
Spectrum of illness in pediatric common variable immunodeficiency

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Background: Common variable immunodeficiency (CVID) may present at any age but usually presents during adulthood.

Objective: To study the presentation and associated medical conditions found in pediatric patients with CVID.

Methods: A medical record review of patients diagnosed as having CVID before the age of 18 years was performed at a tertiary care immunology clinic from 1992 to 2005. Inclusion criteria consisted of presentation with recurrent infections and decrease in 2 of 3 immunoglobulin isotypes (IgG, IgA, IgM) 2 SDs below the age-specific range, with a poor or absent response to immunization. There had to be no other identifiable predisposing cause of the immunodeficiency.

Results: A total of 12 patients were identified. The mean age at presentation was 8 years. All patients had low IgG levels with poor functional antibody responses. The most common presenting infections were sinusitis (75%), otitis media (67%), and pneumonia (58%). Bronchiectasis was seen in 3 children. One patient presented with chronic diarrhea due to *Giardia*. Two patients presented with failure to thrive. Asthma was seen in 10 patients (83%) but was usually diagnosed after the initial presentation. Autoimmune disorders were seen, including 1 patient with idiopathic thrombocytopenia and 2 with neutropenia. Other disorders encountered were growth hormone deficiency, hypothyroidism, end-stage renal disease, and sarcoma.

Conclusions: CVID is a difficult diagnosis in the pediatric population because of an unpredictable presentation. Autoimmune disease, growth hormone deficiency, renal disease, and cancer were noted in our population. A high incidence of asthma also may be associated with pediatric CVID.

Ann Allergy Asthma Immunol. 2006;97:653–656.

INTRODUCTION

Common variable immunodeficiency (CVID) is an idiopathic state of immune dysregulation in which the main result is impaired antibody synthesis and response. This heterogeneous disorder involves both B- and T-lymphocyte immune dysfunction. Affected patients are prone to recurrent bacterial infections and a wide variety of other systemic conditions. Although the onset of symptoms is usually in the second and third decades of life, some patients present in childhood. Pediatric patients with this disorder have not been as commonly studied as adults. This study was undertaken to further elucidate the presentation of CVID in pediatric patients.

METHODS

A medical record review was performed of children younger than 18 years who presented with CVID between the years of 1992 to 2005 to the West Virginia University immunology clinic after approval of the local institutional review board. Patients diagnosed as having CVID were selected for inclusion in this retrospective case review if their conditions were diagnosed before the age of 18 years, they presented with recurrent infections without another identifiable cause, they had a decrease in 2 of 3 immunoglobulin isotypes (IgG, IgA, IgM) 2 SDs below the age-specific range, and they had a poor

or absent response to immunization.^{1,2} A poor response to diphtheria and tetanus immunization was defined as an IgG antibody concentration of less than 0.1 IU/mL. A poor response to the polyvalent pneumococcal vaccine (Pneumovax, Merck & Co, Whitehouse Station, NJ) was defined as IgG antibody concentration of less than 1.0 IU/mL in 7 or fewer of the 14 types. Asthma was defined as 3 or more episodes of wheezing that improved in response to a bronchodilator. In those children able to perform pulmonary function testing, an increase of 12% in forced expiratory volume in 1 second after a bronchodilator was used to diagnose asthma.

RESULTS

In total, 12 patients were identified for review (Table 1). The mean age at presentation was 8 years, and the youngest age at diagnosis was 2 years. Most of our patients (67%) were male. Most patients presented with otitis media (67%), sinusitis (75%), or pneumonia (58%). Bronchiectasis was noted at the time of diagnosis in 25% of the children. Three had chronic diarrhea from *Giardia* or *Salmonella*, and 2 others had failure to thrive (Table 2). None of the male patients had complete agammaglobulinemia or flow cytometry consistent with X-linked infantile agammaglobulinemia, but 1 female patient had profoundly low IgG, IgA, and IgM levels. None of the patients had low albumin levels or hypoproteinemia, thus ruling out a secondary immunodeficiency due to a protein-losing condition.

The most common comorbid diagnosis in this population was a clinical history of asthma (83%). Based on the criteria

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Received for publication January 23, 2006.

Accepted for publication in revised form July 3, 2006.

