COMPLEMENT DEFICIENCIES AND MENINGOCOCCAL DISEASE

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Investigation of inherited diseases often provides insight illuminating both abnormal and normal physiology and improves the diagnosis and care of affected individuals. These precepts are certainly true for the complement deficiency states as exemplified by the recognition of distinct clinical syndromes depending on which component is abnormal. Delineation of these clinical patterns has emphasized the critical importance of the complement cascade in the host defense against systemic infections caused by neisseria, especially *Neisseria meningitidis*. Lastly, knowledge of the role of capsular and subcapsular meningococcal antigens in producing immunity to subsequent infection has provided a basis for treating deficient patients that relies on recruiting immune mechanisms which help to bypass the genetic defect. The purpose of this paper is to review the epidemiology of complement deficiency states, to discuss the pattern of clinical infection associated with different deficiency states, and to compare and contrast three aspects of meningococcal disease in complement deficient and sufficient individuals: clinical features, immune response to infection, and importance of antibody to distinct meningococcal antigens for protection.

EPIDEMIOLOGY OF COMPLEMENT DEFICIENCY STATES

Data on the prevalence of individual complement deficiency states are scarce and largely reflect the Caucasian populations of western Europe and North America. In these populations homozygous C2 deficiency is probably the most common inherited complement defect, occurring in 0.01% of the general population (1). Studies in populations of patients with specific illnesses suggest that C7 and C8β deficiencies occur predominantly in Caucasians whereas as C6 and C8α-γ deficiencies are more common in blacks or Hispanics (2). In contrast, C9 deficiency is rare in Caucasian populations but it is quite common among Japanese occurring in 0.045 to 0.104 % of normal blood donors (3). Together these statistics serve to underscore the critical importance of the ethnic makeup of a given population in determining the most prevalent individual complement component deficiencies and hence, to some extent, the clinical patterns of disease manifest by these individuals. Moreover although different complement component deficiency states predominate in various ethnic populations, their prevalence as a group seems to be relatively constant. The best data on the overall prevalence of these deficiencies indicate that they occur in about 0.03% of the general population (4).

Since inherited complement deficiencies are uncommon, screening patients for these conditions will have its greatest utility in populations displaying the clinical correlates of abnormal complement inheritance, that is in individuals with rheumatologic diseases or recurrent bacterial infections. I will focus here only on the association of these conditions with bacterial infections. In a recent prospective study we discovered 7 unrelated complement deficient individuals among 544 persons with meningitis or bacteremia caused by encapsulated bacteria (5). Six of the seven deficient patients experienced meningococcal infection and one had pneumococcal bacteremia. The prevalence of complement deficiency states among the 85 individuals with meningococcal disease (7.1%) was significantly greater than among individuals with pneumococcal or hemophilus infections and was similar in magnitude to that reported in other United States based studies involving smaller numbers of patients.

Curiously, the reported prevalence of complement deficiency states among individuals presenting with a first episode of documented meningococcal disease has varied widely (0–50%) in different countries around the world (2). Examination of these data in conjunction with the reported incidence of meningococcal disease in these countries reveals an interesting inverse correlation between the incidence of meningococcal disease and the prevalence of associated complement deficiency in patients with meningococcal disease (Table 1). This inverse relationship suggests that the spread of an epidemic strain among a population in which most individuals are susceptible will affect a proportionally greater number of complement sufficient than complement deficient individuals because the former vastly outnumber the

latter. As the level of immunity in the population increases, there is a disproportionately greater decrease in susceptibility to infection in complement sufficient individuals compared to complement deficient individuals who remain at risk by virtue of their complement defect. Consequently, complement deficiency becomes a relatively greater determinant of the risk of infection and the prevalence of these deficiencies among individuals with meningococcal disease increases. Thus, the incidence of meningococcal disease in the general population is a crucial determinant of the frequency with which these defects are observed among individuals with this infection. These epidemiologic considerations must be taken into account before making recommendations regarding the utility of screening patients with meningococcal disease for associated complement deficiency states.

