Inherited Classical and Alternative Pathway Complement Deficiencies in Children: A Single Center Experience

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ABSTRACT

Background: Primary complement deficiencies are rare diseases. **Objective:** To retrospectively evaluate the clinical and laboratory findings and complications of patients to increase awareness of pediatricians about complement deficiencies, which are rarely encountered. **Methods:** In this study, the clinical and immunological characteristics of 21 patients who consulted the Immunology Department of our hospital between 2003 and 2017 and were diagnosed with classical or alternative pathway complement deficiency were obtained from the file records. **Results:** Ten patients with C1 inhibitor deficiency, four patients with factor I deficiency, three patients with properdin deficiency, two patients with C8 deficiency, one patient with C1q deficiency, and one patient with C4B deficiency were assessed. The mean age of the patients at diagnosis was 11.4±4.7 years, the age of onset of symptoms was 7.9±3.9 years, and the follow-up period was 6.7±3.9 years. Fourteen cases had a similar medical history in the family. All patients with C1q, factor I, properdin, C8, and C4B deficiencies presented with an infection, and vasculitic rash was present in two patients with factor I deficiency. In addition, immune complex glomerulonephritis was present in one patient with factor I deficiency. Meningococcal, Haemophilus influenzae type B, and pneumococcal vaccines were administered and prophylactic antibiotic treatment was initiated in all patients except patients with C1 inhibitor deficiency. **Conclusions:** Early diagnosis of complement deficiencies can facilitate prevention of life-threatening complications such as severe bacterial infections by considering prophylactic antibiotics and vaccines. In patients with C1 inhibitor deficiency, achieving an acurate early diagnosis will assist in the management and timely treatment of life-threatening attacks such as upper airway obstruction and improve outcomes.

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INTRODUCTION

The complement system is an important part of innate immunity. However, it is also necessary for adaptive immune system function. It consists of more than 40 proteins, of which soluble proteins are produced in the liver (1-5). While genetic deficiency of any component (C1q, C1r/s, C2, or C4) of the classical pathway is frequently associated with autoimmune diseases and proneness for bacterial infections, an increased susceptibility to meningococcal disease is observed in individuals with terminal component (C5–C9) or alternative pathway deficiencies, particularly properdin deficiency. C1 inhibitor deficiency (hereditary angioedema [HAE]) is characterised by episodic angioedema, and rarely, autoimmunity may be observed (5,6). Mutations affecting factor H, factor I, CD46, C3, and factor B, which lead to severe dysregulation of the alternative pathway, are associated with renal disorders such as atypical hemolytic uremic syndrome (aHUS) and less frequently, membranoproliferative glomerulonephritis (MPGN). Age-related macular degeneration can also result from disorders related to the complement system (4,7,8).

Acquired deficiencies are more common and can result from the inadequate production of complement components (e.g., severe liver dysfunction), increased consumption of complement (autoimmune disorders, diseases associated with immune complex formation), autoantibodies against C1q or C1 inhibitors, or increased excretion of complement components (e.g., protein-losing nephropathies) (9,10).

The aim of this study was to evaluate the clinical and immunological features of 21 patients from 14 families with classical and alternative pathway complement deficiencies (10 patients with C1 inhibitor deficiency, four patients with factor I deficiency, three patients with properdin deficiency, two patients with C8 deficiency, one patient with C1q deficiency, and one patient with C4B deficiency) and to increase awareness of paediatricians to complement system deficiencies, which are rarely encountered (11-16).

MATERIALS AND METHODS

Study populations. In this study, the clinical and immunological characteristics of 21 patients who consulted the Immunology Department of Dr. Behcet Uz Children's Hospital between 2003 and 2017 and were diagnosed with complement deficiency were obtained from the file records. Patients diagnosed with complement deficiency due to an autoimmune disease or who developed complement deficiency due to severe liver dysfunction or protein-losing nephropathies were excluded from the study. The ethics committee approval (2016/91) was received for the study.

Clinical findings were recorded retrospectively for each patient using standardised forms. Age, gender, age at presentation, first complaint leading to the complement deficiency diagnosis, physical examination findings, age at diagnosis, genetic diagnosis, comorbidities, vaccine records, treatments administered, consanguinity, and family history were recorded.Complement deficiency was identified as a low concentration of at least one component of the complement system without concomitant complement consumption. Mannose-binding lectin (MBL) deficiency cases were excluded from the study.The localisation and frequency of the attacks, family history, C1 inhibitor level,

C1 inhibitor function, C4 level, genetic examination results, and treatments administered were obtained from the medical records of patients with HAE diagnosis.

