CASE REPORT

Recurrent Meningococcal Disease: An Alert Sign

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Abstract

Recurrent meningococcal disease is a red flag for immune deficits with increased susceptibility for *Neisseria meningitidis* infections. Meningococcal disease still causes high morbidity and mortality throughout the world, despite the advances in understanding its pathophysiology and implementing effective treatment. Recurrent meningococcal disease mandates the exclusion of complement deficiencies.

The authors report a case of recurrent meningococcal disease in a 5-year-old girl who was positive for complement component C7 deficiency. Thorough clinical surveillance, tailored immunization, and early antibiotic treatment are fundamental in preventing morbidity and mortality related with the disease.

Keywords: Child, Preschool**;** Complement C7/deficiency; Meningococcal Infections; Portugal

Introduction

Meningococcal disease still causes high morbidity and mortality throughout the world, despite the advances in understanding its pathophysiology.[1] The role of the complement system in the innate immune response (*via* opsonization and phagocytosis of invasive agents) and its relation to meningococcal invasive disease are well established. Included in a heterogeneous group of over 200 primary immunodeficiencies primary complement deficiencies are considered rare. The approximate prevalence of 0.03% is probably an underestimation. Presentation includes increased susceptibility to infections, autoimmunity, inflammatory phenomena, severe allergies, and cancer.[2] The complement system is made of serum proteins and membrane linking proteins that participate in defense responses and inflammation. Its three activation pathways are the classical pathway, the lecithin pathway and the alternative pathway. Membrane attack complex formation is the end stage of the complement activation cascade. It triggers the osmotic lysis of cells and apoptosis. Membrane attack complex component deficits (C5 to C9) compromises bactericidal activity increasing the risk for recurrent bacterial infection. Complement component deficiency prevalence varies with ethnic background. Complement component C7 and C8β deficits are more common in Caucasians, C6 and C8α-γ in blacks and Hispanics, C9 in Asian descendants.[1,3]

Neisseria spp infections clearly standout. Humans are the only known host. Only six of 13 identified serogroups are considered pathogenic: A, B, C, W, Y, and X. Pathogenic serogroup distribution varies with time and geographic location. In Europe the most common are serogroups B and C, with an increase in serogroup W and Y lately. In Africa and Asia, serogroups A and C are the most common.[4,5]

Portugal surveillance numbers show a reduction in the global incidence of meningococcal invasive disease in the country (from about 2:100,000 inhabitants in 2003 to 0.53:100,000 inhabitants in 2014). Incidence still peaks during the first year of life. Decreasing numbers are partly explained by the cyclical nature of serotype B meningococcal infection and the immunization with meningococcal C conjugate vaccine.[6]

Clinical presentation varies. Fever, fatigue, and discomfort as well as headaches and an evolving rash may be present. The evanescent macular rash progresses to a petechial rash with purpura. Light to moderately severe recurrent bacterial infections are the norm. Associated mortality is usually lower compared to immunocompetent individuals. Presentations include bacteremia, sepsis, and/or meningitis.[3,7]

Even when effective treatment is started early, there is an estimated 10%-15% of children that do not survive or survive with severe sequelae, such as severe scarring and amputation, sensorineural deafness, epilepsy, and developmental problems.[3]

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The global mortality rate for invasive meningococcal disease in Portugal from 2003 to 2014 was of approximately 7%, with proportionally higher numbers in the elderly population.[6]
The most effective measure to control meningococcal infection is prevention through immunization.

Case Report

A previously healthy 5-year-old girl with no personal history of recurrent infections nor past hospital admissions was taken to the pediatric emergency department twice within nine months.
Height, weight, and psychomotor development were all within average for age and gender. Her immunizations were according to the Portuguese national vaccination program (2008) and include three doses of meningococcal C conjugate vaccine (at 3 months, 5 months, and 15 months) and 4 doses of the 13-valent pneumococcal conjugate vaccine. Both clinical presentations are summarized in Table 1.
Due to the high suspicion for meningococcal disease prophylaxis was offered to close contacts after each episode. Mandatory national surveillance case reports were filed.
There was no need for organ failure support and intensive care admission. The clinical outcome and evolution were always favorable.
A primary immunodeficiency was suspected, most likely a terminal complement component deficiency, so post-discharge outpatient surveillance was arranged in the local hospital.

Low levels of C7 and CH50 were detected (C7 = 2.4 mg/dL, range 5.5-85 mg/dL; CH50 = 0.6%, range 69%-129%) while the other complement components were within the normal range. The results were verified and confirmed by the immunodeficiencies unit of Centro Hospitalar do Porto upon patient referral. Complement component C7 deficiency was highly likely at this point. Next generation sequencing for 33 genes implicated in complement deficiencies was positive for homozygous *c.2350+2T>C p* variant in gene 7. Loss of exon 17 is the likely cause for this variant, which is to be classified as pathogenic according to the available literature.
Specialized follow-up has been regular with no new episodes of meningococcal infection and favorable evolution thus far. Additional immunizations include 23-valent pneumococcal polysaccharide vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F), 4-valent meningococcal conjugate vaccine (A, C, Y, W-135) and later the meningococcal B vaccine. Her 2-year-old sister was also screened for complement component deficiencies with negative test results.

