Common variable immunodeficiency: familial inheritance and autoimmune manifestations in two siblings

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SUMMARY: Edeer-Karaca N, Gülez N, Aksu G, Kütükçüler N. Common variable immunodeficiency: familial inheritance and autoimmune manifestations in two siblings. Turk J Pediatr 2010; 52: 89-93.

Common variable immunodeficiency (CVID) is an immunodeficiency syndrome characterized by generalized defective antibody production and recurrent sinopulmonary bacterial infections. Autoimmune disease is common in CVID, occurring in approximately 20% of patients, with a slight female predominance. Familial inheritance of CVID is very rare, and we here report two siblings with CVID presenting remarkable autoimmune manifestations such as relapsing polychondritis, juvenile idiopathic arthritis and chronic inflammatory bowel disease. Autoimmune and inflammatory complications showed minimal improvement under regular intravenous immunoglobulin replacement therapy, prophylactic antibiotics and immunosuppressives in these patients.

Key words: common variable immunodeficiency, autoimmunity, familial inheritance.

Common variable immunodeficiency (CVID; OMIM 240500) is characterized by[1] an impaired ability to produce specific antibodies after exposure to pathogens;[2] markedly reduced serum levels of IgG, IgA and frequently IgM; and[3] the exclusion of other causes of antibody deficiencies[1]. It is also characterized by recurrent bacterial infections, and is complicated by autoimmune manifestations in up to 20% of patients and lymphoproliferation (splenomegaly) in approximately one-third [2-6]. Autoimmunity may be due to the lack of immunologic regulatory mechanisms or ineffective clearance of antigens[2,7]. Idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia are the most common, whereas systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, dermatomyositis, thyroiditis, celiac disease, insulin-dependent diabetes mellitus, and pernicious anemia have also been described[8].

Most cases of CVID are sporadic; however, at least 10% are familial, with a predominance of autosomal dominant over autosomal recessive inheritance. It has been recently demonstrated that 30% of CVID cases may be a monogenic disorder. Four monogenic defects have been described:[1] *TNFRS13B* gene, which is located on 17p and encodes the protein TACI,[2] *ICOS* on 2q,[3] *CD19* on 16p, and[4] *TNFRSF13C* on 22q, which encodes the BAFF receptor[9]. In some cases, family members of CVID patients may present with selective IgA deficiency (sIgAD), and cases of sIgAD have been described that gradually progress to CVID[10].

Familial inheritance of CVID is very rare, and we here report two siblings with CVID presenting remarkable autoimmune manifestations.

Case Reports

Two siblings of nonconsanguineous healthy parents were diagnosed as CVID according to the European Society for Immunodeficiencies (ESID) criteria; they have a healthy 18-year-old brother. Clinical and laboratory findings of the two patients are listed in Tables I and II.

Case 1

A four-year-old boy, the second child of nonconsanguineous healthy parents, admitted to the hospital with recurrent respiratory tract infections, diarrhea and swelling of his wrists. His past medical history revealed upper and lower respiratory infections at least twice a month and swelling of his wrists for five months. He was born at term with a birth weight of

Table I. Clinical Findings of Two Siblings with Common Variable Immunodeficiency

	Case 1	Case 2
Age at diagnosis	48 months	15 months
Age at the beginning of symptoms	12 months	9 months
Weight	10-25 percentile	25-50 percentile
Height	10-25 percentile	25-50 percentile
Follow-up duration	4 years (died at 8 years)	Still under follow-up, 6 years
Recurrent upper and lower respiratory tract infections	+	+
Recurrent sinusitis and otitis media	+	+
Bronchiectasis	+	+
Splenomegaly	+	+
Autoimmune phenomena	+	+
✓ Inflammatory bowel disease	+	–
✓ Relapsing polychondritis	–	+
✓ Chronic arthritis	+	+