Complement assays. C3 and C4 were measured by nephelometry. Complement function of the classical and alternative pathways were analysed by hemolysis-in-gel technique (3). Other complement components (properdin, factor B, H, I, C5, C6, C7, and C8) were measured by electroimmunoassay. Properdin and C1q were measured by ELISA. C9 was analysed by gel diffusion (Ouchterlony technique). Genetic analysis of C1q was performed by exon-specific amplification of genomic DNA by PCR followed by direct sequence analysis. C4 isotype deficiency was analysed by pyrosequencing. Complement measurements and genetic tests were studied at Clinical Immunology and Transfusion Medicine, University and Regional Laboratories Skåne, Lund, Sweden.

Statistical analysis. Numerical data were recorded as mean ± standard deviation. The statistical comparisons of the data were made using Pearson's, Spearman's, chi-square, and correlation analyses, and Mann–Whitney U and independent sample t-tests in the SPSS 18 program. p-values below 0.05 were considered to be statistically significant.

RESULTS

In total, 21 patients from 14 families (10 patients with C1 inhibitor deficiency, four patients with factor I deficiency, three patients with properdin deficiency, two patients with C8 deficiency, one patient with C1q deficiency, and one patient with C4B deficiency) were assessed (Figure 1). The number of registered patients with immune deficiencies being followed in our clinic was 1744. Inherited classical and alternative pathway complement deficiencies accounted for 1.14% of these patients. The mean age of patients with primary complement deficiency was 19.7 ± 8.7 years, age at diagnosis was 11.4 ± 4.7 years, age at onset of symptoms was 7.9 ± 3.9 years, and the follow-up period was 6.7 ± 3.9 years. Fourteen patients (66.6%) had a similar medical history in the family. The consanguinity rate was found to be 23.8% (n=5). All patients with C1q, factor I, properdin, C8, and C4B deficiencies presented with an infection. Following evaluation of the factors detected in infections, meningococcal growth was observed in the cerebrospinal fluid of the female patient diagnosed with C8 deficiency and in the cerebrospinal fluid and blood of the male patient diagnosed with properdin deficiency. Pneumococcal growth was observed in the cerebrospinal fluid of the female patient diagnosed with C1q deficiency. All three cases presented with meningitis. Vasculitic rash was also present in two patients with factor I deficiency. Immune complex glomerulonephritis was present in one patient with factor I deficiency at nine years of age. A renal biopsy revealed immune complex glomerulonephritis with glomerular deposits of immunoglobulin and C3, but normal renal function and microscopic hematuria. One patient with C8 deficiency, two patients with factor I deficiency, and two patients with properdin deficiency were diagnosed by family screening performed due to the index case detected.

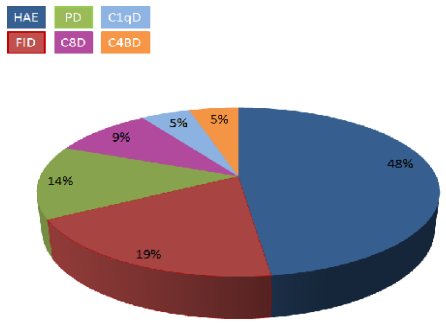

Figure 1. Distribution of specific primary classical and alternative pathway complement immunodeficiencies. HAE: hereditary angioedema, FID: factor I deficiency, PD: properdin deficiency, C8D: C8 deficiency, C1qD: C1q deficiency, C4BD: C4B deficiency was observed.

All of the patients diagnosed with HAE diagnosis presented with angioedema. Abdominal attacks were present in three of the patients at presentation. Laryngeal attacks were not identified in any patient before diagnosis. In the follow-up period, cases had 3–5 attacks per year. Peripheral attacks were mild and laryngeal attacks were observed in three patients during follow-up. The R202Q homozygous mutation was present in the MEFV gene in one patient, who was receiving colchicine treatment. Meningococcal, HIB, and pneumococcal vaccines were administered to and prophylactic antibiotic treatment was initiated in all patients except patients with C1inhibitor deficiency. During the follow-up period, no autoimmunity except for the development of vasculitis in two cases with factor I deficiency (Tables 1 and 2).

Table 1. Demographic and clinical findings of the patients.

