

REVIEW

The immunopathogenesis of meningococcal disease

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This review describes the mechanisms of the immune response to meningococcal disease, examining the extent to which individual variation of the immune response can determine susceptibility. It concludes by summarising the difficulties encountered by recent efforts to develop new immunomodulatory treatments.

20% and 80%, depending on the definition used.⁸⁻¹³

EPIDEMIOLOGY

Invasive meningococcal disease is an important public health concern in both the developed and developing world. Because of its epidemic nature, there can be wide variations in incidence over time and between geographical regions. However, increased ease of travel in modern times has assisted the spread of epidemics between regions, as seen with the recent outbreak of meningococcal disease among Hajj pilgrims.¹⁴ Current figures for annual incidence in England and Wales are 5.2 cases/100 000.¹⁵

Classification by serogroup based on capsular polysaccharides is still the most common system for general purposes. In developed countries, up to 90% of infections are caused by serogroups B and C, whereas in Africa, serogroup A predominates. The excess cases resulting from infections in Hajj pilgrims were notable for being caused by serogroup W135. As shall be seen later, a finding of "unusual" serogroup disease can also be a marker of underlying immune problems.

Invasive meningococcal disease is justly feared for its propensity to attack the young and healthy, with a rapid progression from mild symptoms to extreme morbidity and even death within the space of a few hours. It is notable that despite high public and professional awareness of the disease and prodigious advances in the management of severe sepsis, morbidity and mortality remain high.¹⁻³

"Recent work has emphasised the profound effect of the patient's own immune response in determining the course and outcome of disease"

To make headway against this devastating disease, a fundamentally different approach is required. Recent work has emphasised the profound effect of the patient's own immune response in determining the course and outcome of disease. This suggests that in certain contexts, it can be useful to view meningococcal sepsis as an inflammatory disease, despite its infectious origin.

Accordingly, researchers investigating new treatment strategies for meningococcal disease are seeking to modify the immune response rather than develop ever bigger and better antimicrobial agents.

BACKGROUND

Meningococcal disease is caused by *Neisseria meningitidis*, a Gram negative encapsulated diplococcus, which is an obligate human pathogen.

Invasive meningococcal disease usually takes the form of meningitis or septicaemia, or a combination of the two. Although clear differentiation between these two states is not possible in the clinical setting, there is some evidence that patients presenting with meningitis alone have a milder disease course.⁴ In contrast, meningococcal septicaemia is associated with rapidly progressive shock and coagulopathy, which can be extremely difficult to manage. Although overall mortality from meningococcal disease is reported to be around 6-10% in the developed world,^{1 4-7} estimations of mortality for meningococcal septicaemic shock are much higher and vary between

CARRIAGE TO INVASIVE DISEASE

Mucosal immunity constitutes the first line of defence against meningococcal infection and is generally very effective, as shown by the fact that few carriers develop clinical disease. Although the prevalence of carriers as determined by throat swabs is usually in the order of 10%,^{16 17} more sensitive diagnostic techniques suggest that the rate of carriage may be somewhat higher.¹⁸ Although screening of populations has epidemiological interest, it is not yet possible to identify carrier individuals who are at risk of invasive disease.

The invasion of epithelial and endothelial cells is facilitated by colony opacity associated proteins and bacterial pili.¹⁹ Meningococci have evolved several mechanisms for evading the host immune response at the mucosal level,²⁰⁻²² and many of these mechanisms continue to operate once the bacteria have accessed the circulation.²³⁻²⁵ It has recently been shown that the neisserial IgA1 protease can induce a proinflammatory cytokine response in peripheral blood mononuclear cells.²⁶ Interestingly, IgA1 protease does not seem to induce the anti-inflammatory cytokine interleukin 10 (IL-10); this suggests one possible

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Abbreviations: BPI, bactericidal permeability inducing protein; CSF, cerebrospinal fluid; IL, interleukin; LPS, lipopolysaccharide; MBL, mannose (or mannan) binding lectin; TLR, toll-like receptor; TNF, tumour necrosis factor

mechanism for the excessive inflammatory response characteristic of invasive meningococcal disease.