Table 1. Relationship Between the Incidence of Meningococcal Disease in the General General Population and the Prevalence of Associated Complement Deficiency

	Meningococcal Disease	
Country	Incidence (Per Million Population)	Prevalence of Associated Complement Deficiency (%)
Japan	1	50
United States	9	10.3
Israel	14.6	11
South Africa	26	1
Denmark	35	< 1%

CLINICAL PATTERNS OF INFECTION IN COMPLEMENT DEFICIENCY STATES

The complement system is a principal mediator of inflammation. It contributes to the processing of immune complexes, initiates the inflammatory response, promotes chemotaxis, enhances opsonophagocytosis, modulates the immune response, and mediates the direct killing of certain gram negative bacteria. Because individual components often subserve distinct functional activities and are activated in a step wise manner, activities mediated by components proximal to a specific defect are preserved whereas those mediated by proteins distal to the defect tend to be absent. As a consequence of these considerations and the organization of the complement cascade into two activation pathways converging on C3, complement deficiency states can be categorized according to the segment of the cascade affected by the defect (Table 2). The clinical syndrome produced by complement deficiencies within a particular group is similar because the overall functional defect is comparable despite the involvement of distinct components. These defect categories involve: 1) the early classical pathway proteins; 2) the alternative pathway proteins; 3) absent or markedly reduced C3 levels; and 4) the late complement components (2).

Individuals with a deficiency of C1, C4 or C2 are unable to activate the classical pathway but possess a functionally intact alternative pathway. Collagen vascular disorders such as systemic lupus erythematosus appear to predominate in these patients. Nevertheless 20% of these individuals will experience systemic infection. Infections begin early in life and are caused by a variety of encapsulated bacteria, most typically *Streptococcus pneumoniae*. These infections most commonly involve the sinopulmonary tree, the blood stream, or the meninges. Recurrent systemic infection caused by the same organism is unusual.

Individuals with a deficiency of one of the alternative pathway proteins (properdin or factor D) are unable to activate this pathway effectively but possess an intact classical pathway. These deficiencies appear to be less common than those of other complement proteins and homozygous factor B deficiency has yet to be reported. Systemic meningococcal infection is the chief clinical manifestation recognized to date in properdin and factor D deficiencies. Approximately 60% of affected individuals experience this

infection, typically when they are in their mid teens. The infection tends to be more severe resulting in a case fatality rate approaching 50%. Recurrent meningococcal infection is uncommon, possibly because acquisition of specific antibody promotes the efficient utilization of the classical pathway and may facilitate alternative pathway activity even in the absence of properdin (6).

C3 deficiency occurs either as a primary inherited disorder or secondarily due to its consumption as a consequence of the inherited absence of factors H or I or the presence of acquired C3 nephritic factor. As a consequence of the position of C3 at the convergence point of the two pathways, neither one can be activated effectively. Consequently these individuals exhibit profound defects in complement mediated function (Table 2). Fully 80% of these individuals experience severe sinopulmonary, meningeal or blood stream infection. Infections begin early in life and are typically caused by encapsulated bacteria, particularly *Neisseria meningitidis* and *S. pneumoniae*. Recurrent infection occurs in more than half of these individuals.

Table 2. Clinical Patterns Of Infection In Complement Deficiency States

Clinical Variable	CP (C1,C4,C2)	AP (P,D)	C3 (C3,H,I)	LCCD (C5–C9)
Functional defect	↓C' Act. ↓IC Metab. ↓Imm. Resp.	↓C' Act	↓IC Metab. ↓Ops./Phag. ↓Imm. Resp. ↓PMN ↓CTX ↓SBA	(↓CTX) ↓SBA
Systemic Infection (%)	18	57	78	57
Median Age of first Infection (yr)	2	14	2	17
Organisms*	S. pn. N. mgc. H. inf.	N. mgc.	N. mgc. S. pn. H. inf.	N. mgc.
% of infected patients with infection due to these organisms	40	91	54	99
Recurrent infection with same organism (%)	6.3	3.5	56	50

CP = classical pathway; AP = alternative pathway; LCCD = late complement component deficiency; IC Metab. = immune complex metabolism; C' Act. = complement activation; Imm. Resp. = immune response; Ops. Phag. = opsonophagocytosis; CTX = chemotaxis; SBA = serum bactericidal activity; CVD = collagen vascular disease; S. pn. = *Streptococcus pneumoniae*; N. mgc. = *Neisseria meningitidis*; H. inf. = *Haemophilus influenzae*; and PMN = polymorphonuclear neutrophils.* Listed in order of decreasing frequency. Modified from (17).