	Classical-Alternative pathway defect	**C1 inhibitor deficiency(HAE)**
Number	11	10
%(n) Female	72.7 (8)	50 (5)
%(n) Male	27.3 (3)	50 (5)
%(n) Consanguinity	45.4 (5)	0.0
%(n) Family history	54.5 (6)	80 (8)
%(n) Prediagnostic infection	100 (11)	0.0
%(n) Meningococcemia	45.4 (5)	0.0
%(n) Pneumococcal disease	18.1(2)	0.0
%(n) Postdiagnostic infection	0.0	0.0
%(n) Autoimmunity	18.1 (2)	0.0
%(n) Meningoccocal vaccine	100 (11)	0.0
%(n) Pneumococcal vaccine	100 (11)	0.0
%(n) Prophylactic antibiotic	100 (11)	0.0

Table 2. Clinical data of the patients

Deficiency	The number of patients-	CH50/AP50	Complement level	Age at diagnosis-Age of onset (year)	Genetic Mutation	Associated Symptom	Treatment	Prognosis	Reference
C1q Deficiency	1- Female	Low/ N	C1q <6%	1st case:11-8	Missense novel homozygous mutation in C1q gene codon 48	Recurrent pneumococcal meningitis/pneumonia	Meningococcal, HIB, and pneumococcal vaccines and penicillin prophylaxis	No infection No autoimmunity	**13**
C8 Deficiency	2- Female	Low/ N	1st case:.C8<6% 2nd case: C8<6%	1st case:7-5 2nd case:4-(NS)		Recurrent meningococcal infection	Tetravalent meningococcal vaccine, penicillin prophylaxis	No infection No autoimmunity	
C4B Deficiency	1- Female	Low/ N	C4:0.05 g/L	1st case:2-0,5		Recurrent respiratory tract infections	Meningococcal and pneumococcal vaccines and penicillin prophylaxis	No infection No autoimmunity	
Factor I Deficiency	4- Female (**Family 1**: 1st , 2nd and 3rd case. **Family 2**: 4th case)	N/Low	1st case: factorI <2% 2nd case: factor I < 2 % 3rd case: factor I < 2 % 4th case:factor I < 2 %	1st case:11-4 2nd case:16- 3rd case:17- 4th case: 18-10	Cysteine to tyrosine in Exon 5 c.764G>A,C237Y Adenin to timidine in exon 6;c.866A>T, pD289V	1st case; Meningitis, recurrent respiratory tract infection, vasculitic rash, immune complex glomerulopathy 2nd and 3rd case; recurrent respiratory tract infection 4th case; recurrent infection,vasculitic rash, arthralgia	Tetravalent meningococcal vaccine, penicillin prophylaxis	No infection Vasculitis in the 1st and 4th case	**12** (Publication of the first patient) **14** (Publication of the 4th patient)
Properdin deficiency	3- Male	N/Low	1st case: properdin<0.01 mg/l 2nd case:properdin<0.01 mg/l 3rd case:properdin<0.01 mg/l	1st case:5-4 2nd case:13-7 3rd case:21(NS)		Meningococcal infection	Tetravalent meningococcal vaccine, penicillin prophylaxis	No infection No autoimmunity	**11**

N: normal--**NS:** No Symptom -----**C1q reference range:** 78%-131%----**Properdin normal concentration**: 12,5-36,4 mg/l---**C4 Reference range**: 0.12-0.33 g/L--**Factor I reference range**: 60-152%

