

Common Variable Immunodeficiency Disorders in Children: Delayed Diagnosis Despite Typical Clinical Presentation

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Objective To characterize common variable immunodeficiency disorder (CVID) in childhood.

Study design We retrospectively investigated clinical findings in 32 children with primary CVID by questionnaire and file review.

Results Clinical presentation included recurrent or chronic respiratory tract infections (88%), sinusitis (78%), otitis media (78%), and intestinal tract infections (34%), mainly with encapsulated bacteria. Meningitis was found in 25%, sepsis in 16%, and pyelonephritis in 16% of patients. Poliomyelitis after vaccination occurred in 2 patients and opportunistic infections occasionally. Allergic disorders were present in 38%, and autoimmune disease in 31% of patients. Eighty percent of the patients underwent surgical procedures because of recurrent infections. Growth retardation was seen in 28% of patients, and 16% showed retarded mental development. Bronchiectasis developed in 34%, and lymphoid proliferative disease in 13%. Incidence of allergic and autoimmune diseases was increased in first-degree relatives with normal immunologic findings. Mean time between symptoms and induction of immunoglobulin substitution therapy was 5.8 years (0.2-14.3).

Conclusions CVID in children presents with comparable symptoms and disorders as in adults. We found a significant influence on growth and development. The marked delay of diagnosis may be due to overlap with common pediatric disorders, while also reflecting insufficient awareness of these disorders. (*J Pediatr* 2009;xx:xxx)

Common variable immunodeficiency disorders (CVID) represent the most frequent symptomatic primary immunodeficiency in North America and Europe,¹ with an incidence of 1:25 000 to 1:66 000.² The diagnosis requires a history of recurrent or chronic bacterial infections, significant reduction of immunoglobulin G (IgG) (>2 standard deviations), reduction of immunoglobulin A (IgA) or immunoglobulin M (IgM), as well as a defective specific antibody production after vaccination³ (www.ESID.org). Secondary reasons for hypogammaglobulinemia, such as chromosomal aberrations, medical treatment, leukemia, renal, or gastrointestinal loss of immunoglobulins must be excluded.⁴

This definition is focused on clinical findings and the lack of specific humoral immune responses. The latter is the result of a complex interaction of antigen-presenting cells, T- and B-lymphocytes. Thus a variety of different defects within this system may lead to the findings defining CVID. Linkage analyses suggest a genetic background for CVID supported by familial coincidence of CVID or related immunoglobulin deficiencies, which occur in a minority of patients.¹ However, only a few mutations have yet been found to be causative for CVID. Defects of the inducible costimulator⁵ are present in a small percentage of patients.⁶ Mutations in the CD19 gene were found in single patients, and defects in the interaction of TACI and BAFF-receptor have been shown to influence the risk for development of CVID.^{7,8} The typical delayed onset after a period of normal health status supports the hypothesis that CVID is often the result of genetic predisposition and critical events, such as infections or toxic events. There have been recent attempts to define distinct clinical or immunologic subgroups.^{9,10}

The age at diagnosis shows 2 peaks, between 6 and 10 years of age and in young adulthood (between 26 and 40 years).¹¹ Recently published registry data do not as clearly reflect this age distribution.⁹ Although adult onset of the disease has been well described

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CVID	Common variable immunodeficiency disorders	IgA	Immunoglobulin A
		IgG	Immunoglobulin G
FACS	Flow cytometry (Fluorescent-activated cell sorting)	IgM	Immunoglobulin M
		IVIG	Intravenous immunoglobulin

in large clinical and therapeutic trials^{12,13} and recent registry data,^{9,10} there have been no investigations of the features of early-onset CVID and the special diagnostic approach necessary in the immature immune system in childhood.¹⁴ As such, specific problems related to the development of the immune system have not yet been identified. In adults, because of the small number of affected patients the diagnosis is often delayed, probably due in part to reduced physician awareness of late-onset primary immunodeficiency. However, in children the large variety of primary immunodeficiencies should lead to basic immunologic diagnostic testing at an earlier age, including immunoglobulin concentration measurement in patients presenting with recurrent infections. Undoubtedly, the overlap with diseases of allergic or autoimmune origin, or local anatomic abnormalities, leads to decreased diagnostic specificity. Here, we have characterized the typical manifestation of early-onset CVID in pediatric patients and analyzed the time frame of diagnosis made in relation to clinical presentation of this disease.

