

Letter to the Editor

Early-onset hypogammaglobulinemia: A survey of 44 patients

To the Editor:

Hypogammaglobulinemia corresponds to a heterogeneous group of primary antibody deficiencies (PADs), with or without an absence of B cells.¹ Common variable immunodeficiency (CVID), the most common PAD in adulthood, is, however, much rarer during childhood. A recent analysis of the European Society for Immunodeficiencies Database showed 2 peaks of diagnosis: one before the age of 10 years (33.7%) and the other between the age of 30 and 40 years.² It is thus essential to better describe hypogammaglobulinemia in pediatric patients.¹ Although most of the CVID cases are not associated with identified pathogenic mutations, around 10% of the patients carry a mutation in the gene encoding TACI,³ which appears more likely to be a susceptibility gene than a true CVID-causing gene. Biallelic mutations in the *CD19*, *CD81*, *CD21*, *NFKB*, and *TWEAK* genes were recently shown to cause CVID in children and young adults.¹ More recently, mutations in *PIK3CD* and *PIK3RI*, encoding p110 δ catalytic subunit and p85 α regulatory subunit of phosphoinositide-3-kinase delta (PI3K δ), respectively, were described in patients with PADs and were often associated with a clinical and immunological phenotype resembling CVID.^{4,5}

Our present study sought to better define hypogammaglobulinemia in childhood. We report herein the clinical and biological features of a large retrospective cohort of 44 patients with early-onset hypogammaglobulinemia (onset before the age of 6 years), among the 1098 adult and pediatric patients with hypogammaglobulinemia registered in the CEREDIH.⁶ In the absence of a known genetic defect, diagnosis of hypogammaglobulinemia is difficult. However, strict application of our inclusion and exclusion criteria (Table I), based on immunoglobulin levels (IgG deficiency with or without IgA and/or IgM deficiency, or IgA and IgM deficiency) and T-cell populations, enabled us to exclude other PADs (agammaglobulinemia, defective class-switch recombination) and combined immunodeficiency with T-cell defects. Transient hypogammaglobulinemia of infancy could have been

suspected in younger patients but was unlikely due to our long follow-up period (see Table E1 in this article's Online Repository at www.jacionline.org).

Main clinical and biological characteristics of patients are listed in Table E1 and Fig E1 (in this article's Online Repository at www.jacionline.org). In 40 patients (90%), a diagnosis of hypogammaglobulinemia was prompted by recurrent bacterial infections of the upper and lower respiratory tracts as predominant symptoms. Other infections such as meningitis, cellulitis, gastrointestinal infections, including recurrent salmonella infections, and arthritis were first symptoms in other patients. Most of the cases of pneumonia and bronchiectasis were present at diagnosis (18/20 and 6/9, respectively). Bronchiectasis remained stable or improved under immunoglobulin replacement therapy (IgRT), except in 1 patient in which bronchiectasis occurred under adequate IgRT. We did not observe any peculiar susceptibility to viral or opportunistic infections, as expected for a predominant B-cell defect. Complications such as autoimmune diseases affected 5 patients (11%), and splenomegaly was also found in 5 patients (11%), of which 2 had autoimmunity. One case of Hodgkin lymphoma was reported. Thirty-four patients (77.3%) received IgRT, and 26 received prophylactic antibiotic treatment. Taken as a whole, our observations evoke the clinical features typically observed in CVID of adulthood, except complications such as granuloma and solid cancer, which were not observed. This may be due to the young median age of the study population, early diagnosis and treatment, or to the fact that pediatric hypogammaglobulinemia corresponds to a distinct entity.

With regard to laboratory data, a low total circulating B-cell count (observed only in 7 of 44 patients) was not significantly associated with disease severity. However, a null or low switched memory B (SMB) cell count was found to be associated with a higher frequency of pneumonia and bronchiectasis (Table II). There was no significant association between low circulating SMB cell counts and occurrence of splenomegaly and autoimmunity. Given that all patients with low marginal zone B (MZB) cell counts also had low SMB cell counts, we compared patients with

TABLE I. Inclusion and exclusion criteria of patients

Inclusion criteria	Exclusion criteria
• First symptoms before the age of 6 y • IgG deficiency with or without IgA and/or IgM deficiency, or IgA and IgM deficiency (defined as levels at least 2 SDs below the age-adjusted normal value)	• Agammaglobulinemia (defined as IgM < 0.3 g/L and IgG < 2 g/L and IgA < 0.1 g/L) • Isolated IgG subclass deficiency • Sustained, elevated IgM level • Spontaneous normalization of hypogammaglobulinemia • Syndromic PID (eg, immunodeficiency, centromeric region instability, and facial anomalies syndrome) or other characterized PID with hypogammaglobulinemia (eg, Wiskott-Aldrich syndrome) • Genetically characterized T-cell defect or a combined immunodeficiency (CID) of unknown molecular etiology and defined according to the criteria in the ongoing P-CID study: low T-cell subpopulations (CD4⁺ < 700/mm³ if age < 2 y or < 500 if 2-4 y or < 300 if > 4 y; CD8⁺ < 350/mm³ if < 2 y or < 250 if 2-4 y or < 150 if > 4 y) and/or reduced thymic function (CD45RA⁺CD62L⁺ or CD45RA⁺CD31⁺/CD4⁺ cells < 30% if < 2 y or < 25% if 2-6 y or < 20% if > 6 y) (for more information, please visit www.pcid-study.org)

PID, Primary immunodeficiency.