Case	Gender/ type of HAE	C4 (mg/dl)/ C1 esterase inhibitor level(g/l)/ function(%)	Age at diagnosis-- Age of onset (year)	Genetic Mutation	Localization of firstattack	Localization of the attacks in the follow-up	Treatment	Additional disease	Reference
ELV. T(Family 1)	Female/ HAE type I	5.58/ 0.08/	10-9	-	Abdominal , Peripheral	Upper airway Abdominal	Tranexamic acid, Stanosolol, C1inhibitör concentrate	Bladder tumor	
ELG .T(Family 1)	Female/ HAE type I	6.82/ 0.05/	5-5	-	Abdominal Peripheral	Abdominal Peripheral	Tranexamic acid, Stanosolol, C1inhibitör concentrate		
K.Ç (Family 2)	Female/ HAE type I	<6.93/0.08/	14-14	-	Peripheral	Peripheral	Tranexamic acid, C1inhibitör concentrate		
O.Ç (Family 2)	Male/ HAE type I	<6.93/ 0.06/	13-13	-	Peripheral	Peripheral	Tranexamic acid, C1inhibitör concentrate		
P.A (Family 3)	Female/ HAE type I	6/0.05/7	15-9	-	Abdominal	Upper airway Peripheral Abdominal	Tranexamic acid, Stanosolol, Ecallantide, C1inhibitör concentrate	FMF(R202Q homozygotemutat iondetermined in the MEFV gene)	**15**
G.D (Family 4)	Female/ HAE type II	6/ 0.63/ <5	13-5	aa 444Arg.substituded by Cis	Peripheral	Peripheral Upperairway	Tranexamic acid C1inhibitör concentrate	Migraine	
0.U (Family 5)	Male/ HAE type I	2.1/ 0.03/	12-5	-	Peripheral	Peripheral	Tranexamic acid C1inhibitör concentrate		
0S.U (Family 5)	Male/ HAE type I	<6.6/0.03/	16-16	-	Peripheral	Peripheral	Tranexamic acid C1inhibitör concentrate		
M.E (Family 6)	Male/ HAE type I	8.07/ 0.11/	7-7	-	Peripheral	Peripheral	Tranexamic acid C1inhibitör concentrate	Asthma	
B.Y.K (Family 7)	Male/ HAE type II	<6,65/0.72/ 27.4	5-4.5	Heterozygous p.R466C(c.1396C>T)	Peripheral	Peripheral	Tranexamic acid C1inhibitör concentrate	MVP, AR,MI	

DISCUSSION

The complement system has traditionally been considered a first-line of innate immune defence against invading pathogens. However, over the past several years, several additional roles for the complement system have been uncovered, including modulation of the adaptive immune response, elimination of immune complexes and apoptotic cells, metabolism, angiogenesis, tissue regeneration, and organogenesis (1). Complement activation on surfaces may be initiated through one or more of three pathways: the classical, lectin, or alternative pathways (9). Complement defects may be primary or secondary. Its inheritance is usually autosomal recessive (properdin deficiency X-linked; C1-INH and membrane cofactor protein [MCP])/CD46 autosomal dominant) (5,10).The partial (heterozygous) mutations of the alternative pathway, such as factor H, factor I, and MCP and gain of function mutations in C3 or factor B, cause renal disorders such as aHUS. On the contrary, the classical complement pathway (C1q, C2, and C4) carriers typically remain well (5).

Primary complement deficiencies involve 1–10% of primary immune deficiencies (PIDs) and account for less than 5% of all PIDs according to European data. Published literature consists largely of case reports and small series(4,5). In this study, we observed that the inherited classical and alternative pathway complement-deficient patients constituted 1.14% of PIDs. Turley et al. (5) reported that a large number of patients with primary complement deficiencies present within the first two decades of their lives, but only 24% of the patients are diagnosed in adulthood. In this study, the age of onset of symptoms was 7.9±3.9 years, and the age at diagnosis was 11.4±4.7 years.

The most common complement deficiency is C2 deficiency (MBL deficiency not included). C2 deficiency constitutes 29% of the 77 reported cases in European countries (4,5). The prevalence of homozygous C2 deficiency in the Western European population has been reported to be 1:10,000–20,000. Heterozygous C2 deficiency has a frequency of 1–2% in Caucasian populations. Approximately 10–30% of homozygous C2-deficient patients develop systemic lupus erythematosus (SLE) (17-19). Partial C4 deficiency is observed at a rate of 1:250, mostly in Caucasians. Complete homozygous deficiency of C4 is rare but is strongly related to SLE (20). The incidence of HAE is estimated to be 1:10,000–1:50,000 (4).Initial evaluation for suspected complement deficiency should include the total serum classic hemolytic complement (CH50) test and the alternative hemolytic complement (AP50) test. The CH50 test specifically tests for deficiencies in the classic pathway and the AP50 test assesses alternative pathway activity. Subsequently, direct measurement of individual serum complement proteins should be performed for diagnosis. C4 is the single best-screening test for the diagnosis of HAE type I and II. C1 inhibitor protein and C1 inhibitor functional activity are the major laboratory tests for the definitive diagnosis of HAE type I and II.