METHODS

With data collected by the immunology laboratory and the immunodeficiency clinic, all patients with confirmed or presumed clinical or laboratory diagnosis of CVID between 1990 and 2004 were identified. Patients were evaluated on the basis of laboratory data (IgG and IgM, or IgA levels reduced more than 2 SD, impaired increase of specific antibody titers after vaccination) and clinical history (recurrent infections, exclusion of secondary causes), and whether the diagnosis of CVID was correct following the criteria of the European Society of Immunodeficiencies³ (www.ESID.org). Patients who did not fit all diagnostic criteria were excluded from the analysis. To exclude other primary immunodeficiencies (eg, severe combined immunodeficiency), lymphocyte subset analysis (flow cytometry, FACS) and stimulation assays had to show quantity and proliferative activity of T-cells within 2 SD of normal, besides negative serologic and polymerase chain reaction testing for HIV-infection. Patients with <3% B-lymphocytes were further evaluated for X-linked and autosomal recessive agammaglobulinemia, and in patients with normal IgM levels CD40 and CD40L were analyzed by FACS to evaluate for hyper-IgM syndrome.

A standardized questionnaire was used, consisting of several sections of clinical and laboratory information. After approval from institutional ethical review board, patients were contacted to explain study aims and data safety procedures and were asked for written informed consent. Patients who agreed were interviewed personally or via telephone following the questionnaire. Interviews were performed at a time chosen by the patients to allow them to prepare their records and to avoid influence of shortness of time. Subsequently recalled details could be added any time. If required or desired by the patient, physical and laboratory examinations were repeated in the immunodeficiency outpatient clinics. The questions included biographic information on personal history and siblings affected by CVID, selective IgA deficiency syndrome,

recurrent infections, or autoimmune diseases. Patients were asked for date of first recognized symptoms, health problems in early childhood, and data on clinical course regarding recurrent or chronic local, as well as severe or opportunistic systemic infections, and persisting viral infections. Infections were documented as recurrent (more than 3 episodes treated by physician or hospital per year) or chronic (if they were not resolved under appropriate treatment).

Suspected or proven allergic disorders were documented. Allergy-like symptoms were defined as typical clinical symptoms correlated with exposure to specific antigens or that were recurrent during a specific season or during days of high antigen exposure. Serologically confirmed allergy was concluded if moderate to high specific immunoglobulin E antibodies were found, or a class II or higher reaction was demonstrated in prick or epicutaneous test.

Autoimmune disease was documented, as well as neoplastic or hematologic diseases. The current therapeutic regimen was recorded, as well as current persisting health problems. One section consisted of past surgical procedures and histologic findings. Laboratory and clinical findings at presentation, when diagnosis was confirmed, and missing clinical data were added from the patient records in the hospital, as well as special findings and details of the mentioned disorders (eg, histologic results). Presence of primary immunodeficiency or related symptoms in first-degree relatives (parents and siblings) was documented. Data were collected anonymously in a Microsoft Excel database (Microsoft, Redmond, Washington), and statistical analysis was performed with Sigma-Stat (Systat Software Inc, San Jose, California) and SPSS (SPSS, Chicago, Illinois).

RESULTS

Patient Characteristics

Diagnostic criteria for early-onset CVID were present in 44 patients. Five patients were subsequently diagnosed as autosomal recessive agammaglobulinemia and were excluded from analysis. Seven patients were either diagnosed or confirmed with secondary CVID (3 for development of lymphoid neoplasms within 2 years after diagnosis of hypogammaglobulinemia and 4 for intake of drugs (methotrexate, met-amizole, carbamazepine, phenytoin) with the potential to induce humoral immunodeficiency). One patient was included as primary CVID despite initial diagnosis in the first 2 years of life, because clinical and laboratory findings persisted beyond the fourth year, excluding transient hypogammaglobulinemia.