TABLE II. Characteristics of patients as a function of their SMB and MZB cell counts

SMB cell subset	Low (n = 30)			Normal (n = 13)	
	Low (n = 17)	Normal (n = 13)	P value	Normal (n = 13)	P value
Upper respiratory tract infections	13	11	NS	11	NS
Lower respiratory tract infections	11	12	NS	9	NS
Pneumonia	10	8	NS	2	.017
Bronchiectasis	6	3	NS	0	.041
Autoimmune diseases	2	3	NS	0	NS
Splenomegaly	3	2	NS	0	NS
Gastroenteritis	3	1	NS	6	.02
Invasive acute infection	4	1	NS	2	NS
IgRT	17	6	.0008	11	NS
No response to vaccines	9/14	3/11	NS	1/9	NS
Normal CD40+IL4-induced proliferation	11/16	10/12	NS	9/9	NS
Normal CD40 class-switch recombination	11/16	6/10	NS	9/9	NS
Normal BAFF-induced proliferation	6/13	7/12	NS	2/6	NS
Normal CpG-induced proliferation	6/13	8/12	NS	3/6	NS
Normal anti-A/B allohemagglutinins	2/10	3/9	NS	5/7	NS

BAFF, B-cell activating factor; NS, not significant.

Low SMB and MZB cell counts were defined as being at least 2 SDs below the age-adjusted normal value (NS, $P > .05$).

low SMB cell counts who present either normal or low MZB cell counts. There were no statistically significant differences between these 2 groups, except that the requirement for IgRT was higher in patients with low MZB cell counts, pinpointing the role for this B-cell population in the control of infections (Table II). Two previous studies of CVID reported a correlation between a low memory B-cell percentage (including SMB and MZB) and bronchiectasis, but, in contrast with our observation, also splenomegaly and/or autoimmunity.^{7,8} This discrepancy may be related to the patients' age or the pathogenesis of the B-cell deficiency itself. As observed in adult patients with CVID, we found that autoimmune manifestations were associated with an elevated count of so-called autoreactive (CD21^{low}CD19⁺) B cells⁹: among the 4 tested patients affected by autoimmunity, 2 exhibited high counts of this B-cell subset. Regarding B-cell proliferation or immunoglobulin production induced by different activators (B-cell activating factor, CpG, and CD40L+IL4), we could not find any correlation with poor response and disease severity.

Genetic analyses were performed in some cases. None of the patients was known to be from a consanguineous family; however, a family history of PAD was reported in 13 cases. Nine patients were siblings from 4 unrelated families; 1 had 3 IgA-deficient relatives (the father and 2 brothers); 1 had an IgA-deficient brother and an IgG2-deficient mother; and 2 had a first-degree relative with hypogammaglobulinemia having required IgRT during childhood. This observation argues against the presence of autosomal-recessive disorders but might suggest the presence of either dominant hereditary diseases or polygenic diseases. The *TACI* gene was studied in 14 patients. Two sisters were found to carry compound heterozygous deleterious mutations in *TACI* (C104R and a stop codon mutation S144X). Both patients had normal SMB and MZB cell populations; this is surprising because *TACI* mutations are usually associated with an SMB cell defect.³ CD19[−] or CD81[−] deficiencies were ruled out by normal CD19 expression in all patients. No mutation of *PIK3CD* or *PIK3RI* was found in the 20 tested patients.

Taken together, our data indicate that early-onset hypogammaglobulinemia is a complex disease with not yet defined molecular defect in most cases. Early diagnosis and therapy is

required to avoid complications such as bronchiectasis. Our study clearly shows that counts of SMB and especially MZB cells are good markers for prognosis and adequate follow-up.

We thank Drs Caroline Elie and Marie-Alexandra Alyanakian (Necker Children's University Hospital, AP-HP, Paris, France), respectively, for statistical counseling and for expertise on immunoglobulins plasma dosages. We thank Mrs Monique Forveille and Marie-Céline Deau (Imagine Institute) for technical processing of the samples. Finally, we thank Dr Mathieu C. Tamby for scientific advice. CEREDIH uses the ESID Online Registry to collect data for PID patients.

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This research program received a state subsidy managed by the French National Research Agency as part of the "Investments for the Future" program (reference ANR-01-A0-IAHU). The study was also funded by the French Ministry of Health and the French Association of Patients with Primary Immunodeficiencies (IRIS [Immunodéficience primitive: Recherche, Information, Soutien]). The French National Reference Center for Primary Immune Deficiencies (CEREDIH [Centre de Référence Déficits Immunitaires Hérititaires]) received unrestricted educational grants from LFB, CSL Behring, Baxter Biosciences, GSK, Pfizer, Octapharma, and Orphan-Europe.