Recurrent bacterial infections such as meningococcal meningitis and pneumococcal infections, autoimmunity findings, angioedema without urticaria, and renal and ophthalmic inflammatory disorders have been associated with complement deficiencies. Recurrent bacterial infections are common in classical pathway deficiencies (21). Approximately 20% of patients with disseminated Neisserial infections are considered to have complement deficiencies (4). Inherited deficiencies of C3, the alternative pathway (factor D, properdin, factor H, and factor I), and terminal complement pathway

components (C5–C9) are all strongly associated with an increased incidence of invasive meningococcal infections (9). In patients with C5–C8 deficiency of late complement components, the risk of meningococcal disease is increased 1000–10,000 times compared with the general population (4,22). Severe invasive infection was reported in 50 (65%) of 77 complement deficient patients reported in Europe;61% of Neisseria meningitis infections occurred in patients with terminal pathway defects while 74% of Streptococcus pneumonia infections occurred in patients with classical pathway defects (5). This reflects the importance of cytolytic complement activity in the defence against Neisseria. Meningitis is observed in 40% of individuals with late complement component deficiency and in 6% of properdin deficiencies (9,23,24). MBL deficiency is also associated with increased risk of invasive meningococcal infections (4). The rarely observed factor D deficiency also predisposes patients to invasive meningococcal disease (9,25). In factor H and I deficiencies, functional complement deficiency, which predisposes to meningococcal disease, occurs due to the uncontrolled activation of the alternative complement pathway and consumption of complement components (9,26). Uncommon serotypes of meningococcal disease (X,Y,Z,W, or 29E) are also more frequently identified in patients with complement deficiency (4,27).The predominant organisms are encapsulated bacteria such as pneumococci, H. influenzae, and streptococci (4,9,28). Recurrent and frequent infections caused by these bacteria can be observed in the sinopulmonary tract, meninges, and blood (9). In the present cohort, all patients except for patients with HAE presented with an infection. C1q-deficient patients presented with recurrent pneumococcal pneumonia and meningitis, and C8- and properdin-deficient patients presented with meningococcal infection (11). Although no pathogens were identified, recurrent infections occurred in the factor I-deficient patient who was diagnosed with meningitis and recurrent respiratory tract infection, and in the other three patients diagnosed with factor I deficiency, as well as in the patient with C4B deficiency (12).

Rheumatologic disorders are another symptom of complement deficiencies. SLE, cutaneous lupus, dermatomyositis, Henoch-Schönlein purpura, MPGN, and vasculitis have been reported (28). While renal, pulmonary, and pericardial involvement is reduced in SLE patients with complement deficiency, photosensitive skin rash is more common, and the age of onset is earlier (28). While inflammatory/autoimmune diseases were not observed in any of the patients with terminal pathway deficiencies among the 77 complement-deficient patients reported in European countries, inflammatory/autoimmune diseases were present in one-third of patients with classical and alternative pathway deficiencies (5). The autoimmune diseases associated with classical component deficiencies are variable. It has been reported that while severe autoimmunity develops in 95% of C1q-deficient patients, less than 40% of complete C2 deficient-patients develop autoimmunity (4). Genetic deficiency of early components of the classical pathway results in impaired humoral response and inadequacy in clearing apoptotic material and immune complexes and increases the tendency to autoimmunity (29). Complement over-activation, the presence of C1q antibodies and immune complexes that activate complement in the circulation and kidney glomerulus also lead to the same disease, although with different mechanisms. Therefore, it has been reported that both the absence of activation and increased activation of the classical pathway may be associated with autoimmunity (2,30). While recurrent meningitis and respiratory tract infections were identified in our patients with C1q and C4B deficiency, no autoimmunity development was detected at diagnosis or during the follow-up period in

patients with classical pathway deficiencies (13). Cutaneous vasculitis was observed in two of our patients with factor I deficiency, which leads to an alternative pathway deficiency, at diagnosis and during follow-up. There had been a histologically diagnosed immune complex glomerulonephritis history in one of these patients when she was nine years old. We did not observe any autoimmunity development in the remaining patients during the follow-up period (12).

Immunisation against Neisseria meningitis is strongly recommended in patients with meningococcal disease and complement deficiency (22,31-33). The Advisory Committee on Immunization Practices (ACIP) recommends the tetravalent conjugate capsular polysaccharide vaccine for all individuals with complement deficiency due to the increased risk of meningococcal disease, followed by a booster dose every 3–5 years. While most terminal complement-deficient persons elicit primary antibody responses comparable to normal individuals, antibody responses in other high-risk groups such as persons with anatomic or functional asplenia or advanced HIV infection may be impaired, which has prompted recommending the two-dose primary vaccination regimen for high-risk groups (22). Streptococcus may cause benign diseases such as otitis media, as well as severe life-threatening diseases such as pneumonia, arthritis, peritonitis, septicemia, and meningitis. Especially in children older than two years of age, immune deficiency is detected in ratios up to 26% in invasive pneumococcal disease. Complement deficiencies constitute one group of these immune deficiencies (34). Pneumococci are the predominant cause of infections.