IMMUNE RECOGNITION OF INVASIVE DISEASE

Complement

The complement system of plasma proteins is strongly activated in response to meningococcal infection.^{12 27 28}

There are three principal pathways by which complement may be activated: the classical pathway, which is antibody mediated; the alternative pathway, which is initiated by direct binding of complement components to the pathogen surface; and the more recently described mannose (or mannan) binding lectin (MBL) pathway. MBL, as the name suggests, is able to recognise and bind to mannose on pathogen surfaces.^{29 30}

The importance of these pathways in the defence against meningococci is illustrated by the fact that individuals who are deficient in complement proteins have a greatly increased risk of meningococcal disease. This will be discussed in more detail in a later section.

Recognition of meningococci by the innate immune response

Recent research has shed new light on the innate immune response to meningococci, particularly with respect to lipopolysaccharide (LPS), an important component of the Gram negative cell wall.

The concept of pattern recognition receptors is central to an understanding of the innate immune response. These are non-clonal receptors that can recognise structures common to many pathogenic organisms, known as pathogen associated molecular patterns.³¹ Thus, they can distinguish self from non-self, albeit with less specificity than adaptive immunity. The MBL pathway described above is an example of this non-specific recognition, as are LPS binding protein, bactericidal permeability inducing protein (BPI), soluble CD14, and acute phase reactants, such as C reactive protein and serum amyloid P, all of which have been implicated in the recognition of meningococci.^{27 32–38} There has been much recent interest in the role of toll-like receptors (TLRs) in innate immunity^{39–42}; TLR4 and TLR2 have both been investigated in the context of neisserial disease.^{43–45} TLR4 is of particular interest because it is believed to be the principal receptor for Gram negative organisms.⁴⁶

The role of adaptive immunity

Antibody plays an important role in the defence against meningococcal disease, as a powerful activator of complement.^{28 47 48}

The importance of antibody is illustrated by the distinctive age distribution of meningococcal infection. The first, and larger, peak of incidence occurs in early childhood, between the ages of 6 months and approximately 2 years, with a second, slightly smaller, peak occurring in the late teenage years. The first peak coincides with the loss of maternal antibody from the infant circulation, whereas the second peak occurs when adolescents leave their communities to enter university halls of residence or military barracks, thus encountering new strains to which they may not have acquired immunity.^{17 49} Adaptive immunity may be induced spontaneously by *Neisseria meningitidis* encountered in the community, or by cross immunity with non-pathogenic organisms such as *Neisseria lactamica*.

In view of the considerable morbidity and mortality of invasive disease, there is much interest in supplementing naturally acquired immunity by immunisation. Vaccines are now available for some, but not all, meningococcal serogroups. Polysaccharide vaccines for serogroups A/C/W135/Y have been available for many years, but unfortunately are not immunogenic in young children. In the UK, a conjugate meningococcal C vaccine is now given to all children, and this offers good

protection in the very young.⁵⁰ Vaccines for serogroup B disease are technically more challenging: the group B capsular polysaccharide is poorly immunogenic because of its similarity to host antigens, such as the neural cell adhesion molecule.⁵¹ Research is currently under way to develop serogroup B vaccines that can overcome this problem. For a more detailed discussion of meningococcal vaccines, see Jódar *et al*,⁵² MacLennan,⁵³ and Peter.⁵⁴

From recognition to effector pathways

The complement system has both recognition and effector functions. Once the cascade is activated, downstream effects include opsonisation and phagocytosis,⁵⁵ lysis of meningococci by the membrane attack complex C5–9, and further activation of the inflammatory response via complement fragments.³⁰

Pattern recognition receptors may be subdivided into two main classes: those mediating phagocytosis and those leading to the activation of proinflammatory pathways.^{56 57} For example, CD14 is now known to associate with TLR4 on the cell membrane, initiating the cytokine response via the nuclear factor κ B pathway.⁵⁸

Cytokines

Cytokine activation is an important event in the pathogenesis of meningococcal disease,⁵⁹ and has considerable bearing on the clinical course. A fine balance must be achieved, because underactivation will result in an inadequate immune response, whereas overactivation can be extremely destructive.

