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Case Report

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A Novel Mutation Identified in Complement C6 Deficiency

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Keywords:

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Abbreviations:

AH50: Alternate Complement 50% Activity; CH50: Complement Hemolytic 50% Activity; C6: Complement 6; C6D: Complement 6 Deficiency; C6SD: subtotal C6 deficiency; SLE: Systemic lupus erythematosus

1. Abstract

We present a Case Report of a 15-year-old African-American female with C6 deficiency due to compound heterozygous C6 mutations and a novel C6 mutation.

2. Introduction

The complement system is a crucial part of innate immunity in defense against pathogens and removal of dead cells and immune complexes [1]. The complement system is comprised of the classical, lectin, alternative and terminal complement pathways. The terminal complement pathway is comprised of complement 5 (C5), C6, C7, C8, and C9. Upon activation of C5, the activated complex of C5bC6C7C8C9 is formed generating the membrane attack complex (MAC) forming pores in the cell membranes causing osmotic lysis. Deficiencies of terminal complement proteins lead to susceptibility to Neisseria infections and autoimmune disorders. C6 deficiency is one of the more common complement component deficiencies. In the United States, it is felt to occur with a frequency of 1:1600 (0.062%) in African Americans [2,3]. In the following Case Report, a 15-year-old African-American female who was being evaluated for possible systemic lupus erythematosus (SLE) was found to have an absent Complement Hemolytic 50% Activity (CH50). She was referred to Immunology for evaluation and was diagnosed with C6 deficiency due to compound heterozygous C6 mutations and a novel C6 mutation.

3. Case Description

The patient, a 15-year-old African-American female, was being evaluated by Rheumatology for a several year history of diffuse joint pain, joint swelling, morning stiffness, chronic fatigue, peripheral extremity changes concerning for Raynaud's disease, nausea, and anorexia with a twenty-pound weight loss over four months. She had mild arthritis on examination. She also had allergic history significant for exercise-induced bronchospasm, allergic rhinitis, and oral allergy syndrome. Due to concern for SLE and/or other autoimmune disorders, laboratory studies of autoantibodies (ANA, anti-dsDNA, Sm, SS-A, SS-B, RNP, RF, and chromatin antibodies), IgG, IgA, IgA, C-reactive protein (CRP), erythrocytes sedimentation rate (ESR), HLA-B27 typing were normal. Complement studies of C3 and C4 were normal, but CH50 was <17 mg/dl (normal 31-66 mg/dl). The Alternate Complement 50% Activity (AH50) was not examined. The patient was treated with naproxen 500 mg twice daily for arthritis.

The patient was referred to Immunology for further evaluation. In our Immunology clinic we found that the patient had a history of recurrent bronchitis, rhinosinusitis, otitis media, and conjunctivitis. Notably, there was no history of Neisseria infections. Initial complement studies revealed normal C3 and C4 levels, but absent CH50 <17 mg/dl (normal 31-66) and absent AH50 0 mg/

dl (normal 77-157) (Table 1). Absent CH50 and AH50 indicated that a complement deficiency was in the terminal complement pathway. Therefore, individual complement components were examined which revealed an isolated C6 deficiency, <18 mg/dl (normal 28-69) (National Jewish Health Advanced Diagnostic Laboratory) (Table 1). Genetic analysis revealed two compound heterozygous mutations of C6: The first mutation (c.1879del, p.Asp627Thrfs*4) causes a premature translational stop signal. The c.1879del mutation was previously described in literature as c.1936delG mutation causing absent to decreased C6 protein (Figure 1). The second variation (c.828dup, p.Ser277Glufs*15) causes a frameshift mutation resulting in a reduplication of a single nucleotide which leads to a premature translational stop signal (Figure 1). Family genetic studies of the mother and 3 half-siblings revealed that the mother and oldest half-sister were carriers of the C6 c.828dup, p.Ser277Glufs*15 mutation. The biologic father was unavailable for testing. Streptococcus pneumoniae antibody titers were protective to 43% of S. pneumoniae serotypes and Neisseria meningitidis antibody titers were protective to 2 of 4 serotypes following Meningococcal Conjugate Vaccine (MCV4).

Table 1: Complement studies in a patient with C6 Deficiency.

Study	Patient	**Normal**
C1q, mg/dl	122	11.8 – 24.4
C2, mg/dl	2.3	1.2 – 4.0
C3, mg/dl	11.1	85 – 193
C4, mg/dl	33	12 – 36
C5, mg/dl	46	55 – 113
C6, mg/dl	**<18**	28 – 69
C7, mg/dl	92	35.3 – 95.5
C8, mg/dl	52	49 – 106
C9, mg/dl	52	33– 95
CH50, mg/dl	**<17**	31 –66
AH50, mg/dl	**0**	77-157

Complement C1-9 levels performed by National Jewish Health Advanced Diagnostic Laboratory

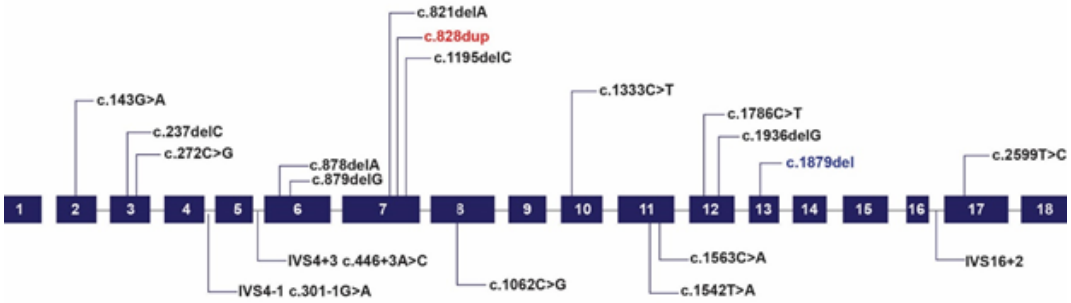

Figure 1. Map of all known C6 mutations including our patient's previously reported mutation, c.1879del (highlighted in blue) and a novel mutation, c.828dup (highlighted in red).