It is important to administer pneumococcal vaccine, especially in classical complement pathway defects (5). Individuals with early complement component deficiency are also at risk of invasive infections such as meningitis, epiglottitis, pneumonia, septic arthritis, cellulitis, pericarditis, and bacteremia due to H. influenzae, and 4% of infections may result in death. The ACIP recommends vaccination for this patient group with increased risk of invasive HIB infection (35). Our patient, who was diagnosed with C1q deficiency, presented with recurrent pneumococcal meningitis and pneumonia (13). Meningococcal infection was the primary complaint at consultation in our patients diagnosed with C8 and properdin deficiencies, and infection was the primary symptom in our other complement-deficient patients, with the exception of HAE patients. Since the HIB and conjugate pneumococcal vaccines are routinely administered in our country, our patients have been vaccinated with the polysaccharide pneumococcal and tetravalent meningococcal vaccines, which are not presently part of our routine vaccination schedule.

Angioedema without urticaria accounts for 2% of all cases of urticaria and/or angioedema. It may occur due to histaminergic and non-histaminergic accumulation of bradykinin (36). HAE does not predispose to infection and is rarely associated with autoimmune disease (5). HAE is characterised by acute and paroxysmal edema in the hands, arms, legs, gastrointestinal tract (colic), lips, and eyelids. If the edema is localised in the larynx, it can be life threatening. Findings such as intestinal obstruction, urinary retention, and headache can also accompany the edema. Stress, trauma, infections, and hormonal changes (menses, pregnancy, contraceptives, and hormonal reposition) can trigger an attack. Prodromal symptoms such as serpiginous erythema, irritability, and anxiety can be observed before the attack. Attacks can last for 3–7 days, and if left untreated, can lead to asphyxia in 25–40% of patients (37). Acquired angioedema develops as a result of hypercatabolism of C1 inhibitor or blocking of autoantibodies (38). HAE may result from low synthesis (HAE type I, the most

common form), or from synthesis of a dysfunctional C1 inhibitor (HAE type II). In HAE type II, the plasma levels of C1 inhibitor are normal, but its function is decreased (37). Type III HAE was named angioedema related to estrogen or estrogen-dependent when it was first described. Although the mediator that likely causes the formation of this form is unknown, it is thought that a coagulation factor 12 (Hageman factor) mutation, which has been found in patients and in some of their relatives, leads to increased bradykinin production (37). Clinical findings, normal C4, and C1 inhibitor together with family history may be diagnostic criteria in these HAE patients without C1 inhibitor deficiency (39). While eight out of ten HAE patients in our study had HAE type I, two patients had HAE type II. There was an abdominal attack in three patients at presentation. While laryngeal attacks were not observed in any of the patients before diagnosis, such attacks were observed in three cases during follow-up. The R202Q homozygous mutation was present in the MEFV gene in one patient, who was receiving colchicine treatment (15).

Treatment of HAE is fundamentally different from treatment of other types of edema. Since HAE does not respond to antihistamine and corticosteroids, C1 inhibitor replacement is used in the treatment of acute attacks while androgens (danazol and stanozolol,which act by increasing synthesis of the C1 inhibitor) or plasmin inhibitors (e.g., tranexamic acid) are used in prophylaxis. C1 inhibitor substitution can also be used prophylactically. New drugs with specific activity in the kinin-kallikrein system such as the selective inhibitor of plasma kallikrein (ecallantide) or bradykinin B2 receptor (B2R) antagonist (icatibant) can also be used in the treatment of acute attacks (37). Our patients were also receiving standard treatments, and no autoimmunity was observed during the follow-up period (Table 3).

Renal disorders due to complement dysregulation are also observed, such as HUS (40). Within the last decade, it has been revealed that dysregulation of the alternative pathway is the main cause of aHUS. C3 glomerulopathy including dense deposit disease is another renal disorder associated with complement dysregulation. C3 glomerulopathy is a rare chronic renal disease frequently characterised by mesangial cell proliferation, particularly at the glomerular basal membrane and mesangium, and extensive C3 deposits in the glomerulus. Turley et al. (5) reported recurrent Henoch–Schönlein purpura (typical rash and arthritis) in two Spanish siblings with heterozygous factor I deficiency. This complication is rarely reported in the literature. They drew attention to the fact that clinicians should be on the alert due to this potential association. Among our patients, those diagnosed with factor I deficiency presented with Henoch–Schönlein purpura-like vasculitic rash and symptoms of infection. A history of immune complex glomerulonephritis was present in one patient.

