

A Korean familial case of hereditary complement 7 deficiency

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= Abstract =

Meningococcal infections can be associated with abnormalities of the complement system, which contains 5 terminal complement proteins. Furthermore, deficiencies in 1 of these 5, complement component 7 (C7), leads to the loss of complement lytic function, and affected patients show increased susceptibility to recurrent meningococcal meningitis and systemic *Neisseria gonorrhoeae* infection. In September 2003, an 11-year-old female patient presented at our outpatient department with high fever, lower leg pain, headache, and petechiae. She rapidly progressed to coma but later achieved full recovery due to prompt treatment. Her final diagnosis was meningococcal sepsis and arthritis. Her elder brother also had a similar bacterial meningoen- cephalitis history, which encouraged us to perform analyses for complement component and gene mutations. Resultantly, both the brother and sister were found to have the same mutation in the C7 gene. Subsequently, vaccinations of the meningococcal vaccine meningococcal vaccine (Menomune[®]) were administered. However, in September 2006, the brother expired due to acute micrococcus meningoencephalitis. At present, the 16-year-old female patient is healthy. Here, we report a Korean family with a hereditary C7 deficiency with susceptibility to meningococcal infections due to C7 gene mutation. (**Korean J Pediatr 2009;52:721-724**)

Key Words : Meningococcal infection, Complement 7 deficiency, Korean, C7 gene mutation, Meningococcal vaccine

Introduction

Meningococcal infections may be associated with complement system abnormalities¹⁾. Genetically determined deficiencies of any of the terminal complement components are associated with increased risk to recurrent systemic infections primarily by *Neisseria meningitides* during the age range 10-30 years^{2,3)}, when anti-meningococcal antibodies are presumed present⁴⁾. Complement component 7 (C7) is one of five terminal complement proteins that upon activation of either the classical or the alternative complement pathway interacts sequentially to form a large protein-protein complex, called membrane attack complex (MAC). The assembly of MAC on target cells results in the formation of transmembrane pores that can lead to cell death^{5,6)}. The single poly-

peptide chain of C7 is composed of 821 amino acid residues and is structurally similar to those of the other MAC components, C6, C8 α , C8 β , and C9^{7,8)}. The C7 gene has been shown to span about 80kb of DNA and to be encoded by 18 exons⁸⁾. It is located on chromosome 5p13, as are the genes that encode C6 and C9⁹⁾. C7 deficiency leads to the loss of complement lytic function, and patients so affected, show increased susceptibility to recurrent meningococcal meningitis and systemic *Neisseria gonorrhoeae* infections, although many siblings that share the deficiency may remain healthy¹⁰⁾.

We report a Korean family with a hereditary C7 deficiency conferring susceptibility to meningococcal infection due to a G-to-T transversion (g.IVS4-1G>T) at the 3' splice acceptor site of intron 4 of the C7 gene.

Case report

A 11-year-old girl was admitted via outpatient department in August 2003 with a high fever, headache, a right lower leg pain, and petechiae and 3 hours after admittance rapidly progressed to a comatose state. Upon initial physical examination, her body temperature was 39.6°C, heart rate 95

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beat/minute, blood pressure was 100/70 mmHg. A laboratory investigation and brain MRI were initiated promptly. The laboratory evaluations revealed: hemoglobin 9.1 g/dL, hematocrit 27.3%, WBC 1,500/mm³, platelets 57,000/mm³, sodium 140 mmol/L, potassium 3.7 mmol/L, GOT/GPT 16/18 IU/L, BUN/Cr 10.9/0.7, CRP 22.5 mg/L, PT/aPTT 20.7/48.5 seconds, and antithrombin III 87.85%. Brain MRI findings were normal, but foot MRI revealed right calcaneus osteomyelitis, and a subsequent immediate CSF study revealed a clear color with a cell count of 2/μL, CSF protein 77 mg/dL, CSF/serum glucose 80/144 mg/dL, and no bacteria on Gram staining.

Intravenous cefotaxime sodium 200 mg/kg/24hr, teicoplanin 6 mg/kg/24hr, and acyclovir 30 mg/kg/24hr were promptly administered under the impressions of bacterial sepsis, early bacterial or viral meningococcal meningitis, or septic arthritis. Three days post-admission, her mental condition recovered and her general condition slowly improved. At 5 days post-admission, a blood culture grew *Neisseria meningitidis*, but no organisms were not detected in the CSF.

At 29 days post-admission, she made a full recovery and was discharged with a final diagnosis of meningococcal sepsis and septic arthritis.