Of the 32 remaining patients included as primary CVID, 15 were male and 17 were female. Median age at diagnosis was 10.4 ± 4.3 years (range 1.1 to 17.4 years). Age distribution showed highest incidence at 4, 9 and 15 to 16 years of age. All patients were Caucasians of European origin. All included patients were alive at the time of evaluation.

Table I. Chronic or recurrent infections before diagnosis in 32 children with primary CVID

Infectious disease	Patients affected
Bronchitis	28 (88%)
Pneumonia	25 (78%)
Sinusitis	25 (78%)
Otitis media	22 (69%)
Fungal infections (including skin)	15 (47%)
Gastrointestinal infections	10 (34%)
Skin infections	7 (22%)
Parasites	5 (16%)
Conjunctivitis	3 (9%)
Oral/Dental	3 (9%)

Clinical Presentation at Diagnosis

INFECTIOUS DISEASES. Before diagnosis of CVID, chronic or recurrent infections were present in the vast majority of patients (Table I). Most patients were affected with infections of the upper and lower respiratory tract.

There was a markedly higher rate of severe or systemic infectious diseases than in the general pediatric population. Meningitis was found in 8 patients (25%), culture-proven sepsis in 5 (16%), pyelonephritis in 5 (16%), mastoiditis in 3 (10%), and soft-tissue infections in 2 (6%) patients. Pleural empyema, septic arthritis, submandibular abscess, and periorbital cellulitis were each diagnosed in 1 patient (3%).

Analysis for persisting viral infections or infections with potential to influence the immune system (Epstein Barr virus, cytomegalovirus, HIV, hepatitis B or C, or herpes simplex, all performed by polymerase chain reaction) did not reveal higher frequency than the general pediatric population. Two patients had severe *Varicella* infection and 2 had measles complications. Two patients showed clinical manifestations of poliomyelitis with pareses and persistent viral excretion (6 and 13 months) after life attenuated vaccination. These patients did not show particular differences in the documented immunologic findings compared with the rest of the cohort.

ALLERGY OR ALLERGY-LIKE SYMPTOMS. Overall allergy-like symptoms or confirmed allergy were found in 12 patients (38%). The manifestations were food intolerance with consequent rash or dyspnea (6 patients), eczema (4 patients), urticaria (2 patients), serous rhinitis (2 patients), and asthma (1 patient). Specific immunoglobulin E-antibodies were found mainly against food ingredients and medical drugs (~33 % each), animal antigens, mites, and pollen in ~10%, and nickel in ~5%.

AUTOIMMUNE DISEASES. Autoimmune phenomena were found in 31% (n = 10) of the total patient population. They presented as hemolytic anemia (2 patients) and thrombocytopenia (2 patients). Arthritis, vasculitis, gluten-sensitive enteropathy, diabetes mellitus, vitiligo, and psoriasis were each diagnosed in 1 patient.

SURGICAL PROCEDURES. Eighty percent of the patients underwent surgical procedures before CVID diagnosis. Most frequent were adenoidectomy (16 patients [50%]), tonsillectomy (8 patients [25%]), excision of suspicious lymph nodes (7 patients [22%]), tympanic paracentesis (6 patients [19%]), excision of pulmonary lobes (4 patients [13%]), nasal sinus fenestration (3 patients [9%]), mastoidectomy (2 patients [6%]), gastrointestinal fistulas (2 patients [6%]), and splenectomy (1 patient [3%]).

PHYSICAL EXAMINATION. Suspicious clinical findings for immunologic disease were found in nearly half of the included patients at the presentation for first diagnosis. Lymph nodes were increased in size (>1 cm diameter) locally in 15 patients (47%) and diffusely in 3 (9%). An enlarged spleen was found in 14 patients (44%) and an enlarged liver in 9 (28%).

GROWTH AND DEVELOPMENT. Nine of the patients (28%) showed significant growth retardation with height below the third percentile. Analysis for differences of the patients with impaired growth relative to those with regular development is shown in Table II. Atopic symptoms and especially food intolerance were far more present in growth-impaired patients than in those with regular growth. Also chronic diarrhea caused by gastrointestinal infection was more frequent. Because of small patient numbers, these differences were not significant with the Fisher exact test ($P < .05$). Four patients had reached normal height at the point of evaluation after immunoglobulin treatment.