The complement system plays an essential role in the innate immune response, modulation of the adaptive immune response, elimination of apoptotic cells, metabolism, angiogenesis, tissue regeneration, and organogenesis. Both complement deficiencies and over-activation are associated with severe and life-threatening diseases. Therefore, the early recognition and diagnosis of complement deficiencies can facilitate the prevention of life-threatening severe bacterial infections such as meningitis by enabling adequate clinical recommendations such as prophylactic antibiotics and vaccines. In patients with C1 inhibitor deficiency, achieving the correct diagnosis early will assist in management and timely treatment of life-threatening attacks, such as upper airway obstruction, and improve outcomes. For early diagnosis of complement system deficiencies, widespread screening of CH50, AP50, and C4 is critical.

REFERENCES

1. Ricklin D, Hajishengallis G, Yang K, Lambris JD. Complement: a key system for immune surveillance and homeostasis. Nat Immunol. 2010; 11:785–97.
2. Merle NS, Noe R, Halbwachs-Mecarelli L, Fremeaux-Bacchi V, Roumenina LT. Complement System Part II: Role in Immunity. Front Immunol. 2015; 6: 257.
3. Truedsson L. Classical pathway deficiencies - A short analytical review. Mol Immunol. 2015; 68:14–9.
4. Grumach AS, Kirschfink M. Are complement deficiencies really rare? Overview on prevalence, clinical importance and modern diagnostic approach. Mol Immunol. 2014; 61:110–7.
5. Turley AJ, Gathmann B, Bangs C, Bradbury M, Seneviratne S, Gonzalez-Granado LI, et al. Spectrum and management of complement immunodeficiencies (excluding hereditary angioedema) across Europe. J Clin Immunol. 2015; 35:199–205.
6. Triggianese P, Chimenti MS, Toubi E,Ballanti E, Guarino MD, Perricone C, et al. The autoimmune side of hereditary angioedema: insights on the pathogenesis. Autoimmun Rev. 2015; 14:665–9.
7. Joseph C, Gattineni J. Complement disorders and hemolytic uremic syndrome. Curr Opin Pediatr. 2013; 25:209–15.
8. Toomey CB, Kelly U, Saban DR, Bowes Rickman C. Regulation of age-related macular degeneration-like pathology by complement factor H. Proc Natl Acad Sci. 2015: 9;112:E3040-9.
9. Lewis LA, Ram S. Meningococcal disease and the complement system. Virulence. 2014; 5:98–126.
10. Botto M, Kirschfink M, Macor P, Pickering MC, Würzner R, Tedesco F. Complement in human diseases: Lessons from complement deficiencies. Mol Immunol. 20094; 6:2774–83.
11. Genel F, Atlihan F, Gulez N, Sjöholm AG, Skattum L, Truedsson L. Properdin deficiency in a boy with fulminant meningococcal septic shock. Acta Paediatr. 2006; 95:1498–1500.
12. Genel F, Sjöholm AG, Skattum L, Truedsson L. Complement factor I deficiency associated with recurrent infections, vasculitis and immune complex glomerulonephritis. Scand J Infect Dis. 2005; 37:615–618.
13. Gulez N, Genel F, Atlihan F, Sjöholm AG, Skattum L, Truedsson L. Homozygosity for a novel mutation in the C1q C chain gene in a Turkish family with hereditary C1q deficiency. J Investig Allergol Clin Immunol. 2010; 20:255–8.
14. Nita IM, Genel F, Nilsson SC, Smart J, Truedsson L, Choo S, et al. Molecular characterization of two novel cases of complete complement inhibitor Factor I deficiency. Mol Immunol. 2011; 48: 1068–72.
15. Erdem Bahceci S, Genel F, Gulez N, Nacaroglu HT. Nacaroglu. Coexistence of hereditary angioedema in a case of familial Mediterranean fever with partial response to colchicine. Centr Eur J Immunol. 2015; 40: 115–116.
16. Nilsson SC, Trouw LA, Renault N, Miteva MA, Genel F, Zelazko M, et al. Genetic, molecular and functional analyses of complement factor I deficiency.Eur J Immunol. 2009; 39: 310–323.
17. Atkinson JP. Complement deficiency: predisposing factor to autoimmune syndromes. Clin. Exp. Rheumatol. 1989; 7:95–101.
18. Johnson CA, Densen P, Wetsel RA, Cole FS, Goeken NE, Colten HR. Molecular heterogeneity of C2 deficiency. N. Engl. J. Med.1992; 326:871–4.
19. Jönsson G, Truedsson L, Sturfelt G, Oxelius VA, Braconier JH, Sjöholm AG. Hereditary C2 deficiency in Sweden: frequent occurrence of invasive infection,atherosclerosis, and rheumatic disease. Medicine (Baltimore). 2005; 84:23–34.
20. Macedo AC, Isaac L. Systemic Lupus Erythematosus and Deficiencies of Early Components of the Complement Classical Pathway. Front Immunol. 2016;24;7:55.
21. Skattum L, van Deuren M, van der Poll T, Truedsson L. Complement deficiency states and associated infections. Mol Immunol. 2011; 48:1643–55.