Table 1. Immunoglobulin Levels in Pediatric Patients With Common Variable Immunodeficiency*

Patient No.	Age at diagnosis, y	Current age, y	Sex	IgG, IU/mL	IgA, IU/mL	IgM, IU/mL
1	7	21	M	456	49	28
2	17	26	F	301	15	41
3	10	21	M	404	<7	17
4	6	22	M	310	<7	29
5	9	24	M	238	<7	32
6	14	21	F	128	<7	49
7	10	24	F	29	<7	7
8	5	25	M	542	22	46
9	7	10	F	41	<7	20
10	2	15	M	18	<7	89
11	2	9	M	245	<7	26
12	11	16	M	609	13	47

* Levels of antibody are at patient presentation to our institution. Patient 1 presented to our institution while receiving intravenous immunoglobulin therapy, and thus this value reflects a trough IgG level. Abnormal laboratory values appear in bold.

described in the "Methods" section, 10 of our 12 patients had a clinical history of asthma; 5 of the 10 patients had a decrease in FEV₁ that significantly improved with bronchodilator on spirometry. Of these children, one had symptoms of allergic rhinitis and had multiple allergies confirmed by skin testing, another had a history of moderate atopic dermatitis, but none had elevated IgE levels. Most episodes of wheezing were related to upper respiratory tract viral infections or sinusitis and were not usually secondary to an atopic condition. Most of these patients' episodic wheezing also became easier to manage as they progressed toward adulthood, consistent with nonatopic childhood asthma.

Neutropenia and hypothyroidism were seen in 2 patients, whereas growth hormone deficiency was seen in 3. Growth hormone deficiency was diagnosed by a pediatric endocrinologist in all 3 patients with growth failure after growth hormone provocation testing. One patient with growth hormone deficiency and hypothyroidism had no other autoimmune diseases or abnormal antibody tests such as antithyroglobulin antibodies, but this patient had a genetic defect of ring chro-

mosome 18. Another patient with growth hormone deficiency had no chromosome abnormalities or autoimmunity but had profound developmental delay, similar to both of his parents. Both of these patients responded well to growth hormone therapy. The final patient with growth hormone deficiency also had hypothyroidism, but these conditions were believed to be complications from radiation treatment for his nasopharyngeal sarcoma.

Other disorders encountered were immune thrombocytopenic purpura, Bell palsy, end-stage renal disease of unknown origin, and poorly differentiated nasopharyngeal soft tissue sarcoma 6 years before the diagnosis of CVID in 1 patient. This patient completed his chemotherapy 5 years before his diagnosis of CVID (Table 3). Two of our 12 patients had a low CD4 T-lymphocyte count defined as less than 382/ μ L and a high CD8 cell count defined as more than 813/ μ L with a low CD4/CD8 ratio less than 1.³ These 2 patients had normal proliferation of peripheral blood lymphocytes when

Table 2. Presenting Infections and Complications in Pediatric Patients With Common Variable Immunodeficiency

Patient No.	Infections and complications before presentation
1	Otitis media, sinusitis
2	Sinusitis, pneumonia, dental abscess
3	Sinusitis
4	Sinusitis, otitis media, failure to thrive, bronchiectasis
5	Chronic diarrhea (<i>Giardia</i>), otitis media, pneumonia, sinusitis
6	Sinusitis, otitis media
7	Pneumonia
8	Chronic diarrhea (<i>Salmonella</i>), sinusitis, pneumonia
9	Otitis media, pneumonia, bronchiectasis
10	Chronic diarrhea (<i>Giardia</i>), otitis media, failure to thrive
11	Otitis media, pneumonia, sinusitis
12	Otitis media, pneumonia, sinusitis, bronchiectasis

Table 3. Associated Autoimmune and Other Disorders in Pediatric Patients With Common Variable Immunodeficiency

Patient No.	Associated conditions
1	Bell palsy
2	Asthma, nasal polyps, ESRD
3	Asthma, GI lymphoid hyperplasia
4	Asthma, nasal polyps
5	Asthma
6	Asthma, hypothyroidism, GHD, DD
7	Asthma
8	ITP, autoimmune neutropenia, ring chromosome 18
9	Asthma
10	Asthma, autoimmune neutropenia
11	Asthma, DD, GHD, microcephaly, hypotonia
12	Asthma, sarcoma, hypothyroidism, GHD

Abbreviations: DD, developmental delay; ESRD, end-stage renal disease; GHD, growth hormone deficiency; GI, gastrointestinal; ITP, idiopathic thrombocytopenia.

stimulated with mitogens. One of the patients with a persistently low CD4 cell count had hypothyroidism, growth hormone deficiency, and the remote history of nasopharyngeal sarcoma. The other 10 patients had normal CD4 and CD8 T-lymphocyte counts on flow cytometry with normal mitogen response.