Five (16%) patients with growth retardation showed delayed development measured in reaching at least 1 milestone of mental and motor development later than 97th percentile. Two patients were diagnosed with inherited syndromes (Klippel-Feil syndrome and Arnold-Chiari malformation) that do not typically occur with immunodeficiency.

Laboratory Findings at Diagnosis

All patients presented with IgG serum levels below 2 SD of the age-related normal levels.¹⁵ No correlation was seen between age at diagnosis and IgG serum concentration (Figure 1). IgM concentrations were within the normal age-dependent range in only 2 patients and were reduced in 30 (Figure 1). IgA serum concentration was normal in only 1 patient and below detection limit of 6 mg/dL in 15 patients (47%) (Figure 1). Thus 29 of 32 patients showed significantly reduced serum levels in all 3 immunoglobulin classes, IgG, IgA, and IgM.

FACS-analysis of lymphocyte subsets showed regular distribution for T cells and CD4/CD8 subsets, as well as natural killer cells (CD16+). B-cells (CD19+) ranged within the lower limits of normal (Figure 2).

Diseases and Symptoms in Relatives

None of our patients was diagnosed because congenital immunodeficiency was known in a close relative. All were the

Table II. Comparison of clinical findings in patients with long-term sequelae: retarded growth compared with regular growth, presence versus absence of bronchiectasis

	Delayed growth (n = 8)	Regular growth (n = 24)	Bronchiectasis (n = 11)	No bronchiectasis (n = 21)
Age at diagnosis (y)	7.8 ± 4.7	10.8 ± 4.4	11.0 ± 4.9	9.51 ± 4.1
Time from symptoms to diagnosis (y)	5.9 ± 3.1	3.8 ± 4.5	6.32 ± 4.7	5.19 ± 3.6
Chronic bronchitis	8 (100%)	20 (83%)	11 (100%)	18 (86%)
Recurrent pneumonia	7 (88%)	18 (75%)	10 (91%)	16 (77%)
Allergies	5 (63%)	7 (29%)	5 (45%)	7 (33%)
Food-induced diarrhea	5 (63%)	1 (5%)	2 (18%)	4 (19%)
Chronic diarrhea	4 (50%)	7 (29%)	5 (45%)	6 (29%)