Discussion

The complement system is made of a network of proteins crucial for both the innate and the adaptive immune response, from microorganism opsonization to chemoattraction triggering necrotic and/or apoptotic cell removal.

Table 1. Summary of the clinical presentation, investigation, treatment, and outcome of two episodes of recurrent meningococcal disease in a 5-year-old girl

Episode	Presentation	Clinical exam	Clinical investigations	Treatment	Outcome
First	< 24 hours of: - Discomfort - Headaches - Vomiting - Normothermia around 37.5ºC < 18 hours of: - Petechial rash	Good general impression Diffuse petechial and purpuric rash Nuchal rigidity	Leukocytosis (23 400 cells/µL) Neutrophilia (21 200 cells/µL) Abnormal coagulation (PT 22.4 s, aPTT 37.7 s) CRP 18.2 mg/dL CSF analysis: - 42 cells/mL - PMN predominance - Glucose 85 mg/dL (55% of serum glycaemia) - Proteins 15 mg/dL Microbiology (blood/CSF) positive for serogroup B *Neisseria meningitidis*	Droplet precautions Isolation Ceftriaxone (100 mg/kg/day) Fresh frozen plasma (3 units)	Favorable Discharge after 10 days of IV antibiotics Outpatient clinic asymptomatic No late term sequelae
Second	- Diarrhea - Myalgia (lower right limb) > 24 hours of: - Persistent fever around 39.4°C - Vomiting - Petechial rash (abdomen right foot)	Pallor Localized petechial and purpuric rash (right thigh and foot)	Leukocytosis (18,100 cells/µL) Neutrophilia (16,300 cells/µL) CRP 18.9 mg/dL CSF analysis Normal cytology and biochemistry Microbiology (blood/CSF) positive for serogroup W135 *Neisseria meningitidis*	Droplet precautions Isolation Ceftriaxone (100 g/kg/day) Vitamin K (10 mg) Fresh frozen plasma (1 unit)	Favorable after coagulopathy control in day 2 Discharge after eight days of IV antibiotics Outpatient clinic asymptomatic No late term sequelae

aPTT - activated partial thromboplastin time; CRP - C reactive protein; CSF - cerebrospinal fluid; IV - intravenous; PMN - polymorphonuclear neutrophils; PT - prothrombin time.

Clinical presentation depends on specific complement component deficits. It includes immune complex mediated disease, pyogenic recurrent infection, hereditary angioedema, and hemolytic uremic syndrome, among others. Complement component deficits (C5 to C9) reduce the bactericide activity with recurrent pyogenic infections. Recurrent capsulate bacterial infection requires complement component deficit exclusion. Membrane attack complex deficit is highly likely in cases of recurrent meningococcal infections, especially when rarer serogroups are involved.[8,9] In these cases, the incidence of meningococcal invasive disease is about 10,000 times superior to the general population and the risk of recurrence is very high.

However, meningococcal disease related mortality in membrane attack complex deficit patients is about 10 times lower compared to healthy individuals.[10] A possible explanation is the low level of endotoxin as membrane attack complex formation is impaired.[11] This would diminish the severity of toxic shock response, cerebral edema, secondary coagulopathy, and tissue damage.

There is no specific treatment for complement component deficit. The prevention and prompt treatment of infections are key for survival and maintaining an adequate quality of life. Antibiotic prophylaxis should be considered upon diagnosis as well as prompt immunization against capsulate bacteria, namely *Pneumococcus spp*, *Haemophilus spp* and *Neisseria spp*.[4,15] Immunization is the only rational and effective strategy for the prevention of infectious disease in these patients. The 4-valent polysaccharide meningococcal vaccine for serogroups A, C, Y, and W135[12] as well as the 23-valent polysaccharide pneumococcal vaccine for serogroups 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F as well as the new meningococcal vaccine for group B,12 are all highly recommended for these patients.[4,12,14]

Hereditary pattern for primary complement diseases is mostly autosomal recessive.[14] In case of heterozygous mutations, individuals may present with up to 50% reduction in complement functional proteins. Patient family screening is important in identifying asymptomatic carriers.

Clinical surveillance, adequate immunizations, and prompt antibiotic treatment upon infection are essential to reducing long-term consequences. Educating the patients and their families on early recognition and the prevention of bacterial infection is key to their long-term follow-up.