At 25 days post-admission, we analyzed complement component in all family members because of the family history (Fig. 1). In December 2002, her elder brother had experienced bacterial meningitis that showed gram negative bacilli by CSF gram staining, but a CSF culture exhibited no growth. C7 concentration analyses results, obtained using C7 a Behring Nephelometer Analyzer (BNA; Dade Behring,

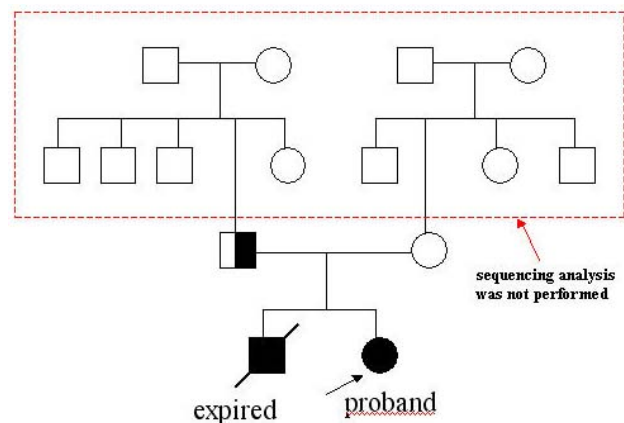


Fig. 1. Pedigree of the family with a C7 deficiency. The solid circle and square represents the patient (proband) and her brother, and the hemisolid square represents the carrier. The mother was normal. Sequencing analyses of C7 were not performed in other family members.

Marburg, Germany), revealed that her parents were at slightly lower than the normal level, but the patient and her brother were confirmed to be C7 deficient (Table 1). Other complement component results were normal.

To detect the C7 gene mutation all exons and exon-intron junctions of the C7 gene in all family members were amplified by PCR and sequenced using forward and reverse primers. Direct sequencing analysis demonstrated a G-to-T transversion (g. IVS4-1G>T) at the 3' splice acceptor site of intron 4 of the C7 gene, which presumably causes skipping of exon 5 of the C7 gene during RNA processing and splicing (reference sequence, NM_000587). This mutation is the same as that reported in another Korean family¹¹. In the present study, the father was heterozygous and patient and brother were homozygous (Fig. 2).

After discharge, she intermittently visited outpatient de-

Table 1. Terminal Complement and CH50 Activities in the Sera of Family Members

	Father	Mother	Brother	Proband
CH50 (Normal: 23-46 U/mL)	33	36.2	3.9	4.1
C5 (Normal: 7.4-11.7 mg/dL)			8.7	7.2
C6 (Normal: 4.3-8.1 mg/dL)			6.4	3.3
C7 (Normal: 5.4-11.2 mg/dL)	4.5	4.5	<0.9	<0.5
C8 (Normal: 6.5-15.4 mg/dL)			20.9	8.7
C9 (Normal: 3.1-7.5 mg/dL)			6.9	4.4

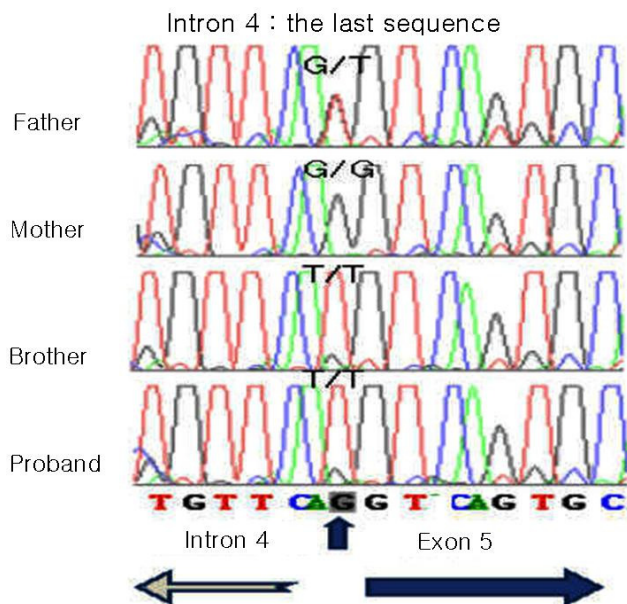


Fig. 2. Direct sequencing analysis demonstrated a G-to-T transversion (g.IVS4-1G>T) at the 3' splice acceptor site of intron 4 of the C7 gene (arrowed). The father is heterozygous, and the proband and brother are homozygous for this mutation.

partment because of a mild fever, a migraine headache, and a skin rash. Therefore, we decided that prophylactic meningococcal vaccination was required, but this is not available in Korea. Nevertheless, we persisted, and finally, all family members were vaccinated with tetravalent polysaccharide meningococcal vaccine (PSV-4), Menomune[®] (A/C/ Y/W-135, Aventis Pasteur, Canada), which was obtained from Canada in October 2004.

However, in September 2006, about two years after the first prophylactic meningococcal vaccination, her elder brother was admitted to our emergency room due to a headache and high fever, and later expired due to acute micrococcus meningoencephalitis. Other family members were administered a secondary meningococcal vaccination in November 2006, and the female patient was administered a third prophylactic vaccination in September 2008. At present, she is 16 years old and is healthy. In the future, we will either administer PSV-4 as a prophylaxis every 2 years or switch to the novel tetravalent conjugate meningococcal vaccine.

Discussion

The complement system is composed of a series of 19 plasma and 9 membrane proteins, and was first discovered at the turn of the twentieth century. However, it was not until the 1960's that the first complement deficient patient was described. The complement system is usually divided into classical and alternative pathways.