Disclosure of potential conflict of interest: S. Kracker has received research support from the Fondation pour la Recherche Médicale (grant no. ING20130526624), la Ligue Contre le Cancer (Comité de Paris). P. Frange has received consultancy fees from and has provided expert testimony for MSD; has received research support from SIDACTION; has a patent with Roche; has received payment for the development of educational presentations from Janssen-Cilag and Bristol Myers Squibb; and has received travel support from Bristol Myers Squibb, Astellas, MSD, ViiV Healthcare, Gilead Sciences, and Janssen-Cilag. P. Cony-Malhoul is a board member for Novartis, has received lecture fees from BMS, has a patent with University Bordeaux 2, and has received travel support from BMS and Novartis. A. Fischer has been supported by a senior European Research Council grant "PIDIMMUN" (grant no. 249816). The rest of the authors declare that they have no relevant conflicts of interest.

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<http://dx.doi.org/10.1016/j.jaci.2015.03.038>

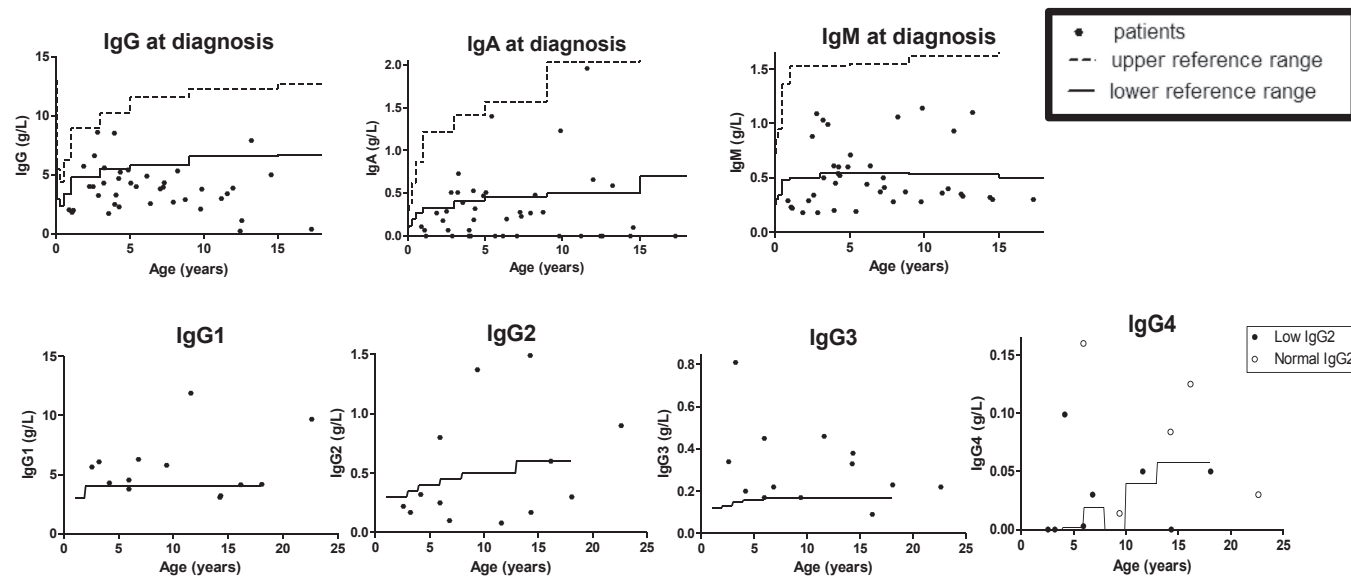


FIG E1. Immunoglobulin classes and isotypes serum levels. IgG₁, IgG₂, IgG₃, and IgG₄ were monitored if IgG levels were above 5 g/L. Data on IgG₄ are represented as a function of low (○) and normal (●) IgG₂ serum levels.

TABLE E1. Demographic, clinical, and biological characteristics of patients

Characteristic	No. (%) or median (min; max)
Sex: male	20 (45.4)
Age at onset (y)	1.77 (0.06; 5.9)
Age at diagnosis (y)	5.15 (0.33; 17.3)
Age at last follow-up (y)	14.46 (4.17; 35.87)
Time between symptom onset and diagnosis years	3.00 (0.0; 13.23)
Follow-up period (y)	6.29 (0.23; 27.09)
Patients with another case in their family	13 (29.5)
IgG deficiency	6 (13.6)
IgG and IgA deficiency	9 (20.4)
IgG and IgM deficiency	3 (6.8)
IgA and IgM deficiency	1 (2.2)
IgG, IgA, and IgM deficiency	25 (56.8)
Patients with upper respiratory tract infections	35 (79.5)
Patients with lower respiratory tract infections	33 (75)
• Repeated acute bronchitis	17 (38.6)
• Pneumonia	20 (45.5)
• Bronchiectasis	9 (20.4)
Patients with gastroenteritis	10 (22.7)
Patients with autoimmune diseases	5 (11.4)
Patients with splenomegaly	5 (11.4)
Patients with lymphoma	1 (2.2)