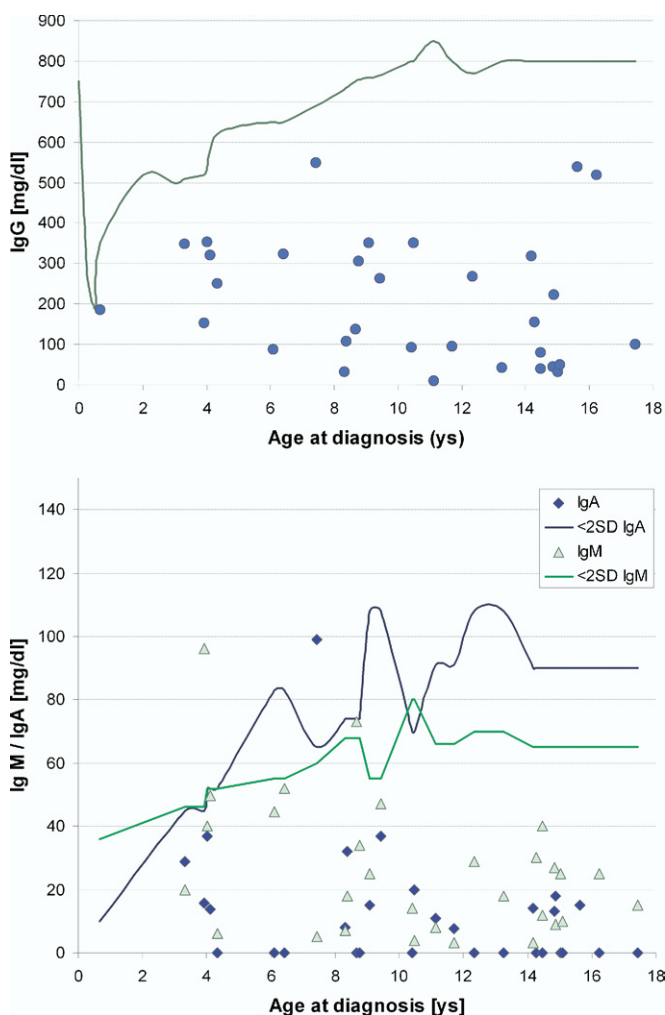


Figure 1. IgG (circles), IgM (triangles), and IgA (diamonds) serum level in each patient at first diagnosis. The line in upper chart shows age-related third percentile of normal IgG values, in the lower chart normal values for IgM (light line) and IgA (dark line) for each age as published by Uffelmann et al¹³ with adult values for children aged more than 14 years.

index patient for their families. Primary immunodeficiency was diagnosed as CVID in a brother of one patient and selective IgA deficiency syndrome in a sister of another patient. Autoimmune disease was found in 9 patients' first-

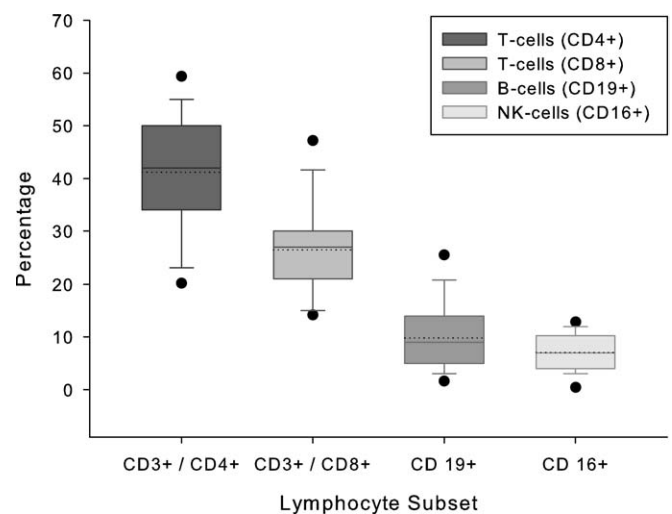


Figure 2. Lymphocyte subset distribution in pediatric CVID-patients at first diagnosis: Normal percentage for CD4+ T-cells (41.2 ± 10.9), CD8+ T-cells (26.5 ± 8.5), natural killer cells (7.5 ± 3.6). B-cells within lower normal range (9.7 ± 6.6). Boxes represent 25th, 50th and 75th percentile, range bars show 10th and 90th percentile, and black circles represent 5th and 95th percentile. Dotted line represents the geometric mean.

degree relatives (siblings or parents) (28%), including psoriasis (n = 4), diabetes mellitus type I (n = 2), systemic lupus erythematosus (n = 1), Crohn's disease (n = 1), and multiple sclerosis (n = 1). Allergies were found in relatives of 19 patients (59%), including 3 relatives with asthma and 2 with atopic dermatitis.

Time between Clinical Presentation and Diagnosis

The median duration between first symptoms with probable relation to the immunodeficiency (recurrent or chronic infections, allergy-like symptoms) and the definitive diagnosis was 5.8 ± 4.2 years with a range of 0.2 and 14.3 years. Seven patients showed clinical symptoms since birth.

Clinical Course

HEMATOLOGIC AND ONCOLOGIC DISEASES. Patients with development of lymphoid malignancies less than 2 years after

diagnosis of immunodeficiency were classified as potential secondary hypogammaglobulinemia and therefore excluded from the analysis. In this cohort, 4 patients (13%) presented with neoplasm in the follow-up period: 2 patients with Hodgkin's disease, 1 patient with non-Hodgkin's, and 1 patient with Burkitt's lymphoma. All were treated with chemotherapy with a survival rate of 100%. One patient had surgery for central nervous system glioma and remained in complete remission.

