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REVIEW

Properdin deficiency and meningococcal disease—identifying those most at risk

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The complement system plays an important role in host defence against a variety of microorganisms and also makes a crucial contribution to the generation of humoral immune responses. Over the past 30 years a wide variety of inherited complement deficiency states have been described and careful evaluation of these deficiencies has contributed not only to an understanding of the physiological function of the individual components but also to a more general appreciation of the functions of the affected complement pathway [1,2].

Properdin is a soluble glycoprotein which has a unique role as a positive regulator of the alternative complement pathway by binding and stabilizing the inherently labile C3/C5 convertase enzymes, C3bBb and C3bBbC3b, substantially increasing their half-lives [3]. Properdin, found in plasma at a concentration of about 5–15 μg/ml, comprises a mixture of oligomers of a 53-kD monomer, mainly dimers, trimers and tetramers in a ratio of approximately 1:2:1, with functional activity increasing with the size of the oligomer [4–6]. Properdin deficiency was first described in a Swedish family in 1982 in association with fulminant meningococcal disease [7]. Subsequently, over 100 individuals have been described in about 30 kindreds and three distinct variants of properdin deficiency identified. Type I deficiency is characterized by the absence of detectable protein in plasma, type II by the presence of low but detectable plasma properdin (< 10% of normal) and the rare type III by a normal serum concentration of a dysfunctional variant of properdin.

Diagnosing properdin deficiency is not straightforward. The standard screening assays for complement deficiency, such as measurement of total haemolytic complement (CH50), C3 and C4, are often unhelpful. The classical pathway CH50, C3 and C4 are usually normal while the alternative pathway haemolytic activity (AP50) is low but often within the normal range. A good infection history and family history and a high index of suspicion are thus extremely important factors in identifying possible cases. These can then be screened at specialist centres for properdin by immunochemical assays (identifies types I and II properdin deficiencies) and by functional tests (specifically if type III deficiency is suspected). As a consequence of these difficulties, properdin deficiency is underdiagnosed. It is likely to be a relatively common immune defect in Caucasians, although it is remarkable to note that no cases have yet been reported in races other than Caucasians.

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All three forms of properdin deficiency are inherited in an X-linked manner and family studies have subsequently mapped the properdin gene to the short arm of the X-chromosome [8]. Investigation into the molecular basis of properdin deficiency has revealed a marked degree of genetic heterogeneity even within geographically related families [9,10]. The most common genetic basis in type I deficiency is a point mutation in exons 4–6, leading to the generation of a premature stop codon—this is exemplified by the large kindred described by Spath *et al*. in this issue and elsewhere [11,12]. Normal mRNA transcription has been reported in one individual in the absence of detectable intracellular protein, suggesting that the truncated molecule is rapidly degraded [13]. In type II individuals, two distinct mutations have been described in exons 4 and 8 respectively, each giving rise to amino acid substitutions. Further investigation suggests that although the mutant properdin may be produced and secreted normally, it fails to form active polymers in correct ratios and may be rapidly catabolized extracellularly [11,13]. In one kindred with type III properdin deficiency, the defect has been shown to be a single base substitution in exon 9, causing a substitution Tyr_{387} > Asp. The resultant properdin species had near normal capacity to form oligomers but lacked convertase stabilizing function [14]. The mutated region lies close to the C3b binding site in the molecule and appeared to cause conformational changes which blocked C3b binding.

The enormous genetic heterogeneity described above for mutations causing properdin deficiency makes carrier identification difficult, particularly as uneven X-chromosome inactivation in carrier females can produce a wide range of serum properdin levels with overlap into the normal range. Haplotyping with a panel of five microsatellite markers closely linked to the properdin gene locus has however proved informative within the members of individual families and offers the possibility of accurately detecting at-risk presymptomatic individuals [10].

All three variants of properdin deficiency are clinically characterized by a significant risk of meningococcal disease, particularly in association with unusual infective serotypes such as W-135 and Y [15,16]. Infection with *Neisseria meningitidis* serogroup B has been reported less commonly and anecdotally seems to be associated with milder disease and good outcome, in accordance with the experience of Spath *et al*. reported here and elsewhere [12,17–19]. Different defence mechanisms predominate against type B meningococcus (phagocytic killing) and atypical meningococcal serotypes (serum bactericidal activity), which may explain the differences in disease susceptibility and severity in properdin-deficient individuals [20].

The specific individual risk of meningococcal infection in properdin deficiency has been calculated at around 50%, a 250-fold increase over the baseline incidence of meningococcal infection in the general population [15,16,21]. Whereas the peak of incidence of meningitis in the normal population is at 3 years of age, the peak incidence in properdin-deficient individuals is at 14 years [15]. This finding has caused some confusion, but close analysis of the data clearly shows that properdin-deficient individuals suffer at least as many infections in the early years of life as do normal individuals. Properdin-deficient individuals are at greater risk of fulminant clinical disease, with early studies reporting mortality rates as high as 75% [22]. A more recent retrospective review estimated mortality at 33% in comparison with rates of 5–7% for individuals with terminal complement component deficiencies and complement-sufficient populations [21]. Recurrent infections are extremely rare [15,16], presumably reflecting a capacity for properdin-deficient individuals to develop antibody-mediated defences against subsequent meningococcal infection which can promote bactericidal and phagocytic activity via the intact classical pathway. Recent evidence suggests that properdin-deficient individuals respond well when immunized with the tetravalent polysaccharide meningococcal vaccine (A,C,Y,W135), generating anticapsular antibodies and bactericidal anti-meningococcal activity against serotypes covered by the vaccine which translates into a lower incidence of new or re-infection [23]. The tetravalent vaccine does not protect against group B meningococci and adjunctive chemotherapy is currently required for full protection [24].

Not all properdin-deficient individuals get meningococcal infections, suggesting that there are additional contributory susceptibility factors. In this issue, Spath and colleagues have attempted to identify such additional susceptibility factors for meningococcal disease in a large family containing nine properdin-deficient males, only two of whom had meningococcal disease [12]. No difference was observed in C4 alleles between previously infected individuals and healthy uninfected properdin-deficient family members, excluding the possibility that partial deficiency of C4 contributed to disease susceptibility. However, analysis of IgG subclasses revealed a lack of the G2m(n) allotype in both individuals with previous meningococcal disease but in none of the deficient relatives with no history of meningococcal disease. Absence of the G2m(n) allotype has previously been associated with a reduced immune responses to T-independent antigens such as meningococcal capsular polysaccharide carbohydrate [25,26]. The authors postulate that this subtle aberration in immunoglobulin function might impair the acquisition of natural antibodies cross-reactive with meningococci which, in combination with properdin deficiency, might enhance susceptibility to infection. It is speculated that this combinatorial effect might be particularly relevant for infections with group B meningococcus, as seen in the kindred studied.

Although it is clear that the observation made by Spath and co-workers is preliminary and does not fully explain the heterogeneity in disease susceptibility, it does focus attention on the need to identify additional risk factors in properdin-deficient kindreds to improve risk prediction and avoidance strategies. It is relevant to note that IgG Fc receptor allotypes have been implicated in susceptibility to meningococcal infection in terminal component-deficient individuals [27].

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