TWO RELATED CASES OF PRIMARY COMPLEMENT DEFICIENCY

A. Farhoudi, Nasrin Bazargan, Zahra Pourpak, and Maryam Mahmoudi

Department of Allergy and Clinical Immunology, Children's Hospital Medical Center, Tehran University of Medical Science, Tehran, I.R.. Iran.

ABSTRACT

Primary complement deficiencies are rare and two related patients are reported here. The first patient is a 41- year- old man with eighteen episodes of pneumococcal meningitis and other purulent infections. The serum C3 level was checked at three separate times, showing that this was a primary C3 deficient case; other immunological tests were however normal. This patient now takes prophylactic antibiotics and the meningitis has not recurred, but he does have glomerulonephritis. The second case is a 40 - year-old woman with repeated episodes of orofacial and laryngeal edema and dyspnea. The serum C1INH levels were 4.3 to 7 mg/dL which were very low compared with normal healthy subjects (C_1INH was 40-50 mg/dL in ten normal controls) and C_4 was lower than normal but other immunological tests were normal. Other causes of angioedema such as lymphoproliferative disorders were excluded. She had hereditary angioedema without a family background. The condition may be due to genetic mutation. The angioedema was controlled with Danazol and Stanasol. As our patients are related, this may suggest a genetic relationship between these two disorders.

Keywords: Primary C3 deficiency, Hereditary angioedema, C1 esterase inhibitor, Stanazol.

INTRODUCTION

The complement system is an important part of innate immunity that collaborates with acquired immunity to kill pathogens and to facilitate the clearance of immune complexes. This system plays an important role in the host defense against infections and inflammations.[1] Complement is made up of 20 distinct plasma proteins and different membrane regulatory proteins.[2,3] The complement cascade can be activated via the classical or the alternate pathways. The major components of the classical pathway are C_1, C_4, C_2, and C_3. Factors B and D are components of the alternate pathway. Properdin is an enhancing control protein and C1 inhibitor (C^1 INH), factor H, factor I, C_4 binding protein, S protein and anaphylatoxin inactivator are suppressing proteins. The membrane attack complex consists of C_5, C_6, C_7, C_8 and C_9. The third component of complement (C_3) is the most important factor in the complement system because it participates in both the classical and alternate pathways of complement activation as well as in the amplification loop.[1] C_3 is the most widely investigated component in immune regulation.[4] Congenital deficiencies of some classical and membrane attack proteins and factor D of the alternate pathway have been described.[3,5] Immune complex diseases have been described among patients with congenital deficiencies of single complement components.[1] Classical pathway component deficiencies C_1, C_4 and C_2 commonly cause pyogenic infections and immune complex diseases, as does deficiency of C3. Deficiencies of factors

*: Corresponding Author: Z.Pourpak Ph.D. Immunology, Asthma and Allergy Research Institute; Children Hospital Medical Center; Tehran University of Medical Sciences , Tehran, IR Iran, Tel: 0098 21 6935855, Fax: 0098 21 642 8995, Email: zpourpak@yahoo.com

