Original Article

Exclusion of Patients with a Severe T-Cell Defect Improves the Definition of Common Variable Immunodeficiency

Rémi Bertinchamp, MD[a], Laurence Gérard, MD[a,b], David Boutboul, MD[a,c], Marion Malphettes, MD[a,c], Claire Fieschi, MD, PhD[a,c], and Eric Oksenhendler, MD[a,b]; for the DEFI study group *Paris, France*

What is already known about this topic? In 2014, European Society for Immune Deficiency (ESID) proposed a more restricted definition for common variable immunodeficiency (CVID). This definition has not been yet evaluated in a large cohort of patients with primary hypogammaglobulinemia.

What does this article add to our knowledge? Within the French DEFI cohort, the ESID 2014 definition of CVID excluded 18% of the patients considered as CVID with the ESID/Pan-American Group for Immunodeficiency 1999 definition. However, only 2% with profound T-cell defect were excluded.

How does this study impact current management guidelines? Opportunistic infections or very low naive CD4 T cells define a group representing 20% of the initial CVID population (12% with consanguinity and 77% of the deaths), which require specific genetic studies and clinical care.

BACKGROUND: In 2014, the European Society for Immune Deficiencies (ESID) revised the common variable immunodeficiency (CVID) diagnosis criteria by incorporating new clinical and biological markers. The new definition appeared more restrictive but had not yet been evaluated in a large cohort of patients.

OBJECTIVE: The objective of this study was to evaluate the impact of this new definition in a large cohort of patients with primary hypogammaglobulinemia.

METHODS: Evaluation of 3 different CVID definitions (ESID/Pan-American Group for Immunodeficiency [PAGID] 1999, ESID 2014, DEFI 2015) in 521 patients included in the French DEFI study with a diagnosis of primary hypogammaglobulinemia.

RESULTS: Using the ESID/PAGID 1999 definition, 351 patients were classified as CVID. The new ESID 2014 definition excluded 62 (18%) patients. Most of them (n = 56; 90%) had a less severe disease, whereas 6 (10%) presented with a severe disease with major T-cell defect. We propose different criteria (occurrence of opportunistic infection or very low naive CD4+ T-cell count) to define this population with severe T-cell defect. Sixty-two patients fulfilled these criteria, represented 20% of the initial CVID population but accounted for 77% of the deaths, with a 5-year overall survival of 67.6% (95% confidence interval, 51.0-79.6), and were considered as late onset combined immunodeficiency (LOCID).

CONCLUSIONS: The new ESID definition for CVID still fails to exclude a large number of patients with severe T-cell defect. We propose a new definition (DEFI 2015) that excluded more patients with a T-cell defect and consider these patients as LOCID. This population has a poor outcome and should be considered as a distinct group requiring specific care. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2016;4:1147-57)**

Key words: *CVID; Definition; Hypogammaglobulinemia; Immunodeficiency; Late onset combined immunodeficiency; Prognosis*

Common variable immunodeficiency[1] (CVID) is an immunologically and genetically heterogeneous condition characterized by hypogammaglobulinemia on at least 2 immunoglobulin isotypes. CVID, usually categorized as a B-cell defect, is the most frequent symptomatic primary antibody disorder, with a prevalence of approximately 1: 50,000 to 1: 25,000 in the Caucasian population.[2] In the majority of cases, the complex genetic factors leading to this syndrome remain unknown. Genetic mutations/deletions have been found, mainly as homozygous defects (ICOS, CD20, CD19, CD21, CD81, LRBA, TWEAK, CXCL12, NFKB1, NFKB2, IKAROS), and more recently with an autosomic dominant transmission (PI3KCD, CTLA4) in a

[a]Department of Clinical Immunology, Hôpital Saint-Louis, Assistance Publique Hôpitaux de Paris (APHP), Paris, France
[b]EA3518, Université Paris Diderot Paris 7, Paris, France
[c]Inserm U1126, Centre Hayem, Hôpital Saint-Louis, Paris, France
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Corresponding author: Eric Oksenhendler, MD, Department of Clinical Immunology, Saint-Louis Hospital, 1 Avenue Claude Vellefaux, 75010 Paris, France. E-mail: eric.oksenhendler@aphp.fr.
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Abbreviations used
CID- Combined immunodeficiency
CVID- Common variable immunodeficiency
ESID- European Society for Immune Deficiency
HGUS- Hypogammaglobulinemia of undetermined significance
IPH- Idiopathic primary hypogammaglobulinemia
LOCID- Late onset combined immunodeficiency
OS- Overall survival
PAGID- Pan-American Group for Immunodeficiency
SmB- Switched memory B cell

few kindreds.[3] However, these defects still concern only a few percentage of the patients with a CVID or CVID-like phenotype and the penetrance can be incomplete with possible asymptomatic carriers.