22. Cohn AC, Mac Neil JR, Clark TA, Ortega-Sanchez IR, Briere EZ, Meissner HC, et al. Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep.2013; 62:1–28.
23. Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. Medicine (Baltimore). 1984; 63: 243–73.
24. Sjöholm AG, Söderström C, Nilsson LA. A second variant of properdin deficiency: the detection of properdin at low concentrations in affected males. Complement.1988; 5:130–40.
25. SprongT, Roos D, Weemaes C, Neeleman C, Geesing CL, Mollnes TE, van Deuren M. Deficient alternative complement pathway activation due to factor D deficiency by 2 novel mutations in the complement factor D gene in a family with meningococcal infections. Blood. 2006; 107:4865–70.
26. Bay JT, Katzenstein TL, Kofoed K, Patel D, Skjoedt MO, Garred P, Schejbel L. Novel CFI mutation in a patient with leukocytoclastic vasculitis may redefine the clinical spectrum of Complement Factor I deficiency. Clin Immunol. 2015; 160:315–8.
27. Rosain J, Hong E, Fieschi C, Martins PV, El Sissy C, Deghmane AE, et al. Strains Responsible for Invasive Meningococcal Disease in Patients With Terminal Complement Pathway Deficiencies. J Infect Dis. 2017; 215:1331–1338.
28. Pettigrew HD, Teuber SS, Gershwin ME. Clinical significance of complement deficiencies. Ann N Y Acad Sci. 2009; 1173:108–23.
29. Elkon KB, Silverman GJ. Naturally occurring autoantibodies to apoptotic cells. Adv Exp Med Biol. 2012; 750:14–26.
30. van Schaarenburg RA, Magro-Checa C, Bakker JA, Teng YK, Bajema IM, Huizinga TW, et al. C1q Deficiency and Neuropsychiatric Systemic Lupus Erythematosus. Front Immunol. 2016; 7: 647.
31. Overturf GD.Indications for the immunological evaluation of patients with meningitis. Clin Infect Dis. 2003;36:189–94.
32. Keiser PB, Broderick M. Meningococcal polysaccharide vaccine failure in a patient with C7 deficiency and a decreased anti-capsular antibody response. Hum Vaccin Immunother. 2012; 8:582–6.
33. Eibl MM, Wolf HM. Vaccination in patients with primary immune deficiency, secondary immune deficiency and autoimmunity with immune regulatory abnormalities. Immunotherapy. 2015;7:1273–92.
34. Gaschignard J, Levy C, Chrabieh M, Boisson B, Bost-Bru C, Dauger S, et al. Invasive pneumococcal disease in children can reveal a primary immunodeficiency. Clin Infect Dis. 2014; 59:244–51.
35. Briere EC, Rubin L, Moro PL, Cohn A, Clark T, Messonnier N. Prevention and Control of Haemophilus influenzae Type b Disease Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2014; 63:1–14.
36. Walford HH, Zuraw BL. Current update on cellular and molecular mechanisms of hereditary angioedema. Ann Allergy Asthma Immunol. 2014; 112:413–8.
37. Cicardi M, Aberer W, Banerji A, Bas M, Bernstein J.A, Bork K, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema. International Working Group. Allergy 2014;69: 602–616.
38. Cicardi M, Zanichelli A. Acquired angioedema. Allergy Asthma Clin Immunol. 2010; 28: 6:14.
39. Zuraw BL, Bork K, Binkley KE, Banerji A, Christiansen SC, Castaldo A, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. Allergy Asthma Proc. 2012; 33:145–56.
40. Joseph C, Gattineni J. Complement disorders and hemolytic uremic syndrome. Curr Opin Pediatr. 2013; 25:209–15.