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Infections Revealing Complement Deficiency in Adults

A French Nationwide Study Enrolling 41 Patients

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Abstract: Complement system is a part of innate immunity, its main function is to protect human from bacterial infection. As genetic disorders, complement deficiencies are often diagnosed in pediatric population. However, complement deficiencies can also be revealed in adults but have been poorly investigated. Herein, we describe a case series of infections revealing complement deficiency in adults to study clinical spectrum and management of complement deficiencies.

A nationwide retrospective study was conducted in French university and general hospitals in departments of internal medicine, infectious diseases enrolling patients older than 15 years old who had presented at least one infection leading to a complement deficiency diagnosis.

Forty-one patients included between 2002 and 2015 in 19 different departments were enrolled in this study. The male-to-female ratio was 1.3 and the mean age at diagnosis was 28 ± 14 (15–67) years. The main clinical feature was *Neisseria meningitidis* meningitis 75% (n = 31/41) often involving rare serotype: Y (n = 9) and W 135 (n = 7). The main complement deficiency observed was the common final pathway deficiency 83% (n = 34/41). Half of the cohort displayed severe sepsis or septic shock at diagnosis (n = 22/41) but no patient died. No patient had family history of complement deficiency. The mean follow-up was 1.15 ± 1.95 (0.1–10) years. Half of the patients had already suffered from at least one infection before diagnosis of complement deficiency: meningitis (n = 13), pneumonia (n = 4), fulminans purpura (n = 1), or recurrent otitis (n = 1). Near one-third (n = 10/39) had received prophylactic antibiotics (cotrimoxazole or penicillin) after diagnosis of complement deficiency. The vaccination coverage rate, at the end of the follow-up, for *N meningitidis, Streptococcus pneumonia*, and *Haemophilius influenzae* were, respectively, 90% (n = 33/37), 47% (n = 17/36), and 35% (n = 14/34).

This large study emphasizes that complement deficiencies can be revealed in adults by infectious episodes. Most of them were meningococcal infections revealing common final pathway deficiency. To avoid undiagnosis or late diagnosis, adult displaying first episode of *N meningitidis* infection should be tested for complement deficiency.

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Abbreviations: MAC = membrane attack complex, MBL = mannose-binding lectin.

INTRODUCTION

The complement system is a part of the innate immunity. Its main function is to protect human from bacterial infections especially encapsulated ones and to clear immune complexes. The complement system is composed of more than 30 soluble or membranous components.[1] The classical pathway involves C1qrs, C2, and C4, the lectin-binding pathway involves, among others, mannose-binding lectin (MBL) and the alternative pathway involves C3, factor B and properdin. The terminal pathway involves C5, C6, C7, C8, and C9. There are several and complementary mechanisms through complement protects against bacteria. The two main mechanisms are opsonisation by anchoring C4b and C3b to bacterial membrane that promotes phagocytosis and the formation of the membrane attack complex (MAC) which induces lysis of gram-negative bacteria through membrane pore formation. Genetic deficiencies involving most complement proteins have been described since many decades and lead susceptibility to autoimmune diseases and infections. Most of them are autosomal recessive, except for properdin deficiency that is X-linked. The prevalence of complement deficiency is difficult to assess depending on the population studied and the protein involved, but ranges from few cases (C1q) to 10 to 15% of the population (MBL).[2]

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Complement deficiencies result in a wide variety of clinical spectrum.[3] The common clinical feature of alternative and terminal pathway deficiencies is *Neisseria meningitidis* infection especially with rare serotypes in Europe such as serotypes Y and W135.[4] Patients with complement deficiency have a 1000 to 10,000-fold increased risk of meningococcal disease. Meningococcal infection linked with complement deficiency has a high recurrence rate but is rarely fatal.[5] Furthermore, classical pathway deficiencies are often related with encapsulated bacteria such as *Streptococcus pneumoniae*.