3.7 kg after an uncomplicated pregnancy. He had a healthy brother. On admission, his weight was 14.5 kg (10-25th percentile) and height was 99 cm (10-25th percentile). His physical examination was normal except for swelling of his wrists. The laboratory results were as follows: white blood cell count 9500/mm^3 with 76% polymorphonuclear cells, 22% lymphocytes, 2% monocytes on peripheral smear, hemoglobin (Hb) 10.6 g/dl, hematocrit (Hct): 34%, mean corpuscular volume (MCV): 60 fl, platelets 613000/mm^3, erythrocyte sedimentation rate (ESR) 16 mm/hr, and C-reactive protein (CRP) 1.5 mg/dl. Protein electrophoresis showed a decrease on gamma band. Serum immunoglobulin (Ig) levels were very low (IgG: 207 mg/dl, IgM: 38 mg/dl, IgA: 6.68 mg/dl). Lymphocyte subsets were as follows: CD3: 57%, CD19: 15%, CD3+CD4+: 23%, and CD3+CD8+: 42%. Anti-nuclear antibody was found to be negative. With the positive pathological findings like recurrent infections, arthritis, chronic diarrhea, anemia, thrombocytosis, and hypogammaglobulinemia, he was diagnosed as CVID and intravenous immunoglobulin (IVIG) replacement therapy was given every month (0.5 g/kg). He had slightly recovered after IVIG therapy.

On the fourth year of follow-up, the patient began to admit to the hospital with severe diarrhea, nausea and vomiting, which could not be explained with bacteriologic, fungal, viral (rotavirus) or parasitic examinations, or malabsorption tests. Colonoscopy and biopsy findings indicated an inflammatory bowel disease. Besides regular IVIG therapy, 1.5 mg/kg oral prednisolone and 1500 mg/day mesalazine (5-aminosalicylic acid) were given to the patient. In three weeks, the symptoms disappeared and the medications were tapered gradually to very low doses. Colonoscopy was performed every four months, and colonoscopic and histologic features resolved gradually. One year after this diagnosis, he died due to pneumonitis and irreversible respiratory failure at eight years of age.

Case 2

Our second patient is the brother of the first patient, who was born after his death and was admitted to the hospital at 15 months of age because of recurrent otitis media for the last six months. His eldest brother had had no complaints thus far. His weight was 9.2 kg (25-50%) and height 78 cm (50-75%), and vital signs were normal. Laboratory examinations revealed mild anemia and hypogammaglobulinemia (RBC 4.1×10^6/mm^3, Hb 10.7 g/dl, Hct 31.7%, MCV 71.4 fl, IgG: 348 mg/dl, IgM: 57 mg/dl, IgA: 5.58 mg/dl). Specific vaccine response to tetanus was inadequate. With the results of lymphocyte subsets (CD3+: 49%, CD19+: 5%, CD3+CD4+: 19%, CD3+CD8+: 29%, CD3-CD56+: 40%, CD19+CD40+: 2%,

Table II. Laboratory Findings of Siblings with Common Variable Immunodeficiency

	Case 1	Case 2
White blood cell count (mm^3)	9500	5100
Absolute lymphocyte count (mm^3)	2090	1581
Hemoglobin (g/dl)	10.6	10.7
Platelet (mm^3)	613 000	373 000
Total protein (g/dl)	6.5	6.1
Albumin/globulin	3.9/2.6	3.5/2.6
IgG (mg/dl)	207	348
IgM (mg/dl)	38	57
IgA (mg/dl)	6.68	<5.8
IgE (kU/L)	<2	<2
CD3+ (%)	57	49
CD19+ (%)	15	5
CD3+CD4+ (%)	23	19
CD3+CD8+ (%)	42	29
CD3-CD56+ (%)	27	40
CD19+CD40+ (%)	ND	2
CD40L after T lymphocyte stimulation (%)	ND	35
Anti-tetanus (pre-IVIG replacement)	ND	inadequate
Anti-*Haemophilus influenzae B* (pre-IVIG replacement)	ND	1.46 mg/ml
Anti-HBs (pre-IVIG replacement)	negative	negative
Genetic analysis CD40 CD40L TACI BAFF-R	ND	negative
Thorax computed tomography	Bronchiolitis obliterans, Bronchiectasis involving left lung	Bronchiolectasis involving lower lobes bilaterally
Colonoscopy	Mucosal erosions, erythema, ulcers, friability, exudate, and edema	ND
Anti-nuclear antibody	Negative	Negative
Anti-dsDNA	Negative	Negative
Anti-neutrophil cytoplasmic antibody	Negative	Negative
Rheumatoid factor	Negative	Negative
HLA-antigens	A*01, A*02 B*38, B*39 Cw*07, Cw*12 DRB1*14, DRB1*13, DRB3 DQB1*05, DQB1*06	A*01, A*24 B*39, B*51 Cw*07, Cw*15 DRB1*14, DRB3 DQB1*03, DQB1*05

ND: Not determined.