BRONCHIECTASIS. Bronchiectasis was found in 11 patients (34%) at the time of clinical evaluation for this study. All affected children had a history of recurrent or chronic bronchitis, and 10 (31%) had recurrent pneumonia before diagnosis. These clinical findings were less frequent in patients without bronchiectasis. Because of small patient numbers, differences were not significant with Fisher's exact test ($P < .05$). Comparison of the patient characteristics suggests that patients with bronchiectasis have been diagnosed at older age and after a longer symptomatic period (Table II). Because of small patient numbers, these findings were not significant (t test and Mann-Whitney rank sum test $P < .05$).

IMMUNOGLOBULIN SUBSTITUTION. At the time of evaluation 94% of the patients were treated with regular immunoglobulin replacement. The main therapeutic formulation was intravenous immunoglobulin (IVIG), received by 85% of patients; 9% received subcutaneous substitution. Two patients were off immunoglobulin replacement for noncompliance, one of whom had a more than 5-year period free of severe infections without IVIG. None of the patients received plasma infusions. Additional therapies like regular inhalations and constant or interval antibiotic prophylaxis were not analyzed. None of the patients with immunoglobulin replacement showed severe infections except the patients treated with chemotherapy for hematologic disorders.

DISCUSSION

This retrospective study is an evaluation of the clinical presentation and course of early-onset CVID. The aim of this study was to illuminate the clinical presentation in pediatric patients, with emphasis on specific pediatric disorders, and to determine whether the diagnosis was made in an appropriate amount of time after first characteristic clinical symptoms.

The leading symptoms in our patients were recurrent infections, mainly of the upper and lower respiratory tract and the middle ears. Generally, these are the main infection sites in childhood because of specific anatomic considerations, for example, of the eustachian tube.¹⁶ However, 3 or more infections requiring antibiotic treatment, as found in more than 90% percent of our patients, would not be accepted as normal.^{16,17} The results correspond well to the clinical presentation described in a larger cohort of mainly adult patients with CVID,¹³ where 90% of the patients had recurrent infections. The higher incidence of middle-ear infection in our cohort is probably due to anatomic differences in pediatric patients,

which leads to higher incidences in this age group compared with older patients.^{16,17}

The high incidence of severe and systemic infections was striking, with 25% of the patients diagnosed with bacterial meningitis, 16% with culture-proven sepsis, and many patients with unusual infection sites or courses. These severe manifestations should be an indication to the attending pediatrician to consider an underlying immunodeficiency, carefully extend the patient history and physical examination toward specific symptoms, and if necessary, follow with the appropriate laboratory testing. The vast majority of our patients showed significant reduction in all three immunoglobulin classes giving a clear abnormality on testing.

The presence of bronchiectasis as one of the main long-term complications in 34% of our patients was comparable to the incidence reported in adults.⁹ The study of our cohort did not reveal significant risk factors. In recently published data of the European CVID registry, a significant correlation was found between severe pneumonia/sepsis and bronchiectasis.⁹ Our analysis showed a tendency toward diagnosis later in life along with prolonged time between clinical symptoms and confirmed diagnosis/beginning of IVIG-treatment. However, Quinti et al¹² reported development of bronchiectasis despite IVIG therapy in some patients, probably caused by local inflammation and mucous obstruction.^{12,18} We also found a high frequency of surgery associated with lymphoid tissue or chronic infection in our cohort, including highly invasive procedures such as splenectomy and lobectomy. One could speculate that earlier diagnosis and treatment could have avoided these interventions, at least in some cases.

We found no evidence for a causative role of immunotropic viruses as Epstein-Barr virus or cytomegalovirus in development of CVID in any of our patients. Chronic or persistent infection with these viruses was not detectable. Interestingly, there were 2 cases of vaccination-induced poliomyelitis and 2 cases of severe measles, pointing out the heterogeneous pathology of this immunodeficiency. It can lead not only to impaired serologic immunity, but frequently is a complicated disorder of T- and B-cell cooperation that can impact cellular immunodeficiency.^{19,20}