As genetic disorders, complement deficiencies are often diagnosed in pediatric population.[6] Complements deficiency can also be revealed in adults [7–10] but have been poorly investigated: most of them were reported in cases record or very small case series.[11] Consequently, data on clinical spectrum, management of complement deficiencies revealed in adulthood are cruelly lacking. Herein, we describe a case series of infections revealing complement deficiency in adults.

METHODS

Design and Patients

This retrospective survey was conducted in French university and general hospitals in the departments of internal medicine, infectious diseases and pneumology. Patients included in the French Reference Center for Primary Immune Deficiencies (CEREDIH) registry were also screened for eligibility. Patients enrolled in a French monocentric survey in New Caledonia on meningococcal infection were also enrolled if they completed the inclusion criteria.[12] The inclusion criteria for the study were 1 age >15 years, 2 complement deficiency, and 3 clinical infection. Both inpatients and outpatients were included. MBL deficiency and hereditary angioedema were excluded. Autoimmune diseases leading to complement consumption were also excluded. All cases of complement deficiencies were reviewed by two independent biologists skilled in the field of complement deficiencies (DP and VFB). The study was performed in accordance with ethical standards of the Helsinki Declaration and was approved by Institutional Review Board.

Clinical data and Complement Assay

Clinical data were retrospectively recorded for each patient by the practitioners with the use of a standardized form. The form included the following information: gender, month and year of birth, date of first symptoms of diagnosis of complement deficiency, clinical or biological manifestations, significant comorbidities, prophylactic antibiotics, and vaccine coverage at the end of the follow-up. Complement deficiency was defined by decrease of at least one component of complement pathway without evidence of complement consumption. Immunochemical assays for individual components were measured by ELISA, Western blotting, or nephelometer technique according to the practice of the laboratory.

Statistical Analysis

Descriptive statistics included the mean (SD), median, interquatile, when appropriate for continuous variables, and frequencies (percentage) for categorical variables.

RESULTS

Patients' Characteristics

Forty-six patients collected between 2002 and 2015 in 19 different departments were enrolled in this study. Five patients were excluded (2 MBL and 3 patients without precise characterization of terminal pathway complement deficiency). Forty one patients were finally enrolled in the survey. Male-to-female ratio was 1.3 (23 males and 18 females). The mean age at diagnosis for the entire cohort was 28 ± 14 (15–67) years. Age distribution of the patients is represented in Figure 1. Most of the patients (60%, n = 25) were diagnosed between 15 and 25 years and the others were diagnosed until 67 years. The proteins involved in the complement deficiencies are shown in Figure 2. Most patients had common final pathway deficiency 83% (2 C5, 13 C6, 17 C7, 2 C8). There were also 4 patients with C2 deficiency, 1 C4, 1 factor I and 1 properdin deficiency.

Clinical manifestations are described in Figure 3. The main clinical feature was meningitis 80% (n = 33). Pneumonia, bone or joint infection, salpingitis, and otitis were scarcer, respectively diagnosed in 4, 2, 1, and 1 patient (s). Bacteria involved in these infections are described in Figure 4. The most frequent bacteria involved was *N meningitidis* 75% (n = 31). Others bacteria were more scarce *Neissseria gonorrhoeae* (n = 2), *S pneumoniae* (n = 2) and *Staphylococus warneri* (n = 1)). In 5 patients, no microorganism was detected. The serotypes of *N meningitidis* were Y (n = 9), W135 (n = 7), B (n = 7), C (n = 2), A (n = 1), and not determined in 5 patients. Among the 31 patients presenting with meningococcal infection, 97% (n = 30/31) had final common pathway complement deficiency and one had properdin deficiency. Half of the cohort displayed severe sepsis or septic shock (n = 22) at diagnosis but no patient died from these infections.

Personal and Family History of the Patients

No patient presented family history of complement deficiency. Near half of the entire cohort (n = 18) had already experienced at least one infectious episode before the diagnosis of complement deficiency: meningitis (n = 13, including 4 with >2 occurrences), pneumonia (n = 4), fulminans purpura (n = 1), and recurrent otitis (n = 1). Of note, the clinical feature of these previous infections was severe sepsis or septic shock in 7 patients.