4. Discussion

Complement C6 is one of five protein components that together comprise the terminal complement pathway that forms the membrane attack complex (MAC), including C5b, C6, C7, C8, and C9 [4,5]. Formation of this lytic complex on lipid membranes causes cell death [4,5]. Classic C6 deficiency is associated with a markedly low or absent CH50 and AH50. C6 deficiency is the most common terminal complement component deficiency [1,2] and is inherited as an autosomal recessive trait. The gene encoding for C6 is found on Chromosome 5, 5p13.1 and spans about 80kb of DNA and contains 18 exons [4]. C6 deficiency is found more commonly in African Americans from the Southeastern region of the US with an estimated prevalence of 1:1600 (0.062%) [2] and in individuals with North Central African descent [3]. Our patient inherited two pathogenic variants, including c.1879del, p.Asp-627Thrfs*4, which has been previously described as 1936delG [1] causing a frameshift mutation, altering the protein's amino acid sequence beginning at position 627, leading to a premature termination of codon 4 amino acids downstream. The patient's variant, c.828dup, p.Ser277Glufs*15, creates a premature translational stop signal. Both of these frameshift mutations are predicted to lead to a truncated or absent protein.

Patients with C6 deficiency are susceptible to infections and development of autoimmune diseases, as seen in our patient. El Sissy

et al [1] reported that 33 of 50 (73%) of patients with C6 deficiency had recurrent infections with N. meningitidis infection. None of the patients had infection with Streptococcus pneumoniae. In addition, 10 of 50 patients (20%) had autoimmune disease. Zhu et al [3] reported that autoimmune disease may be particularly severe in early childhood. Two distinct types of complement 6 deficiency have been identified: a complete C6 deficiency where C6 levels are undetectable as seen in our patient and a subtotal C6 deficiency (C6SD) where C6 levels are decreased but not absent [6,7]. Complement C6 is encoded by a single-copy gene on chromosome 5p13, with close proximity to C7 which leads to an association between C6SD and C7 deficiency [4]. C6SD is typically associated with normal CH50 levels without increased risk of Neisseria infections.

Patients with C6 deficiency should be counseled on the increased risk of disseminated N. meningitidis infection. Initial management should include vaccination against meningococcus which will help confer adaptive immunity. “Hypervaccination” with the quadrivalent meningococcal conjugate vaccine (MCV4) has been a treatment option by some providers, although no prospective randomized control studies have been run to evaluate its efficacy [4]. Providers may also consider prophylactic antibiotics in patients with poor response to meningococcus vaccine as seen in our patient; however, this has also not been fully studied [4,5]. Our patient was counseled on the increased risk of Neisseria infections and was vaccinated against N. meningitidis, although she showed a poor response to two of the four subtypes. All quadrivalent conjugate and serogroup B meningococcal vaccines have a caution that patients at high-risk have an increased risk of N. meningitidis, even if they develop an antibody response after vaccination. Therefore, our patient will undergo yearly screenings for vaccine responses. Genetic counseling should be performed in families that are affected because complement deficiencies are heritable autosomal recessive traits.

References

1. El Sissy C, Rosain J, Vieira-Martins P, Bordereau P, Gruber A, Devriese M, et al. Clinical and genetic spectrum of a large cohort with total and sub-total complement deficiencies. Front Immunol. 2019; 10: 1936.
2. Zhu Z, Atkinson TP, Hovanky KT, Boppana SB, Dai YL, Densen P, et al. High prevalence of complement component C6 deficiency among African-Americans in the south-eastern USA. Clin Exp Immunol. 2000; 119(2): 305-10.
3. Zhu ZB, Totemchokchyakarn K, Atkinson TP, Volanakis JE. Molecular defects leading to human complement component C6 deficiency in an African-American family. Clin Exp Immunol. 1998; 111(1): 91-6.
4. Dragon-Durey MA, Fremeaux-Bacchi V, Blouin J, Barraud D, Fridman WH, Kazatchkine MD. Restricted genetic defects underlie human complement C6 deficiency. Clin Exp Immunol. 2003; 132(1): 87-91.
5. Rauscher CK, Fajt ML, Bryk J, Petrov AA. Clinical implications of C6 complement component deficiency. Allergy Asthma Proc. 2020; 41(5): 386-388.
6. Zhang A, Liu Y, Jin J, Wang C, Fan L, Xu D, et al. Identification of a novel mutation in the C6 gene of a Han Chinese C6SD child with meningococcal disease. Exp Ther Med. 2021; 21(5): 510.
7. Hobart MJ, Fernie BA, Fijen KA, Orren A. The molecular basis of C6 deficiency in the western Cape, South Africa. Hum Genet. 1998; 103(4): 506-12.