During the acute phase of meningococcal infection, greatly raised plasma concentrations of tumour necrosis factor α (TNF- α), IL-1, IL-6, and IL-10 can be demonstrated.^{60–62} Furthermore, cytokine values can be related to clinical severity: high concentrations of TNF- α and IL-6 in severe sepsis are associated with an increased risk of mortality, as are high concentrations of IL-10.^{60 61 63 64} Current research is directed at elucidating genetic determinants associated with this variation in the cytokine response; this will be discussed in a later section.

“Cytokine activation is an important event in the pathogenesis of meningococcal disease, and has considerable bearing on the clinical course”

The distinction between cause and effect—and hence benefit and harm—may be crucial when assessing candidate agents for immunomodulatory treatment. However, the relative roles of proinflammatory and anti-inflammatory cytokines are not clearly defined.⁶⁴ In addition, mechanisms of cytokine control may vary with the disease course and with the clinical presentation: van Deuren *et al* report differences in the modulation of IL-1 β in plasma and cerebrospinal fluid (CSF) in meningococcal disease (implying differences between septicaemia and meningitis), and between early and late stages of infection.⁶⁵

CLINICAL CONSEQUENCES OF IMMUNE ACTIVATION

The well known clinical picture of purpuric skin rash and shock emerges when the activation of inflammatory mediators causes endothelial damage and capillary leakage.^{66 67} The high likelihood of disseminated intravascular coagulation in meningococcal disease⁶⁸ is reflected in the close relation between the inflammatory and coagulation pathways.^{69–72} The combination of poor tissue perfusion and coagulopathy in turn causes the multiple organ failure and necrosis of extremities seen in the most severe cases, which may result in death or permanent disability.^{6 9 73}

Table 1 Characteristic features of meningococcal disease in patients with complement deficiency

Feature	Comment
Unusual serogroup	Infection with an unusual serogroup organism such as W135 is strongly suggestive of complement deficiency
Recurrent disease	This seems to be particularly associated with terminal complement component deficiency
Family history	Complement deficiency inheritance is usually autosomal recessive or X linked (see text)

A finding of any of these features should prompt testing of complement function.

IMMUNOLOGICAL RISK FACTORS FOR MENINGOCOCCAL DISEASE

Given the profound influence of immune activation and inflammatory mediators on the clinical course of meningococcal infection, it is tempting to speculate whether individuals at higher risk can be identified, and hence protected from the deleterious consequences of invasive disease.

This is not generally practical at a clinical level. However, several factors have been identified that have the potential to alter either the risk or the prognosis of infection.

Age

As previously mentioned, age is a risk factor in the incidence of meningococcal disease, and is related to antibody function. This informed the strategy for the introduction of meningococcal C vaccine in the UK, which initially targeted individuals under the age of 18.⁵³

Age may also determine the outcome of invasive infection, with a poorer prognosis seen in those at either extreme of age.⁴

Mucosal immunity

Several sources have reported an increased incidence of meningococcal disease among smokers and those exposed passively to cigarette smoke^{17 74-76} or smoke from cooking fires.⁷⁷ The effect persists after correcting for obvious socioeconomic confounders. Others note a higher incidence of confirmed viral upper respiratory tract infection in the days preceding the onset of meningococcal disease.^{49 78-80} The mechanisms remain unclear,⁸¹ but these findings suggest that compromise of the mucosal barrier is an important risk factor for invasive disease.

Generalised immune deficiency

Interestingly, it appears that susceptibility to meningococcal infection is not necessarily increased in immune deficiency states.