With the exception of individuals with C5 deficiency, the sole defect in persons with a deficiency of one of the late complement components is the inability to assemble the membrane attack complex and express complement dependent bactericidal activity. Approximately 60% of these individuals develop meningococcal disease and half of these will experience recurrent disease. Initial infection typically occurs

in the mid teenage years and is associated with a lower case fatality rate than that in complement sufficient persons. The striking propensity of these individuals to develop meningococcal disease underscores the critical importance of serum bactericidal activity in host defense against this organism. The inability of these patients to express complement dependent bactericidal activity is directly responsible for their susceptibility to meningococcal disease as indicated by the following observations. First, serum from C9 deficient individuals can kill meningococci, albeit at a slower than normal rate (7). Second, the risk of meningococcal disease among C7 and C9 deficient Japanese is approximately 10,000 and 1,400 fold greater, respectively, than that in complement sufficient Japanese (3). Thus the limited ability of C9 deficient sera to support meningococcal killing is associated with a ten fold reduction in the risk of meningococcal disease compared to the risk for individuals lacking one of the other terminal complement components whose sera are completely derived of the ability to kill meningococci. These data indicate a dose response relationship between the rate of meningococcal killing and the risk of infection and directly implicate the absence of serum bactericidal activity as the defect responsible for this risk.

MENINGOCOCCAL DISEASE IN COMPLEMENT DEFICIENT AND SUFFICIENT INDIVIDUALS

Considerable evidence supports the notion that the complement system plays a unique role in prevention of meningococcal disease, the clinical manifestations of this disease, and its outcome. These data include: 1) the inverse correlation between complement dependent bactericidal activity and the age related incidence of meningococcal disease in the general population (8,9); 2) the fact that approximately 80% of all identified systemic bacterial infections occurring in complement deficient individuals are caused by meningococci (2); and 3) the direct correlation between the extent of complement activation, the concentration of circulating meningococcal endotoxin, the concentration of circulating cytokines (e.g. TNF-α, IL-1, IL-6), activation of the coagulation cascade, multiple organ system failure, septic shock, and death (10-12).

Comparison of the clinical features of meningococcal disease in complement sufficient and deficient individuals reveals interesting differences in the frequency of systemic infection, the median age at first infection, the most common meningococcal serogroup responsible for infection, the frequency of recurrence, and mortality. These contrasting features, identified originally by Ross and Densen (13), have been confirmed in multiple subsequent reports from different patient populations around the world. In addition to their clinical utility, these differences, although incompletely understood, are important for the insights they provide into the function of the complement system in host defense, the pathogenesis of meningococcal disease and mechanisms of tissue injury in meningococcal disease in particular and gram negative sepsis in general. These features are best illustrated by a comparison of meningococcal disease in normal and late complement component deficient individuals (Table 3) and these two groups will be the focus of the remainder of this paper.

One of the most striking features in this comparison is the observation that despite a several thousand fold increase in the risk of infection, meningococcal disease in late complement component deficient individuals is associated with a five to ten fold reduction in mortality even when the comparison is limited to initial episodes of infection. This relationship suggests that mortality in meningococcal disease is dependent in part upon exuberant complement activation and assembly of the membrane attack complex. Formation of this complex could be linked to outcome either by its disruptive effect on meningococcal membranes with resultant endotoxin release and septic shock or by an injurious effect on bystander cells. Both of these postulated mechanisms would be blocked in late complement component deficient individuals.

An additional interesting feature of potential importance is a relapse rate (meningococcal disease occurring < one month following prior infection) that is approximately ten fold greater than that in normal individuals. This observation suggests the possibility that these organisms may normally be sequestered at an intracellular site (e.g. phagocytic cells in the reticuloendothelial system) and that the terminal complement components may contribute to their intracellular killing.