H and I cause secondary depletion of C3 and thus symptoms similar to those of C_3 deficiency. Properdin deficiency specifically predisposes to Neisseria infection. Terminal component deficiencies also commonly present with Nieseria infection.[6] With a population of 4.45 million people, the total prevalence of primary immunodeficiency disease in Norway (February 1, 1999) is 6.82 per 100,000 inhibitants. Complement deficiencies represented 21% of this prevalence and in complement deficiencies C_1 inhibitor deficiency was 86%, C_2 deficiency 9%, C_4 deficiency 1.25%, C_5 deficiency 2.5% and C_8 deficiency 1.25%.[7] Like most complement components, the third component of complement (C_3) phenotype is inherited in an autosomal codominant pattern.[8] Primary C_3 deficiency is a rare condition.[1] Individuals with C_3 deficiency are presented with recurrent infections caused by a wide range of bacteria and other pathogens, with encapsulated bacteria being especially prominent.[9] Without C_3, the chemotactic fragment from C_5(C_5a) is not generated, and opsonization of bacteria is inefficient. Genetic deficiency of C_3 has been associated with recurrent and severe pyogenic infections due to Pneumococci and Meningococci.[10, 11, 12, 13] Ten to 25% of adults with sporadic meningococcal disease show inherited complement deficiency.[14] Determination of complement activity with use of a screening CH50 assay would be worth while in all sporadic cases of meningococcal disease.[15] Inhibitory factors of the complement system play an important role in control of the system. C_1 inhibitor is a member of the super- familly of serine proteinase inhibitors (Serpins). Its spectrum of inhibitory activity includes the enzymes C_1r, C_1s, Kallikrein and plasmin. Deficiency of C_1 inhibitor is associated with the disease hereditary angioedema (HAE), characterized by recurrent episodes of painless swelling of localized areas of the skin and mucous membranes which may cause fatal obstruction of the upper airways.[6] In the absence of C_1 INH function, activation of C_1 leads to uncontrolled C_1 activity, with the breakdown of C_4 and C_2 release of a vasoactive peptide kinin from C_2. Episodic, localized, nonpitting edema results from the vasodilator effects of the kinin on the post-capillary venule. The mechanism by which C_1 is activated in these patients is not known.[3]

In this study two cases of congenital deficiencies of two components of the complements system are described: one patient with a primary C_3 deficiency and the other with a congenital C_1 esterase inhibitor deficiency.

CASE REPORT

The first case is a 41-year-old man with a history of recurrent bacterial infections. He has been followed up in the Department of Immunology and Allergy of Children's Hospital Medical Center, Tehran university of Mdical Sciences since 1982, and reported in 1988 .[10] He has suffered 18 attacks of pneumococcal meningitis and several episodes of pneumonia and purulent otitis media. The first episode of meningitis occurred

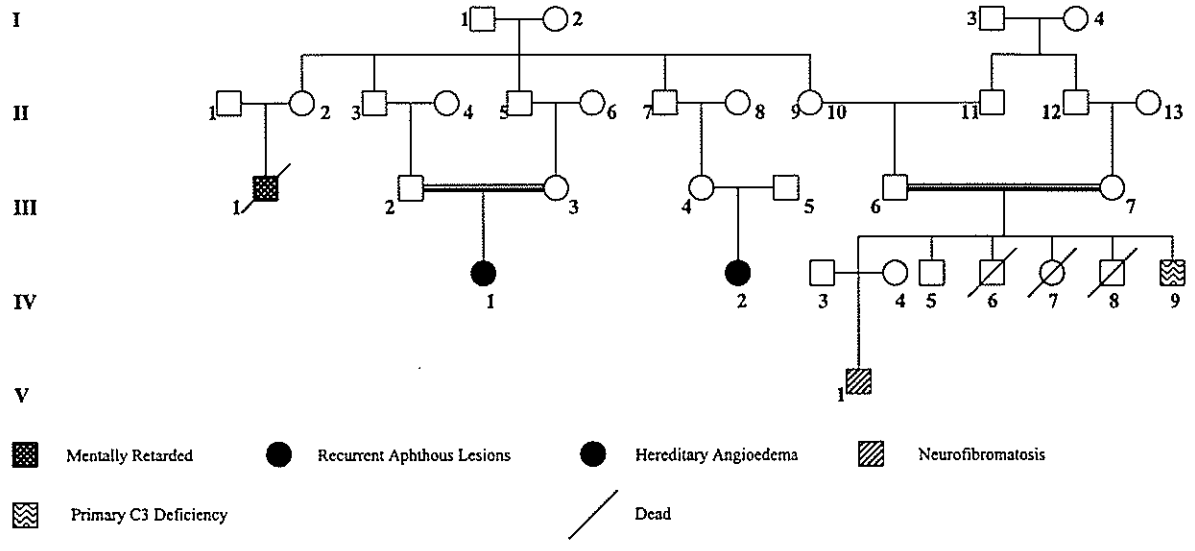

Fig 1. The Family Tree of Two Related Cases. The condition of these two cases is reported according to the family tree: see figure 1. IV2 (patient N1.2) is the hereditary angioedemic patient and IV9 (patient N2.1) is the primary C3 deficient patient. The Family Tree shows some other cases, as follows: The III1 person was a boy and had been mentally retarded and died. The IV1 a woman with severe recurrent aphthous lesions (probably Behcet's disease) and V1 a boy with neurofibromatosis