Patient's Management and Follow-Up

The mean follow-up of the cohort was 0.49;0.98;0.1–10 years (median; interquatile range; min–max). One patient

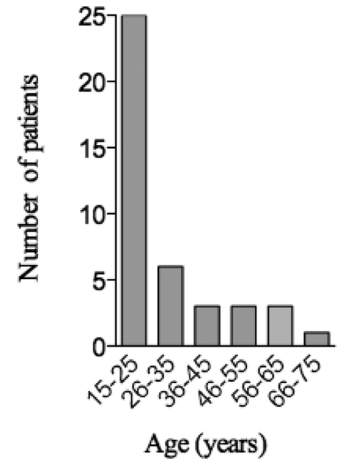

FIGURE 1. Age distribution of the patients at diagnosis of complement deficiency.

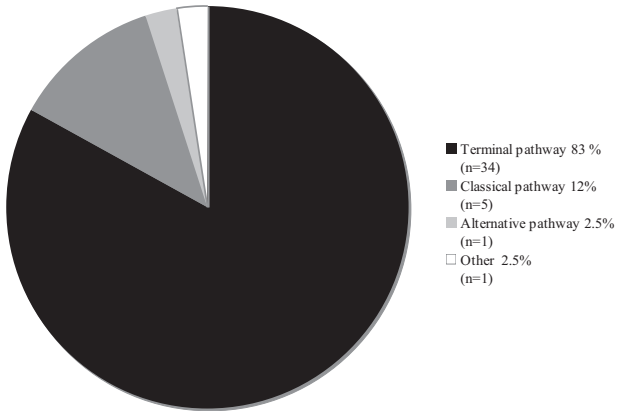

FIGURE 2. Proteins involved in complement deficiencies.

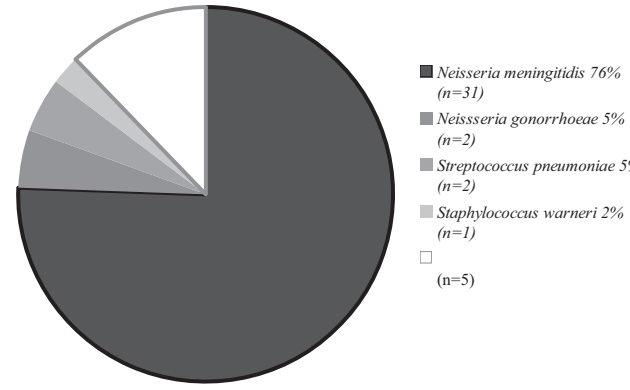

FIGURE 4. Bacteriology of microorganisms involved in complement deficiencies.

was lost to follow-up. Near one-third of the patients (n = 10/39, 2 missing data)) had received prophylactic antibiotics (cotrimoxazole or penicillin) since diagnosis of complement deficiency. Prophylactic antibiotics efficacy has not been assessed. No patient died during the follow-up or had additional infection. The vaccination coverage rate at the last visit for *N meningitides, S pneumoniae and Haemophilius influenzae* were, respectively, 90% (n = 33/37, 4 missing data), 47% (n = 17/36, 5 missing data), and 35% (n = 14/34, 7 missing data).