WHAT THIS CASE REPORT ADDS

- Recurrent meningococcal disease is a red flag for primary immunodeficiencies with high risk for *Neisseria meningitidis* infections.
- Complement deficit screening must be prompted by recurrent bacterial infection to capsulate bacteria.
- Clinical surveillance, adequate immunizations, and early antibiotic treatment are essential to preventing infection sequelae.
- Bacterial infection prevention includes immunizations against capsulate bacteria, namely 13-valent conjugate and 23-valent polysaccharide pneumococcal vaccines as well as the anti-meningococcal vaccines against serotypes A, C, Y, W135, and B.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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The authors declare that they have followed the protocols of their work centre on the publication of patient data.

References

1. Lewis LA, Ram S. Meningococcal disease and the complement system. Virulence 2014;5:98-126. doi: 10.4161/viru.26515.
2. Blázquez OS, García PR, Falcón FA. Imunodeficiencias primaria. In: Fernandez JG, Dominguez JAR, Suso JJM, Tascón AB, editors. Manual diagnóstico y terapéutica en pediatria, 5th ed. Madrid. Cofás; 2009. p.201-9.
3. Prada D, Henriques P, Silva R. Deficiências do complemento. Saúde Infantil 2011;33:137-43.
4. Ali A, Jafri RZ, Messonnier N, Tevi-Benissan C, Durrheim D, Eskola J, et al. Global practices of meningococcal vaccine use and impact on invasive disease. Pathog Glob Health 2014;108:11-20. doi: 10.1179/2047773214Y.0000000126.
5. Figueroa J, Andreoni J, Densen P. Complement deficiency states and meningococcal disease. Immunol Res 1993;12:295-311. doi: 10.1007/bf02918259.
6. Simões MJ, Fernandes T. Doença invasiva meningocócica em Portugal. Vigilância epidemiológica integrada, 2003-2014: Relatório anual da Rede de Laboratórios VigLab Doença Meningocócica. Lisboa: Instituto Nacional de Saúde Doutor Ricardo Jorge; 2016.
7. Pace D, Pollard AJ. Meningococcal disease: Clinical presentation and sequelae. Vaccine 2012;30;B3-9. doi: 10.1016/j.vaccine.2011.12.062.

8. Grimnes G, Beckman H, Lappegard KT, Mollnes T, Skogen V. Recurrent meningococcal sepsis in a presumptive immunocompetent host shown to be a complement C5 deficient – A case report. APMIS 2011;119:479-84. doi: 10.1111/j.1600-0463.2011.02740.x.
9. Hoare S, El-Shazali O, Clark JE, Fay A, Cant AJ. Investigation for complement deficiency following meningococcal disease. Arch Dis Child 2002;86:215-17. doi: 10.1136/adc.86.3.215
10. Figueroa JE, Densen P. Infectious diseases associated with complement deficiencies. Clin Microbiol Rev 1991;4:359-95. doi: 10.1128/cmr.4.3.359.
11. Kuijpers TW, Nguyen M, Hopman CT, Nieuwenhuys E, Dewald G, Lankester AC, et al. Complement factor 7 gene mutations in relation to meningococcal infection and clinical recurrence of meningococcal disease. Mol Immunol 2010;47:671-7. doi: 10.1016/j.molimm.2009.10.017.
12. Stiehm ER. Approach to the child with recurrent infections [accessed 30 October 2016]. Available at: http://www.uptodate.com
13. Comissão de Vacinas da Sociedade de Infecciologia Pediátrica - Sociedade Portuguesa de Pediatria. Recomendações sobre vacinas extra programa nacional de vacinação - Atualização 2015/2016 [accessed 30 May 2016] Available at: http://www.spp.pt/
14. Batalha S, Russo T, Almeida M, Marques F, Sofia H, Queirós G, et al. Imunodeficiências primárias – Revisão da fisiopatologia, classificação, abordagem diagnóstica e terapêutica. Saúde Infantil 2011;33:97-102.
15. Pettigrew HD, Teuber SS, Gershwin ME. Clinical significance of complement deficiencies. Ann N Y Acad Sci 2009;1173:108-23. doi: 10.1111/j.1749-6632.2009.04633.x.

Doença Meningocócica Recorrente: Um Sinal de Alerta

Resumo:
A meningococemia recorrente constitui um sinal de alerta para imunodeficiências com elevada suscetibilidade a infeções por *Neisseria meningitidis*. Apesar dos avanços no reconhecimento da fisiopatogenia da doença meningocócica e da instituição de medidas terapêuticas adequadas, esta continua a cursar com elevada morbi-mortalidade em todo o mundo. Na presença de infeções meningocócicas recorrentes, as deficiências do complemento devem ser pesquisadas. Os autores apresentam um caso de meningococemia recorrente numa menina de 5 anos a quem foi identificado um défice do componente C7 do sistema do complemento. Nestas situações é imperiosa a vigilância clínica, vacinação adequada e instituição de terapêutica antibiótica precoce, que são estratégias fundamentais para a redução da mortalidade e do risco de sequelas e a mortalidade.

Palavras-chave: Complemento C7/deficiencia; Criança Pré-Escolar**;** Infecções Meningocócicas; Portugal