

Alternative pathway complement activation in secondary thrombotic microangiopathies: is genetics the smoking gun?

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Two different reports in the current PJHN highlight the mist that surrounds the role of the alternative pathway complement activation in secondary forms of thrombotic microangiopathies (TMA). Depending on whether such a role is validated or not, what is at stake is a more disseminated use of anti C5 therapy. The latter has been restricted to the atypical forms of Hemolytic Uremic Syndrome (aHUS), which are the TMAs caused by dysregulation of the alternative complement pathway¹.

According to accepted guidelines, aHUS diagnosis is to be considered only after secondary forms of TMA have been excluded¹. The challenge presented by the well-documented cases reported by Teixeira AC, *et al*² and Diniz H, *et al*³ is that even in immune-mediated glomerulonephritis, defects of the alternative pathway complement activation may coexist together with the activation of the classical (by IgG or IgM containing immune complexes) or lectin (by galactose deficient IgA1 containing immune complexes) complement pathways⁴.

In both cases, the hematological evidence of an ongoing microangiopathic Coombs-negative hemolytic anemia is undisputable. In addition, the histopathological findings of TMA are detailed, affecting arterioles in the case of IgA nephropathy³, while glomerular capillaries are reported to be involved in the hepatitis C virus-associated membranoproliferative glomerulonephritis (MPGN) description². However, for the latter (cryoglobulinemic), one must question if what is displayed are not indeed the *hyaline thrombi* seen in immunocomplex-mediated MPGN rather than the platelet and fibrinogen containing capillary thrombus in TMA. Ultrastructural evaluation of the renal biopsy is warranted before a definite conclusion can be drawn here.

Regarding the phenotype studies on complement pathways, C'3 levels are not detailed in the IgA nephropathy case, although are assumed to be normal. This is relevant, not only because C'3 consumption is associated with a worst prognosis in IgA nephropathy⁵ but also because C'3 levels could help in establishing geno-phenotype correlations in face of the *CFH* and *C3* gene alleles identified in this individual. In the cryoglobulinemic report, and even if the decreased levels for C'3 and C'4 are in line with the detected cryoglobulinemia and classical pathway activation, the absence of anti-FH antibodies determination hampers the pathogenic validation of the *CFHR3-1* locus homozygous deletions, as acknowledged by the authors in the first place.

In both cases, as expected (or unexpectedly), genetic testing was performed in the search for pathogenic variants in the genes coding

for proteins involved in the alternative complement pathway⁶. And the results could not have been more contrasting. While in the IgA case, the *CFH* allele (c.3611G>A, p.Gly1204Glu) in heterozygosity is one of unquestionable pathogenicity and can, alone, account for a TMA/aHUS phenotype, in the cryoglobulinemic case, allele pathogenicity validation is questionable, as acknowledged by the authors in the first place. It is disputable if missense variants in the complement factor H-related proteins (encoded by the *CFHR* genes) are of any significance in aHUS, while the pathogenicity of the *CFHR3-1* homozygous deletion, a polymorphic allele with a frequency in excess of 15% in western populations⁷, cannot be inferred in the absence of documented anti-FH antibodies.

In light of these illustrative cases, the question remains if we should test all TMAs for pathogenic variants in the genes of interest? My personal view is that we should. If found, the impact of these is of the utmost importance in, for instance, transplantation options and outcomes. But this is valid as long as clinicians are able to critically appraise human molecular genetic findings.

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