DISCUSSION

Complement deficiencies are rare, above 1% to 7% of primary immunodeficiency syndromes, most of them are diagnosed during childhood.[13,14] We provided the largest study detailing the description of complement deficiencies revealed by infections in adults. In our study, 41 adults were enrolled from different departments (internal medicine, immunology, infectious disease, and pneumology) and from different centers and thus gave an overview of complement deficiencies revealed by an infectious episode and diagnosed in adulthood. The mean age at diagnosis was 28 ± 14 (15–67) years and 60% most of the patients (n = 25) were diagnosed between 15 and 25 years. The main clinical feature was *N meningitidis* meningitis linked with a common final pathway deficiency. Interestingly, half of the patients had already presented infection before diagnosis of complement deficiency; most of them were meningitis with severe sepsis criteria in half cases. This information could mean that at least a part of complement deficiency diagnosis in adulthood are delayed and would stress physicians to test complement in young adults presenting *N meningitidis* infection. The other part of the case-series which never suffered previous infection represent authentic diagnosis of complement deficiency during adulthood and can be promoted by senescence of immune system.

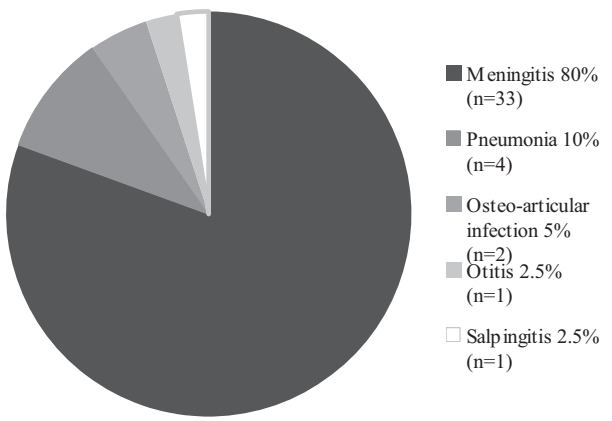

FIGURE 3. Clinical manifestations of infections.

Turley et al recently reported data from 77 patients managed in 18 centers providing an overview of complements deficiency in Europe. In this series, 24% (n = 19) of the patients were diagnosed in adulthood, unfortunately comparison between diagnosis performed at adulthood or childhood has not been performed.[15]

Use of prophylactic antibiotics is high in our series, as in the series of Turley[15] (68%), unfortunately we could not accurately investigate their effectiveness because of the retrospective nature of the survey. Data on prophylactic antibiotics effectiveness and relationship between long-term antibiotics use and prevalence of resistant pathogens are lacking.[16] No prospective randomized trials have been performed because of the rarity of complement deficiencies. One explanation of this high rate of patients treated with prophylactic antibiotics could be the absence of complete efficacy of vaccine in this population. It is now clear that in a complement deficiency population, vaccine does not confer full protection. Data concerning meningococcal vaccine reveal around a quarter of patients presented recurrent meningococcal infections despite tetravalent meningococcal polysaccharide vaccine.[17] However, nowadays quadrivalent meningococcal polysaccharide–protein conjugate vaccines is recommended but data concerning meningococcal B vaccine efficacy in this population are not yet available.[18]

This study is limited by its retrospective design and by the short follow-up (1.15 ± 1.95 years). Moreover, some aspects have not been studied like genetic counselling. Furthermore, as the study was not prospective, patients with infections that were not screened for complement deficiencies have been missed and thus could introduce a bias.

Meningitis was the most frequently revealing infection in our survey. Meningitis generally occurs in 40% of individuals with late component complement deficiency and 6% with properdin deficiency.[19,20] In Caucasians, complement deficiency is reported in 1 to 3% of patients with meningococcal disease. However, in selected groups, prevalence of

complement deficiency is higher as it has been shown in a survey of 125 patients with meningococcal disease: 19 % with rare serotype, 41% with recurrent meningitides and 14% had a family history of complement deficiency.[21] These results were confirmed in another independent study performed in 185 patients with meningococcal infection.[22] It has also been demonstrated that patients with complement deficiency revealed by meningococcal infection are older than general population.[23]

CONCLUSION

Complements deficiency can be revealed in adults by an infectious episode, especially in young adults. The main clinical feature was *Neisseria meningitidis* meningitis linked with a common final pathway deficiency. To avoid undiagnosis or late diagnosis, adult presenting first episode of *N meningitidis* infection should be tested for complement deficiency.

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