Growth retardation was found in 28% of our patients, and 16% showed delayed motor or mental development. A small number of these patients might also have growth retardation as part of an unrecognized minor genetic defect. Cross-sectional analysis for growth hormone deficiency was not performed in this study. Similar findings were described in a smaller series of 12 pediatric patients with CVID, 3 of whom presented with growth hormone deficiency, and all three failed to improve after test substitution of growth hormones.²¹ However, this is not a likely explanation for an 8-fold higher increase of growth retardation than the general population. We therefore analyzed known risk factors for growth retardation and found much higher incidence of allergies, and especially food intolerance, in the patients with retarded growth. Also chronic diarrhea was more common

within these children. Because of small patient numbers, these results did not show statistical significance in χ^2 or Fisher's exact test. In addition to these findings, growth retardation has been observed as one of the sequelae of recurrent infections and persisting inflammatory activation in other diseases with autoimmune disease or chronic infections.^{22,23} This stresses the importance of early recognition and treatment of the immunodeficiency. Four of our patients had returned to normal height at the date of evaluation. It would be of great value to evaluate the influence of the initiation of therapy on growth in a prospective analysis.

The high prevalence of allergies and allergy-like symptoms observed in these patients can be speculated to be the result of a disturbed balance of the cellular and humoral immune system.^{24,25} The inclusion of reported allergy-like symptoms in our cohort may lead to an overestimation of the prevalence. However, overlap between allergic disorders and immunodeficiency may lead to delayed diagnosis. It is well known that pediatric patients with atopic disorders have a higher incidence and more severe course of infectious diseases,²⁶ most likely because of the chronic inflammation of their airways or skin. Therefore symptoms derived from the deficient immune system might be diagnosed as part of the atopic disorder and vice versa.

In addition to related immunodeficiencies in 2 patients, we found a high prevalence of allergies and autoimmune diseases in the relatives of patients with CVID. This might be an indication of minor inherited disorders in the immune system, leading to skewed balance between immune response to infectious agents and self-tolerance. As a limitation, the collection of historical data from an index patient or his parents might contain some bias and therefore cannot support a clear comparison of these symptoms and diseases with general epidemiologic data.

The importance of immunoglobulin substitution is confirmed by the absence of severe, life-threatening, or systemic infections in our cohort during the time of substitution. However, the clinical benefit, that is, reduction of minor infections, was not evaluated in this study. The therapeutic use and clinical safety of IVIG treatment for infectious diseases have been shown in larger studies.^{18,27-30} The influence of immunoglobulin substitution on autoimmune disease, development of neoplastic disorders, and long-term survival is not yet clear. Because of the complicated pathology of CVID with involvement of cellular immunodeficiency, this may be not significant.^{12,13}

Despite this typical clinical presentation, we found a long interval between initial symptoms and diagnosis/beginning of specific treatment (median = 5.8 years) for most patients. With the higher incidence of congenital immunodeficiency in children compared with adults, we expected an earlier evaluation of immunologic laboratory measurements in pediatric patients than that reported from studies in adults.^{12,13} In individual cases, even after diagnosis of hypogammaglobulinemia, children were not referred to the pediatric immunology department, and no specific treatment was initiated over years.

One underlying reason may be the low awareness of this disease entity and treatment options among general practitioners and pediatricians outside specialized centers. On the other hand, the high incidence of recurrent minor infections in children with intact immune systems and the significant clinical overlap with atopic diseases make the recognition of this diagnosis a challenge. In children who appear to have primary atopic or autoimmune disease, recurrent infections should lead to an evaluation of at least immunoglobulin levels to provide specific treatment as early as possible. This will ultimately reduce the risks associated with severe infection and reduction of quality of life caused by chronic infectious disease.