when he was ten months old (1961). He is the 5th child, of parents who are close relatives. Three siblings of his family are dead. One boy at the age of 5, due to unknown disease, one girl at the age of 2, due to meningitis and the 3rd at his birth. More information about their histories was not forthcoming.

The parents and his two other siblings are alive and healthy. He has suffered from renal failure and glomerulonephritis for the last seven years. He is now taking prophylactic antibiotics and the meningitis has not recurred.

The laboratory data are in tables 1 and 2. The complement components as tested on several occasions showed normal results except for C_3 which was zero and undetectable by the Single Radial Immunodiffusion (SRID) method. C_1, C_4, C_2 and C_5 were normal. Properdin, factors I and H were normal too, which indicated the normal levels of inhibitor factors. The CH_{100} activity was defective (20%). Other immunological investigations were as follows: The phagocytic activity of PMN by the Nitroblue Tetrazolium (NBT) was normal, but the serum opsonization activity of the patient[16] was defective. The patient's lymphocyte count (T and B cell with rosette test) was normal.

The second case is a 40- year - old woman with periods of recurrent, episodic and nonpitting edema of different parts of the body, especially lips, lids, face and larynx and she sometimes suffered from dyspnea. Several kinds of antihistamines and corticosteroids were not efficacious. She was referred to our Unit in 1996. Physical examination was normal at time of arrival. Skin prick tests common with pollens and food allergens were negative and the serum IgE level was in the normal range. Serum complement levels measured by SRID were as follows:

C_3 = 68 mg/dL (normal range 88-177), C_4: 5mg/ dL (15-45), CH100 activity 60% (90- 96%) and C_1 INH rechecked 3 times were found to be (4.3, 4.7 and 7 mg/ dL). The level of C_1INH in ten healthy adult control subjects was between 40-50 mg/dl. Treatment with Danazol and Stanazol controlled the attack and the patient now enjoys good health. Our two patients are relatives as shown in Figure 1.

DISCUSSION

Literature of the Past decade shows that primary C_3 deficiency and recurrent associated infections is rare,[17,18] while secondary C_3 deficiency due to immune complex diseases have been described in several diseases. For example sera from patients with chronic membranoproliferative glomerulonephritis (MPGN) contain a protein termed nephritic factor (NeF) which promotes activation of the alternate pathway. NeF is an IgG antibody against the C_3 cleaving enzyme of the alternate pathway, C_3bBb which protects the enzyme from inactivation. This results in increased consumption of C_3. Serum C_3 concentration varies widely from patient to patient. C_3 deficiency, the major opsonin of the complement system, results in severe, recurrent infections with encapsulated bacteria, begining shortly after birth.[19] Pyogenic infections including meningitis may occur if the serum C_3 level drops to about 10% of normal. This disorder has also been found in children and adults with partial lipodystrophy. Adipocytes can synthesize C_3, factor D and factor B; exposure to NeF induces their lysis.[3]

An IgG nephritic factor that binds to and protects C_4b2a, the classical pathway C_3 convertase, has been described in acute post infection nephritis and systemic lupus erythematosus (SLE). Consumption of C_3 which characterizes poststreptococcal nephritis and SLE could be due to this factor, to activation of complement by immune complexes, or due to both.[3]