In view of the importance of the antibody response, it is not surprising that there are reports of meningococcal infection in patients with hypogammaglobulinaemia.⁸² In contrast, the risk of meningococcal disease is relatively small in human immunodeficiency virus positive patients.⁸³

Many authors recommend meningococcal immunisation for asplenic individuals.⁸⁴⁻⁸⁶ However, it is interesting to note that reviews of the literature and of series of asplenic patients do not suggest a high risk of meningococcal disease in these patients.^{86 87}

Complement deficiency

It has long been known that deficiency of proteins in the classical, alternative, or terminal complement pathways predispose to invasive meningococcal disease (MBL will be discussed separately). The relative risk has been estimated at several thousands⁸⁸; however, deficiency of complement proteins is extremely rare in the general population. A large study of military recruits found a prevalence of only 0.03%.⁸⁹

Assessing prevalence of complement deficiency in meningococcal disease

Because population based studies of such a rare condition are unlikely to be fruitful, several studies have looked for complement deficiency in patients known to have had meningococcal disease. Most have found complement deficiency in approximately 1-3% of their patients.^{90 91} Recently, a study from Newcastle (UK) tested almost 300 children with meningococcal disease and identified complement deficiency (of C2) in only one child.⁹²

In contrast, studies in Israel and Japan have found a much higher prevalence of complement deficiency,^{29 93} indicating a strong geographical variation.

If the results from the Newcastle study are representative of the UK as a whole, they imply that complement deficiency accounts for only a very small proportion of meningococcal cases in this country.

Characteristics of meningococcal disease in patients with complement deficiency

Certain factors in the patient history or course of meningococcal disease may help identify individuals with complement deficiency. These factors are summarised in table 1.⁴⁸

It is also noteworthy that the age distribution of meningococcal disease is altered in patients with complement deficiency, with a higher average age at presentation than the normal population.^{88 90 91} In addition, some patients with complement deficiency experience a milder disease course.⁴⁸ However, the cause and magnitude of these effects are difficult to establish because these studies of necessity have small numbers of subjects.

Inheritance

Complement deficiencies show an autosomal recessive inheritance pattern, with the exception of properdin deficiency, which is X linked.^{48 93 94}

Conclusion

Although complement is important in the defence against neisserial infection, complement deficiency accounts for a very small proportion of meningococcal disease overall. Therefore, screening all survivors of meningococcal disease is unlikely to uncover many new cases, but the presence of risk factors such as unusual serogroup, recurrent disease, or a strong family history of meningococcal disease should alert clinicians to this possibility.

THE SEARCH FOR A SUSCEPTIBILITY GENOTYPE

It is reasonable to attribute at least some of the wide variation in the outcome of meningococcal disease to heritable factors. However, apart from the special case of complement, variation in immune response to meningococcal disease is unlikely to be at the simple level of sufficiency versus deficiency. It seems probable that the individual pattern of the immune response is determined by several factors, which may interact in complex ways.

Several polymorphisms have been identified in pattern recognition receptors relevant to meningococcal disease, but not all polymorphisms are clearly associated with risk of sepsis.^{45 95 96}

Among the more convincing results is the finding that genetic variants of MBL are significantly associated with meningococcal disease.^{97 98} This is of considerable interest, because these variants are much more common in the general population than deficiencies in other components of the complement pathway. In addition, several studies report that Fcγ receptor allotypes influence susceptibility to bacterial sepsis.^{99–101}

“Although complement is important in the defence against neisserial infection, complement deficiency accounts for a very small proportion of meningococcal disease overall”

As previously mentioned, there is a strong relation between the outcome of meningococcal disease and concentrations of cytokines in plasma or CSF. The logical next step is to ascertain whether individual variations in cytokine responses are genetically determined. One such study examined first degree relatives of patients who had had meningococcal disease, measuring their capacity to produce TNF-α and IL-10 after ex vivo stimulation. They found that mortality in the patients was associated with low TNF-α and high IL-10 production in their healthy relatives.¹⁰²