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REFERENCES

- Schroeder HW, Schroeder HW III, Sheikh S. The complex genetics of common variable immunodeficiency. *J Invest Med* 2004;52:90-103.
- Cunningham-Rundles C. Common variable immunodeficiency. *Curr Allergy Asthma Rep* 2001;1:421-9.
- International Union of Immunological Societies. Primary immunodeficiency diseases, report of an IUIS scientific committee. *Clin Exp Immunol* 1999;118(Suppl 1):1-28.
- Chapel H, Geha R, Rosen FS, for the IUIS PID Classification Committee. Primary immunodeficiency disease: an update. *Clin Exp Immunol* 2003;132:9-15.
- Grimbacher B, Huttloff A, Schlesier M, Glocker E, Warnatz K, Drager E, et al. Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. *Nature Immunol* 2003;4:261-8.
- Salzer U, Maul-Pavcic A, Cunningham-Rundles C, Urschel S, Belohradsky BH, Litzman J, et al. ICOS deficiency in patients with common variable immunodeficiency. *Clin Immunol* 2004;13:243-50.
- Castigli E, Wilson SA, Scott S, Dedeoglu F, Xu S, Lam K-P, et al. TACI and BAFF-R mediate isotype switching in B cells. *J Exp Med* 2005;201:35-9.
- Salzer U, Chapel HM, Webster ADB, Pan-Hammarström Q, Schmitt-Graeff A, Schlesier M, et al. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. *Nature Genet* 2005;37:820-8.
- Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood* 2008;112:277-86.
- Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. *Blood* 2008;111:77-85.
- Gadola S, Salzer U, Schultz H, Grimbacher B. Adult-onset primary immunodeficiencies. *Der Internist* 2004;45:912-22.
- Quinti I, Soresina A, Spadaro G, Martino S, Donnano S, Agostani C, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol* 2007;27:308-16.
- Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features in 248 patients. *Clin Immunol* 1999;92:34-48.
- Gathings WE, Kubagawa H, Cooper MD. A distinctive pattern of B cell immaturity in perinatal humans. *Immunol Rev* 1981;57:107-26.
- Uffelmann JA, Engelmann WE, Jollif CR. Quantitation of immunoglobulins in normal children. *Clin Chim Acta* 1979;28:185-92.
- Rovers MM, Schilder AGM, Zielhuis GA, Rosenfeld RM. Otitis media. *Lancet* 2004;363:465-73.
- Cripps AW, Otczyk DC. Prospects for a vaccine against otitis media. *Exp Rev Vaccines* 2006;5:517-34.
- Quinti I, Pierdominici M, Marziali M, Giovanetti A, Donnano S, Chapel H, et al. European surveillance of immunoglobulin safety- results of initial survey of 1243 patients with primary immunodeficiencies in 16 countries. *Clin Immunol* 2002;104:231-6.
- Sneller M. Common variable immunodeficiency. *Am J Med Sci* 2001;321:42-8.

20. Goldacker S, Warnatz K. Tackling the heterogeneity of CVID. *Curr Opin Allergy Clin Immunol* 2005;5:504-9.
21. Ogershok PR, Hogan MB, Welch JE, Corder WT, Wilson NW. Spectrum of illness in pediatric common variable immunodeficiency. *Ann Allergy Asthma Immunol* 2006;97:653-6.
22. Woo P. Growth retardation and osteoporosis in juvenile chronic arthritis. *Clin Exp Rheumatol* 1994;12(Suppl 10):87-90.
23. Ansell BM, Bywaters EG. Growth in Still's Disease. *Ann Rheum Dis* 1956;15:295-319.
24. Warnatz K, Wehr C, Drager R, Schmidt S, Eibel H, Schlesier M, et al. Expansion of CD19(hi)CD21(lo/neg) B cells in common variable immunodeficiency (CVID) patients with autoimmune cytopenia. *Immunobiology* 2002;206:502-13.
25. Ko J, Radigan L, Cunningham-Rundles C. Immune competence and switched memory B cells in common variable immunodeficiency. *Clin Immunol* 2005;116:37-41.
26. Chen CF, Wu K-G, Hsu M-C, Tang R-B. Prevalence and relationship between allergic diseases and infectious diseases. *J Microbiol Immunol Infect* 2001;34:57-62.
27. Busse PJ, Razvi S, Cunningham-Rundles C. Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. *J Allergy Clin Immunol* 2002;109:1001-4.
28. Pirofsky B. Intravenous immunoglobulin therapy in hypogammaglobulinemia. *Am J Med* 1984;76:53-60.
29. Pruzanski W, Sussmann G, Dorian W, Van T, Ibanez D, Redelmeier D. Relationship of the dose of intravenous gammaglobulin to the prevention of infections in adults with common variable immunodeficiency. *Inflammation* 1996;20:353-9.
30. Roifmann CM, Levison H, Gelfand EW. High dose versus low dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987;8541:1075-7.