CD40L after T lymphocyte stimulation: 35%), severe combined immunodeficiency and hyper IgM syndromes were excluded. Mutations of CD40, CD40L, TACI, and BAFF-R were scanned and found to be negative. Since he had recurrent sinopulmonary infections and progressive decrease in IgG levels with age, IVIG replacement therapy was started at three years of age with the diagnosis of CVID. Six months later, the patient was noted to have painful swelling of his right knee and first and fifth metacarpophalangeal joints. Laboratory results for autoantibodies such as anti-nuclear antibody and rheumatoid factor were all negative. Ultrasonography of the right knee showed effusion without synovitis. Sulfasalazine treatment for arthritis was started, and partial response to this treatment with regular IVIG substitution therapy and prophylactic antibiotics was achieved.

By four years of age, he had erythematous lesions on the helixes of ears bilaterally. Cartilaginous portions of pinna were tender and had violaceous discoloration. Noncartilaginous parts of the pinna were normal. Under the treatment of local corticosteroid and cicatrizing creams together with systemic anti-inflammatory medications including nonsteroidal anti-inflammatory drugs and methotrexate, the lesions persisted with slight improvement. Skin biopsy of the lesion was reported as "granulomatous dermatitis". He was diagnosed as relapsing polychondritis (RP) based on characteristic auricular chondritis and polyarthritis involving large and small joints (two findings according to McAdam's criteria [11] and two conditions according to Michet et al.'s criteria[12]. His examinations for inner ear, vestibular and ocular involvement of RP were normal. The patient is still being followed carefully for the beginning signs of chondritis of nasal, laryngeal and tracheal cartilages. He has been under follow-up with the diagnosis of CVID with RP for five years.

Discussion

Common variable immunodeficiency is the most frequent primary immunodeficiency in man requiring medical attention. The syndrome is associated with autoimmune and inflammatory complications in addition to recurrent infections. The siblings presented in this report had recurrent sinusitis and pneumonitis, despite receiving regular IVIG therapy. The first child had chronic arthritis and inflammatory bowel disease as autoimmune manifestations, while the second had chronic arthritis and RP.

Most cases of CVID occur sporadically, but approximately 10-20% of CVID cases show at least one additional family member suffering either from CVID or selective IgA deficiency[4,7,8]. Mutations in ICOS, CD19, APRIL and BAFF-R are known genetic defects underlying CVID[8]. sIgAD sometimes shows a progression to CVID. IgA deficiency shares a putative MHC-linked genetic defect with CVID[9,10]. Mutations in TACI were also in relatives of patients with CVID who had IgA deficiency[6]. Brandt et al[5]. reported that family members of CVID patients appear to have an increased risk of autoimmunity. The underlying etiology of autoimmune disease in CVID remains unknown. Genetic as well as persistent antigen exposure in the context of inherited immune dysfunction all likely contribute.

According to similar clinical and laboratory findings, the same but unknown genetic defect leading to CVID was suspected for these siblings, because investigations for mutations in TACI, CD19, ICOS, CD40, CD40L and BAFF-R revealed normal results. Researches for the molecular defect are still ongoing. The second patient is under treatment with regular IVIG, prophylactic antibiotics and inhaler corticosteroids for chronic lung disease, and methotrexate for chronic arthritis and RP. However, no remission was obtained for autoimmune manifestations. Both of the siblings had the HLA-A1DR3 haplotype, which was reported to be related with autoimmunity, but they did not have the HLA-B8 antigen (Table II).

To our knowledge, this is the first report presenting two siblings with CVID and with remarkable autoimmune manifestations such as RP. As regular IVIG, prophylactic antibiotics, and basic immunosuppressive drugs like corticosteroids and methotrexate do not ameliorate autoimmune and inflammatory complications, new treatment strategies like anti-CD20, tumor necrosis factor (TNF) antagonists and hydroxychloroquine have to be considered to control these complications.

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