The incidences of complement deficiencies are both geographically and ethnically dependent¹⁾. C2 deficiencies are common in the USA, and C6 and C8 α - γ deficiencies are common in blacks, whereas C7 and C8 deficiencies are predominantly observed in Caucasians. C9 deficiencies are common in Japan, and C7 deficiencies have been reported more frequently in Spain and Israel than in Japan and Korea¹¹⁾. Thus, the thresholds used for screening complement abnormalities should reflect these epidemiologic variations.

Deficiencies in the terminal components C5-C9 cause poor bactericidal function, especially of *Neisseria species*, and are the components needed to form MAC (membrane attack complex). Late component deficient patients in the US population may have a 1,000 to 10,000 fold increased risk of infection, with a median age at onset in the mid-teens, as compared to the first five years in the normal population. Furthermore, those affected were found to have a relapse rate of approximately 8% and a recurrence rate of 44%^{1, 12)}.

C7 is a single-chain polypeptide composed of 821 amino acid residues and is structurally similar to other components of MAC, that is, C6, C8, C8, and C9^{7, 8, 11)}. The C7 gene spans about 80 kd of DNA and is encoded by 18 exons⁸⁾. To date, more than 15 different molecular defects that lead to total or subtotal C7 deficiency have been reported^{5, 11, 13)}.

Ki et al. reported two novel mutations in the C7 gene in a Korean patient with C7 deficiency, namely, a point mutation at the 3' splice acceptor site of intron 4 (c.281-1G>T) and a large deletion mutation encompassing almost the whole C7 gene from exon 1 to exon 17 (c.1- ?_2350+?del)¹¹⁾. Our patient have the same point mutation in intron 4, but no large deletion mutation was detected.

The prophylaxis of complement deficiency to prevent meningococcal disease can be undertaken by administering prophylactic antibiotics or by vaccination with tetravalent polysaccharide vaccine (PSV-4)¹¹⁾. PSV-4 was developed in response to an increasing rate of bacterial meningitis among military recruits, and following the widespread use of vaccine in the military, a dramatic decrease in the incidence of invasive meningococcal disease has been observed¹⁴⁾. However, PSV-4 is limited by its poor immunogenicity in small infants, a failure to induce a T-cell-dependent immune response, and a lack of long-term protection. In contrast, the novel tetravalent conjugate meningococcal vaccine, which currently is only available in North America, is immunogenic in young infants, induces long-term protection, and reduces nasopharyngeal carriage¹⁵⁾. A tetravalent conjugate meningococcal vaccine was licensed for use in 11-55 year olds in the US in January 2005, and subsequently for use in 2-11 year old children in Canada in May 2006¹⁶⁾.

Our patient had meningococcal sepsis and her elder brother expired due to recurrent bacterial meningitis, and both harbored a G-to-T transversion (g.IVS4-1G>T) at the 3' splice acceptor site of intron 4 of the C7 gene. Although her family members underwent prophylactic vaccination with PSV-4 (Menomune[®] A/C/Y/W-135) to prevent *Neisseria meningococcal* infection, her elder brother later expired due to recurrent bacterial meningoencephalitis. Therefore, we intend to recommend that our C7 deficiency family members change from PSV-4 to a tetravalent conjugate meningococcal vaccine in the future.

요 약

선천성 보체 7번 결핍을 가진 한국인 한 가족

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수막구균(Meningococcus) 질환은 보체계의 이상과 관련이 있을 수 있다. 보체 7번은 5개의 말단 보체 단백질(terminal complement protein) 중 하나로 이것이 결핍되면 보체의 세포를 용해하는 작용을 잃게 되어 반복적인 감염, 특히 수막구균 감염에 대한 감수성이 증가한다. 2003년 9월 고열, 하지 동통, 두통과 점상 출혈로 외래에 내원한 11세 된 여자 환자가 입원 후 급격히 혼수 상태로 빠졌으나 즉각적인 치료로 결국 완전히 회복되었다. 환자의 최종 진단은 수막구균성 패혈증과 관절염이었다. 환자의 오빠도 비슷한 세균성 뇌수막염 가족력이 있어 저자들은 보체계 검사와 유전자 돌연변이(gene mutation)에 대해 분석하였고, 환자와 환자의 오빠는 보체 7번 유전자의 exon 4에 G394C에 돌연변이가 있는 선천성 보체 7번 결핍 환자였고, 아버지는 보인자로 밝혀졌다. 저자들은 예방적으로 4가 수막구균 백신(tetravalent polysaccharide meningococcal vaccine, Menomune[®] A/C/Y/W-135, Aventis Pasteur, Canada)을 3년마다 접종하기로 하였고 2004년 10월에 처음으로 접종하였다. 그러나 2006년 9월 오빠는 급성 세균성 뇌수막염(meningoencephalitis)으로 사망하였다. 이에 저자들은 2년마다 예방적 접종을하기로 하였고, 환자는 2008년 9월에 3번째로 접종하였으며 16세 된 환자는 현재까지 건강한 상태이다. 저자들은 수막구균 감염과 보체 7번 유전자 네 번째 intron의 3' 말단 splice acceptor 위치에 G to T 돌연변이(g.IVS4-1G> T)가 있는 선천성 보체 7번 결핍을 가진 한국인 한 가족을 보고하는 바이다.

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