The low level of C_3 in these immune complex diseases usually returns to normal with successful treatment, and stays in the normal range during the remission period. Ross and coworkers have published a broad study on this matter.[14] They reported 14 cases of recurrent pneumococcal and neisserial infections combined with collagen vascular disease such as SLE, vasculitis and glomerulonephritis. They did not clarify that whether C_3 deficiency primarily caused both recurrent infections and collagen vascular disease or whether C_3 deficiency was secondary to these disorders. However the serum C_3 level of the first case was checked in reliable centers in France in 1982[10] and later in Iran at separate times; it was zero, combined with a normal C_4 level. While in some immune complex diseases such as SLE in addition to a decreased level of serum C_3 the serum C_4 level is also depressed,[20] but in the first case it was normal. The opsonization in the first case was defective, as shown in Table I. It could not be due to the moderatly low concentration of IgG (minimum 300 mg/dL), because even 50 mg/dL of serum IgG is sufficient for opsonization as mentioned by Soothill.[21] However the only cause of defective opsonization in this case is the absence of C_3.

Regarding recurrent bacterial meningitis, we know that fracture through the paranasal sinuses as a result of head trauma may precede meningitis caused by Streptococcus pneumoniae or Haemophilus influenzae, which may be recurrent.[22] In the first case other factors, which may cause recurrent bacterial meningitis, such as skull fracture, fistula in the cranionasal septum or dermoid cysts of skull skin were ruled out by neurosurgen consultation. Hereditary angioedema was first described by Osler in 1888 who studied five generations of a family. In 1962 Landerman related genetic

Table 1: Levels of Immunoglobulins and Complements of the First Case (Tests were performed 3 times with intervals of at least 3 months)

Test	First time test	Second time test	Third time test	Standard values
Immunoglobulin				
IgG (mg/dl)	313	880	547	994(639-1349)[1]
IgA (mg/dl)	359	290	92	171(70-312)[1]
IgM (mg/dl)	144	160	52	156(56-352)[1]
Complement Component				
CH100(%)	20	_	_	90-96[1]
C3 (mg/dl)	0	0	_	125(88-177)[1]
C4 (mg/dl)	71	71	_	28(15-45)[1]
C1q (mg/L)	131	120	_	118-238 (mg/L)[2]
C2 (mg/L)	_	94 (*%standard*)	_	14-25(mg/L)[2]
C5 (mg/L)	_	90 (*%standard*)	_	90-172(mg/L)[2]
Properdin (mg/L)	_	72 (*%standard*)	_	25(mg/L)[2]
Factor I (mg/L)	_	96 (*%standard*)	_	38-58(mg/L)[2]
Factor H (mg/L)	_	100(*%standard*)	_	345-590(mg/L)[2]
Cc, Cd	_	Not detectable	_	

[1]Normal ranges (Schamber et al., 2000)

[2]Standard values (The Binding Site Ltd, Birmingham, U.K.)

deficiency with an inhibitor of coagulation.[23] This is inheredited as an autousomal dominant disease.

The classification of C_1 INH deficiency is:

1. Hereditary (mechanism: genetic defects):

A-Type I. Impaired synthesis of C_1- INH.

B- Type II. Dysfunctional C_1- INH.

II. Acquired (mechanism: antibody to C_1-INH):

A- Anti-idiotype antibody in lymphoproliferative diseases.

B- Autoantibody to C1-INH.[26]