DISCUSSION

The presentation of CVID in pediatric patients has received minimal attention in the literature. Although many medical issues would be anticipated to be similar to adult patients with CVID, children may also have unique problems related to their developmental status. In this review of pediatric patients, we discovered that failure to thrive might also be secondary to growth hormone failure. Other unique findings include that pediatric patients may develop end-stage renal disease or solid tissue tumors. Further, the percentage of children with a history of asthma was higher than expected.

The common immunologic defect in these patients is defective antibody formation. Mechanistically, the basic defect in CVID is a failure of B-lymphocyte differentiation into plasma cells that produce the various immunoglobulin isotypes.⁴ This disorder affects males and females equally, and the estimated incidence is 1 case per 25,000 to 66,000 in some populations.^{5,6} CVID usually occurs after the onset of puberty in the second or third decade of life, but 21% of cases occur at ages younger than 21 years.⁷

CVID patients often experience recurrent pyogenic infections of the upper and lower respiratory tracts, with *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* being the most commonly seen organisms. Unusual organisms such as *Pneumocystis carinii*, *Mycoplasma pneumoniae*, *Giardia lamblia*, and *Herpes simplex* also may occur.⁷ Infections noted in our CVID patients were similar to those reported in adult-onset CVID patients.

Comorbid autoimmune diseases, such as rheumatoid arthritis, hemolytic anemia, pernicious anemia, thrombocytopenia, neutropenia, thyroid abnormalities, or vitiligo, are associated with CVID.⁸ Many patients also have granulomas, villous atrophy, and atypical lymphoid hyperplasia.^{9,10} Our pediatric patients predominately had neutropenia, thrombocytopenia, hypothyroidism, or lymphoid hyperplasia. Adult CVID patients have a higher risk of developing malignant neoplasms, with lymphoma occurring approximately 438 times more frequently in women than in men.¹¹ As expected, no pediatric patients in our series had lymphoma. However, 1 patient had a diagnosis of sarcoma before the diagnosis of CVID.

Patients with CVID frequently have pulmonary airway obstructive disease indistinguishable from asthma. The clinical diagnosis of asthma was observed in 83% of our patients. This is higher than what is reported in the adult literature and in part may be due to recurrent viral illnesses associated with childhood. None of our patients had life-threatening or potentially fatal asthma. Other pulmonary findings included

bronchiectasis in 25% of our patients, which is similar to other reported series.^{12,13}

An unusual finding in this series was the high association of growth hormone deficiency (25%) in our population. The cause in each case did not appear to be autoimmune in nature. Multifactorial causes of growth hormone failure in this population included 2 cases associated with an undetermined genetic defect (Table 3). The third case was likely iatrogenic secondary to prior radiation for the patient's sarcoma. Although growth hormone deficiency has been observed with other immunodeficiency states, it has rarely been associated with CVID.^{14,15}

Intravenous or subcutaneous IgG replacement has decreased the frequency of life-threatening infections in these patients and is the mainstay of treatment. The prognosis is reasonably good if patients do not have bronchiectasis, chronic lung damage, severe autoimmune disease, or malignancy. The survival rate in patients with CVID 20 years after diagnosis is currently 64% for males and 67% for females compared with the expected population survival rate of 92% for males and 94% for females.¹⁶

This review suggests that children with CVID may have additional clinical findings that are not as commonly associated with adult patients with this disorder. Our series revealed a high rate of asthma and growth hormone deficiency. Additional comorbid diseases included end-stage renal disease and sarcoma.¹⁷ Pediatric CVID patients may present with multiple health issues beyond the expected recurrent upper and lower respiratory tract infections.

In conclusion, childhood presentation of CVID is similar to adults with regard to common presenting infections and autoimmune disorders. A high association with obstructive airway disease indistinguishable from asthma can occur in this population subgroup. Other unusual comorbid diseases, such as end-stage renal disease, sarcoma, and growth hormone deficiency, can be observed. Growth hormone deficiency should be considered in the differential diagnosis of growth failure in CVID patients, since 25% of our population had this disorder.

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