade emerged as a necessary course of action. The specific duration of such blockade, however, remains uncertain. Failure to initiate complement inhibition prior to experiencing 4–5 relapses could potentially lead to the development of proteinuria and chronic renal failure over time.

Keywords: aHUS • Complement blockade • MCPggaac

Introduction

We present instances involving the homozygous MCPggaac haplotype in conjunction with other genetic conditions that activate complement, heightening the likelihood and intensity of atypical hemolytic uremic syndrome (aHUS) or secondary HUS activation. This is corroborated by evidence of diminished membrane cofactor protein (MCP) gene transcription in vitro due to the MCPggaac haplotype. Recent findings underscore the heightened risk of graft loss and acute allograft rejection among MCPggaac haplotype carriers. Our study scrutinized follow-up data for patients with the MCPggaac haplotype in correlation with aHUS incidence and recurrence. Cases were drawn from Croatia, Bosnia and Herzegovina, and North Macedonia. The objective was to ascertain the prevalence of the MCPggaac haplotype across three Southeastern European countries, identify accompanying mutations, and formulate guidelines for applying complement blockade in such scenarios [1].

Literature addressing MCPggaac haplotype follow-up in aHUS patients remains scarce. This haplotype, encompassing two SNPs in the promoter region, is associated with a two- to three-fold escalated aHUS risk. It covers a significant portion of the RCA gene cluster, including C4BP, DAF, CR1, and MCP genes [2]. This spans polymorphisms such as c.–652A>G (rs2796267), c.–366A>G (rs2796268), c.IVS9–78G>A (rs1962149), c.IVS12+638G>A (rs859705), and c.4070T>C (rs7144). The MCPggaac haplotype correlates with aHUS in sporadic and familial cases. Its clinical manifestation hinges on additional mutations, especially CFH and CFI, and can be triggered by infections or drugs in genetically predisposed children. MCPggaac compound heterozygosity, alongside other risk polymorphisms, can trigger recurrent aHUS relapses and renal decline. Although not universally affecting MCP expression, the MCPggaac haplotype serves as a robust aHUS risk variant or acts in tandem with other mutations. MCPggaac polymorphism is linked to reduced relapse risk and delayed aHUS onset without triggers or additional mutations.

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Received: 04 July, 2023, Manuscript No. JFM-23-111680; **Editor assigned:** 06 July, 2023, PreQC No. P-111680; **Reviewed:** 18 July, 2023, QC No. Q-111680; **Revised:** 24 July, 2023, Manuscript No. R-111680; **Published:** 31 July, 2023, DOI: 10.37421/2472-1026.2023.8.213

Literature Review

The combination of different complement regulatory gene mutations and polymorphisms (CFH, MCP, IF) heightens aHUS susceptibility. The MCPggaac haplotype may further dampen MCP expression in MCP mutation carriers [3]. However, current literature insufficiently supports the notion that homozygous MCPggaac haplotype alone precipitates aHUS onset, as most cases involve other homozygous or multiple heterozygous mutations.

The MCPggaac homozygous haplotype is prevalent in our aHUS cases, often with additional heterozygous aHUS mutations. Even unaffected individuals may carry one or two risk factors, suggesting that a combination of mutations and the risk haplotype is pivotal for aHUS development [4]. The MCPggaac haplotype, particularly when linked with CHF-H3 risk haplotype, is associated with lower cell surface receptor levels and heightened aHUS severity. However, the contribution of MCPggaac additional mutations to compound heterozygosity and aHUS onset risk remains unclear.

Complement blockade revolutionized aHUS treatment, inhibiting complement protein C5 cleavage and terminal component production. This therapy is effective and safe in both children and adults, reserved for life-threatening cases of complement overactivation. In cases of uncertain clinical

conditions, waiting for genetic analysis is acceptable if the patient's overall condition remains favorable. Monitoring hemolysis parameters and C5-b9 levels guides timely complement blockade. Cases with no apparent alternative complement pathway activation may not warrant immediate blockade [5].

Discussion

Some of our cases did not receive complement blockade due to various reasons. The MCPggaac haplotype is associated with diverse outcomes, often necessitating individualized treatment decisions. Frequent aHUS relapses demand permanent complement blockade, but its optimal duration remains elusive. Immediate blockade is essential in certain patients due to their genetic profile. The MCPggaac haplotype, in conjunction with other genetic factors, heightens aHUS risk. The interplay between mutations and the haplotype shapes disease development. Complement blockade's efficacy, personalized therapy, and vigilant monitoring collectively impact aHUS management [6].

Conclusion

While the MCPggaac haplotype, when combined with initial and recurrent genetic mutations, may achieve remission through PI/PEX without the need for complement inhibition, the disease often experiences swift relapses. For aHUS patients with homozygous genetic mutations, particularly in complement factor H (CHF), prompt implementation of comprehensive complement blockade is crucial. In cases where the MCPggaac haplotype coincides with other heterozygous mutations, notably CHF, there is a susceptibility to recurring aHUS episodes. In cases with clear indications, immediate complement blockade is warranted; however, for cases with uncertain clinical manifestations, a cautious approach to its application is advised. When aHUS coincides with underlying conditions, especially hematologic disorders, rapid complement blockade is essential to prevent underlying disease activation. Failing to initiate complement inhibition within 4-5 relapses subsequent to MCPggaac haplotype onset, with or without accompanying mutations (such as CHF, CD46, C3), can lead to the development of proteinuria, renal impairment, and ultimately chronic renal failure.

Acknowledgment

None.

Conflict of Interest

None.

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How to cite this article: Turudic, Velibor. "Understanding the Basis for Blocking MCPggaac Haplotype Complement Activity after Atypical Hemolytic Uremic Syndrome Incidence in Three Countries of Southeastern Europe." *J Forensic Med* 8 (2023): 213.