As Palacios said, 20% of patients do not present background evidence of the disease, and suggested that the appearance of the condition may be due to a genetic mutation;[23] the family history of the second case is also negative. The laboratory data that suggest the diagnosis are a consistent low serum level of C_4 in the asymptomatic period and decreased serum C_2 level during attacks. The diagnosis is confirmed by a low serum level of C_1 INH.[24] In the second case serum levels of C_4 and C_1 INH were very low. The molecular basis for C_1 inhibitor is heterogeneus, most mutations (more than 85%) are not associated with the production of protein (Type I HAE) and most of the remainder are point mutations leading to the production of normal amounts of antigenic protein that is dysfunctional (Type II HAE).[6] This form of disease is associated with a nonfunctional protein (Type 2) and requires a functional assay to establish the diagnosis. In this form the C_1 INH level is normal or increased.[23] Almost all patients with type II HAE have point mutations within the reactive loop of C_1 inhibitor mutations at Arg^{444} (the P1 residue) are estimated to be present in up to 70% of patients with type II HAE.[25] An acquired form of C_1 INH deficiency associated with lymphoproliferative disorders has the same clinical manifestations but differs in the lack of a familial element; in the reduction of C_1 as well as C_1 INH, C_4 and C_2; and in the presence of an anti-idiopathic antibody to the monoclonal immunoglobulin expressed on the B cell.[24] The antibody that binds to the circulating C_1 INH in these patients also reacts with an epitope of the monoclonal immunoglobulin expressed on the surface of their B cells or in the cytoplasm of marrow pre-B cells. Therefore, it is likely to be an example of antigen mimicry that occurs between the molecular shape of the immunogobulin idiotope and the C_1 INH molecule. Antibodies against tumor cell components may cross-react with the C_1 INH molecule, and eliminate it as antigen-antibody complexes. Accordingly, the rate of C_1 INH synthesis is relatively normal in these patients, whereas the rate of catabolism in the

Table II: Other Immunological Findings of the First Case.

Test		Patient	Control	Normal Ranges
T-Cell Count (% of lymphocytes)		71%	70%	55-80%[1]
B-Cell Count (% of lymphocytes)		22%	38%	6-19%[1]
NBT[2]		90%	90%	90-96%[2]
Chemotaxis[3]	-CF	25μ	25μ	22-54μ [5]
	+CF	100μ	80μ	77-125μ[5]
Opsonization[4]		5%	85%	50-85 %[5]

[1]Normal ranges (Schamber et al., 2000)

[2]NBT was performed via NBT slide test (Beyer et al., 1992)

[3]Chemotaxis was performed through Millipore filters in a Boyden Chamber (Beyer et al., 1992)

[4]Opsonization test was performed (Southwick et al., 1986)

[5]Internal laboratory references.

form of extracellular sequestration of both C_1 INH and C_1q is substantially increased. [26] Unfortunately the C_1s level has not been measured because of limitation of laboratory equipment, but the second case was evaluated for other causes of acquired form of C_1 INH deficiency, such as lymphoproliferative disorders. There was no sign or symptom such as organomegaly, lymphadenopathy and laboratory data did not agree with this diagnosis. There was no anemia, leukocytopenia or thrombocytopenia. Danazol and Stanazol completely controlled the angioedema. Transfusions of purified C_1 inhibitor preparation have been used in the treatment of acute attacks of angioedema,[27,28] but our patient had not recieved such transfusions. Reports of primary C_3 deficiency and hereditary angioedema (HAE) in two related cases are very rare,[17,18] Palacious et al. reported 3 cases of clinical angioedema in 1998. The first patient had a functional deficit in C_1 inhibitor; the second had a decrease in CH50, and the third a reduction in the C_1q, C_3 and C_4 fractions. In another study, a 17 year old boy with C3 deficiency has been reported, while his cousin had a slightly decreased C_1 INH.[6]

Palacios et al., have reported three related cases of clinical angioedema in 1998. The first patient had normal values for C_3 and C_4, but C_1 esterase inhibitor activity was lower than 10%.

In their second patient C_3, C_4 and C_1INH levels were within normal limits and only a reduction in CH50 was found. Their third case of angioedema had presented an etiology which in the course of the disease led to a decrease in C_3 and C_4. They had concluded that hereditary angioedema might develop through acquisition, as most cases lack a family background of the disease.

The condition of these two cases was reported with reference to the Family Tree: see figure 1. IV2 (patient N1.2) is the hereditary angioedemic patient and IV9 (patient N2.1) is the primary C3 deficient patient. The Family Tree shows some other cases, as follows: The III1 person was a boy, had been mentally retarded and died. The IV1 a woman with severe recurrent aphthous lesions (probably Behcet's disease) and V1 is a boy with neurofibromatosis. This Family Tree may suggest that there is some genetic relationship between primary C_3 and C_1 INH deficiency, which presented clinically in these patients. The relationship between these diseases and our cases remains unclear and needs further investigations.

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