Lastly, a curious aspect of meningococcal disease in the late complement component deficient individual is that the initial episode occurs at a median age of 17 years in contrast to 3 years in the general population. Thus, most of these individuals pass through the time of life when their deficiency might be expected to maximally increase their susceptibility to meningococcal disease without evidencing evidence of that susceptibility. This paradox remains insufficiently explained.

Table 3. Comparison of Meningococcal Disease in Normal and Late-Complement Component (LCCD) Deficient Individuals

Parameter	Normal	LCCD
No. of homozygotes	---	267
No. with meningococcal disease	---	151
Frequency of infection (%)	0.0072	57
Male/female ratio	1.3:1	2.2:1
Median age (yr), first episode	3	17
Recurrence rate (%)	0.34	41
Relapse rate (%)	0.6	7.6
Mortality/100 episodes (%)	19	1.5
Infecting serogroup		
No. of isolates	3,184	67
%B	50	19.4
%Y	4.4	32.8

IMMUNE RESPONSE TO MENINGOCOCCAL DISEASE

The immune response to meningococcal disease in persons lacking one of the terminal complement components has been assumed to be similar to that in normal people. Features of meningococcal disease in deficient individuals that challenge this assumption include the substantially later age of initial infection and the high frequency of recurrent disease. Both natural antibody and that occurring after meningococcal infection might be anticipated to afford some degree of protection from infection or recurrent disease in late component deficient persons as it does in the normal population. However a detailed mathematical analysis of this expectation is most consistent with the hypothesis that prior meningococcal disease does not convey protection from subsequent infection in terminal component deficient individuals, that is, the risk of each infection is an independent event and is approximately 39% (2).

As a consequence of this finding we have examined the immune response to meningococcal antigens following a single episode of meningococcal disease in complement deficient and sufficient individuals (14). These studies indicate that an impaired antibody response is not the basis for the enhanced susceptibility to meningococcal disease. The immune response to capsular polysaccharides following infection did not differ in these two groups of individuals. However, responses to subcapsular antigens particularly meningococcal lipopolysaccharide were substantially greater in deficient individuals. These latter antibodies were bactericidal in the presence of an intact complement source. The basis for this altered response to outer membrane antigens is unknown but might reflect a greater organism load during infection in the deficient individuals or altered antigen presentation. The latter effect might occur as a consequence of the lack of membrane disruption associated with the inability to assemble the membrane attack complex.

ROLE OF ANTI-MENINGOCOCCAL ANTIBODIES IN PROTECTION FROM DISEASE

Substantial data support a major role for antibody to subcapsular antigens in protection from meningococcal disease in normal individuals. This evidence includes: 1) that most people never experience meningococcal disease; 2) most normal sera contain very low levels of anticapsular antibody but measurable amounts of antibody to outer membrane antigens; and 3) that meningococcal disease caused by a specific capsular serogroup in normal individuals is rarely followed by disease caused by a different serogroup of meningococci, implying the existence of protective cross-reactive antibodies directed at noncapsular antigens (8,9). These observations coupled with the finding that convalescent

sera from late complement component deficient individuals contain substantial amounts of antibody to subcapsular antigens raises the question as to why these antibodies protect normal individuals but fail to protect complement deficient persons from meningococcal disease. A possible explanation for this paradox is that antibodies to subcapsular antigens fail to promote opsonophagocytic elimination of the organism because the overlying capsule prevents effective interaction with receptors on phagocytic cells. Consequently the protective effect of these antibodies may be mediated solely through direct complement dependent bactericidal activity. In contrast, anticapsular antibodies may be effective in promoting organism clearance by both opsonophagocytic and direct complement bactericidal mechanisms. Preliminary experimental evidence is consistent with this hypothesis.

These data have practical implications for the management of complement deficient individuals and support the aggressive administration of the tetravalent meningococcal vaccine to these persons. These persons exhibit a normal immune response to the vaccine and this response has been shown to promote the elimination of these organisms in *in vitro* assays that correlate with *in vivo* protection (15,16).

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