In an attempt to delineate the specific mechanisms of genetic variation in the cytokine response, several studies have implicated polymorphisms of cytokines or their regulators as determinants of susceptibility or severity of Gram negative sepsis, including meningococcal disease.^{99 103–108} However, it is surprisingly difficult to relate genotype to phenotype, and results of different studies may be contradictory.^{105 109 110}

Finally, given the importance of the coagulation cascade in the pathogenesis of meningococcal disease, it is interesting to note that genetically based variations in plasminogen activator inhibitor 1 concentration are significantly associated with outcome.¹¹¹

Conclusion

As Nadel has pointed out in a recent editorial,¹¹² there are many pitfalls in searching for genetic associations in sepsis, and unless the many confounders and methodological traps are accounted for, a degree of scepticism is required when evaluating these studies. Nevertheless, it is an area of great interest because of the enormous benefits that could ensue from the ability to tailor therapeutic intervention to the genetic profile of the patient.¹¹⁰

FUTURE DIRECTIONS

Immunomodulatory treatment for meningococcal disease is a good idea in theory, but developing therapeutic agents for clinical use is not as straightforward as it may seem. An attempt to block TNF-α bioavailability actually worsened outcomes in some patients with sepsis,¹¹³ and fresh frozen plasma given to a patient with complement deficiency during an episode of meningococcal disease exacerbated the release of endotoxin into the circulation.¹¹⁴ This is very much a field where “a little knowledge is a dangerous thing”.

As well as the unforeseen (with current knowledge, unforeseeable) side effects of treatment, there are several methodological obstacles to overcome in clinical trials. Disease progression in meningococcal disease is often devastatingly swift: there is little time in which to obtain informed consent from distressed relatives, enroll the patient in the trial, randomise for treatment, and administer the study drug.¹¹⁵ In addition, meningococcal disease is relatively rare and multi-centre trials are essential, but standardised treatment is hard

Take home messages

- Meningococcal disease remains an important public health problem
- Although prevention is ideal, until that is achieved a fundamentally different approach is required
- The immune response has a profound effect on the course and outcome of disease, and although we now have a better understanding of this response, merely identifying the relevant pathways and then blocking them is too simplistic an approach
- Successful immunomodulatory treatment requires a more complete understanding of the immune response so that harmful processes can be suppressed without compromising beneficial ones
- Individual variations in the response to meningococcal infection may require management tailored to individual genetic factors
- It is hoped that research in the next few years will provide some answers to these questions

to achieve because it can be difficult to justify rigid treatment protocols in desperately ill patients. The simultaneous use of several new treatment methods may result in a good clinical outcome, but the individual effects are then hard to disentangle.^{116–119} These difficulties are illustrated by a recent study of recombinant BPI in meningococcal sepsis, which showed a trend towards improved outcome, but did not achieve significance.^{115 120}

Nonetheless, immunomodulatory treatment is a promising direction for research, and a large and well designed trial has reported improved mortality in patients with severe sepsis treated with recombinant activated protein C.^{69 121} Interested readers are referred to specialised reviews for further discussion of treatment strategies for sepsis.^{110 122 123}

CONCLUDING REMARKS

Despite advances in prevention and in intensive care management, meningococcal disease remains an important public health problem. Prevention is the ideal, but this will not be possible for some time yet, and meanwhile, we need to explore new strategies for treating these seriously ill patients. Much progress has been made in elucidating the immunological basis for the high morbidity and mortality of this disease. However, it is clear that merely identifying the relevant pathways and then blocking them is too simplistic an approach for such a complex process. Successful immunomodulatory treatment requires a sophisticated understanding of the immune response, allowing us to suppress harmful processes without compromising beneficial ones. In addition, individual variation in the response to meningococcal infection may require management tailored to individual genetic factors. These are important questions for current and future research, and it will be very interesting indeed to see what progress is made in the next few years.

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