Hereditary C1q deficiency: a new family with C1qA deficiency

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Hereditary deficiency of complement component C1q is a rare genetic disorder with susceptibility to recurrent infections with polysaccharide-containing encapsulated microorganisms and a high prevalence of autoimmune diseases, most often systemic lupus erythematosus (SLE). Here, we report a 29-month-old boy who presented with facial rash and history of early death of a sibling with infections, who was found to have a selective deficiency of C1q. The facial rash was composed of patchy erythematous plaques and centrally hypopigmented macules and desquamation. Two siblings had died of severe bacterial infections and his uncle had died of meningitis. Molecular study disclosed a homozygous point mutation in the C1qA chain gene. Five members of the family, including the parents and three healthy siblings, were heterozygous for this mutation.

Key words: C1q deficiency, C1qA chain, infection, systemic lupus erythematosus.

The complement system is a group of plasma and cell surface proteins acting in the innate immune system. It not only contributes to clearance of immune complexes and bacteria via adherence, opsonization and microbial lysis, but also induces cellular and humoral immune response producing anaphylatoxins and chemotactic factors. The complement component C1q initiates the classical pathway of complement activation by binding to immune complexes[1-3]. Deficiency of the complement C1q is a rare genetic disorder with susceptibility to recurrent infections with encapsulated microorganisms and a high prevalence of autoimmune phenomena, most often systemic lupus erythematosus (SLE)[1,2]. Many studies have been reported on the deficiencies of complement components, C1 through C9, but few reports on selective complete C1q deficiency have been described thus far. In this report, we describe a new family in which the index case had SLE-like skin lesion and homozygous mutation in the C1qA chain, whereas two siblings and an uncle had died of severe infections.

Case Report

A 29-month-old boy was referred to Hacettepe University Children's Hospital with rash and desquamation on his face. Family history revealed that the parents were consanguineous and two siblings had died of infections (Fig. 1). A brother experienced pneumococcal meningitis at the age of four years, and a few weeks later he died with a clinical picture of sepsis, and a sister who had undetectable total complement hemolytic activity (CH50) died of sepsis at 1.5 years of age before complement components could be evaluated. Additionally, an uncle had died of meningitis. All other family members including three sisters were healthy. Physical examination revealed patchy erythematous plaques and centrally hypopigmented macules on the cheeks and nose, which tended to crust and desquamate. He had lymphadenopathy on the left submandibular region 2x2 cm

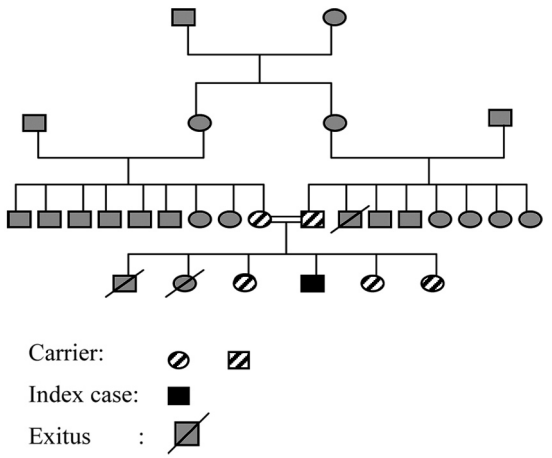


Fig. 1. Family tree.

in size. The skin biopsy revealed atrophy, hyperkeratosis, basal vacuolar degeneration, and numerous dyskeratoses in the epidermis. Examination of the dermis revealed a perivascular mononuclear cell infiltration of the dermoepidermal interface with extravasation of erythrocytes and melanin incontinence. These findings were consistent with SLE-like skin lesions defined in complement-deficient patients.

The results of routine laboratory studies were normal. Serum immunoglobulin levels were within normal limits. He produced antibodies against hepatitis B vaccine. Isohemagglutinin titers were normal. Total hemolytic complement activity (CH50) was zero and C1q was undetectable by single radial immunodiffusion. Anti-nuclear antibody (ANA) was positive with a titer of 1/60 and spotted pattern. Periodic determination of ANA titer during clinical follow-up was planned since in recent years ANA titer up to 1/100 is considered normal.

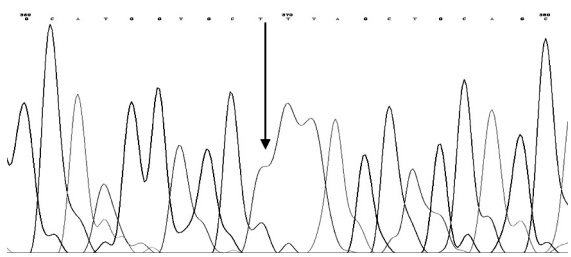
Four of five healthy-looking members who could be tested had normal CH50 levels. CH50 was not studied in one of the siblings who died of infection. Polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis was done in the patient and five family members, which showed homozygosity and heterozygosity (the parents and 3 healthy siblings), respectively. A single band at 260 bp was detected in the patient sample, indicating the presence of a homozygous point mutation in exon 2 of C1qA gene. However, both parents and unaffected siblings had three bands (260 bp, 160 bp and 100 bp), pointing to the heterozygosity. Sequence analysis of the genomic DNA of the patient showed a homozygous C to T transition in exon 2 of the C1qA gene, which resulted in a premature stop codon at amino acid position 186 (Fig. 2).

Discussion

C1q deficiency is a rare hereditary disease associated with an SLE-like syndrome and recurrent infections. Patients with C1q deficiency have an increased risk of fulminant infections with encapsulated bacteria, particularly *Streptococcus pneumoniae*. Because of the patients' inability to clear immune complexes and cellular debris, they also have an increased risk of autoimmune diseases, particularly SLE[2,5-8]. Usually, the clinical manifestation is an apparent SLE-like syndrome with recurrent skin and mucosal lesions, which might accompany severe pyogenic infections. SLE-like syndrome is shown to be highly associated with C1q deficiency[4,6,7]. However, there seems to be a striking clinical variability even in the same family[9]. The clinical spectrum might vary between lack of symptoms to the presence of manifestations of an SLE-like syndrome as a mild skin disease, glomerulonephritis or severe central nervous system vasculitis. Pneumococcal meningitis with encapsulated bacteria is at the other end of the spectrum.

Our patient presented with maculopapular rash and recurrent upper respiratory tract infections and a history of the death of two siblings and an uncle with severe infections.

Due to mutations in any one of the three genes coding for the C1q A, B or C chains, either a nonfunctional C1q antigen is present or no C1q protein is detectable in the patients with C1q deficiency. To date, 7 mutations in 46



DNA sequence picture of the patient showing C to T transition in codon 186 of the C1qA.

patients from 26 families have been reported to be responsible for hereditary C1q deficiency. The most common mutation is a nonsense mutation in the codon for Glu186 (C to T transition) of the C1qA gene. In the present patient, the same homozygous C to T point mutation in exon 2 of the A chain of C1q, which was described in 10 patients previously, was demonstrated. It was first described in two related families from the Slovak Republic[10] and then subsequently identified in four unrelated families of Turkish origin and in a family from Cyprus[4,6,11,12]. All the Turkish patients with C1q deficiency reported to the present shared this mutation. It seems to be the first-line mutation in the Turkish population with C1q deficiency.

We believe that any patient presenting with recurrent infections with encapsulated bacteria and/or SLE-like syndrome, desquamative skin lesions, malar rash, and oral mucosal involvement should be screened for complement C1q deficiency. Screening of families is needed both for identification of heterozygotes, which is important for genetic counseling, and for detecting asymptomatic cases.

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