In 1999, the European Society for Immune Deficiencies (ESID) and the Pan-American Group for Immunodeficiency (PAGID) proposed consensus criteria for CVID to homogenize the description and the diagnosis of patients. More recently, subgroups of patients with CVID with peculiar clinical and biological phenotype have been described. In addition, these subgroups have been shown to have very different prognoses affecting survival.

The major subgroup classification has been proposed by Chapel[4] and the Oxford group: the group of patients with "infections only" accounts for two thirds of the patients with CVID and the group of patients with "disease-related complications" defined as lymphoproliferation/granuloma, autoimmunity, or enteropathy, for the remaining third. Interestingly, the phenotype can be defined early in the follow-up of the patients and the prognosis is markedly different as patients with infections only have an almost normal life expectancy whereas the overall survival (OS) of patients with complications is around 50% at 30 years from diagnosis. These data have been confirmed in the New York and the French DEFI cohorts.[5]

Another subgroup of patients with a diagnosis of CVID has been described and concerns patients with an associated severe T-cell defect.[6,7] This T-cell defect can be defined clinically on the basis of opportunistic infections or biologically on the counts of circulating CD4+ T cells or naive CD4+ T cells. The definition of this late onset combined immunodeficiency (LOCID) group is still not well defined, but there is a consensus to consider these patients as a definite subgroup requiring specific management and care.[6]

A third issue concerns patients with primary hypogammaglobulinemia who do not fulfill the criteria for a CVID diagnosis. This condition, either considered as "idiopathic primary hypogammaglobulinemia (IPH)" or as "hypogammaglobulinemia of undetermined significance (HGUS)" can be associated with infections and often require immunoglobulin substitution. However, it seems that disease-related complications are very unlikely to occur in this patient population.[8]

These issues led, in 2014, to a revision by the ESID of the CVID diagnosis criteria by including more clinical and biological features such as counts of switched memory B (SmB) cells and CD4+ T cells. The major expected modifications of the CVID population would be the exclusion of the patients with minor B-cell defects on one hand and of the patients with severe T-cell defect on the other hand.[9]

To our knowledge, there is no comparison between populations defined with old and new CVID criteria in a cohort study. We took advantage of the DEFI French national study to address this question and to propose and assess a new definition excluding more patients with severe T-cell defect. The DEFI study has included patients with primary hypogammaglobulinemia and provides an access to centralized data of patients with CVID as well as to patients with partial immunoglobulin deficiency and patients with LOCID. Patients with a history of lymphoma were excluded and considered as secondary hypogammaglobulinemia.

METHODS

Patients

DEFI is a French national study of adults with primary hypogammaglobulinemia (serum IgG level < 5 g/L, or IgA < 0.7 g/L, or IgM < 0.4 g/L, or IgG subclass deficiency).[10] The patients were prospectively enrolled in the study, and a blood sample was collected at entry to perform detailed centralized B- and T-cell phenotyping. Inclusion was delayed in the case of active infection or aggressive immunosuppressive therapy. Exclusion criteria were secondary hypogammaglobulinemia and refusal of consent for participation. All patients gave written informed consent, including possible inclusion in genetic studies, and the study was approved by the local ethics committee.

A total of 671 patients with primary hypogammaglobulinemia were enrolled by 47 centers between April 2004 and June 2014. For each patient, infectious, autoimmune, lymphoproliferative, or tumoral complications were compiled in a clinical file along with the family medical history. Patients with a diagnosis of lymphoma before or within 6 months from CVID diagnosis were excluded from analysis. However, patients who developed lymphoma during follow-up (>6 months) were kept in the analysis and classified as CVID with lymphoproliferative complication. The "infection only" and "disease-related complication," that is, lymphoid proliferation including granuloma, autoimmune cytopenia, or enteropathy with villous atrophy, phenotypes were defined according to the classification proposed by Chapel.[5]

Definitions

All definitions are detailed in Table I.

The ESID/PAGID 1999 criteria.

- CVID was defined according to the 1999 ESID/PAGID criteria.[11]
- HGUS was defined by primary hypogammaglobulinemia not fulfilling CVID diagnosis but with a marked decrease (at least 2 standard deviations [SD] below the mean for age) in IgG or in one of the major IgG subclasses (IgG1, IgG2, IgG3). X-linked agammaglobulinemia (XLA), Good syndrome, selective IgA or IgM deficiency, and hyper-IgM syndrome were excluded.

The ESID 2014 CVID definition. It differs from the ESID/PAGID 1999 as it includes more restrictive criteria: presence of clinical symptoms or family history of antibody deficiency, age at diagnosis above 4 years instead of 2, IgA deficiency mandatory, defect in SmB cells or poor vaccine response, and absence of severe T-cell defect. The presence of a severe T-cell defect that is defined as 2 of the following: CD4 $< 200/\mu$L, naive CD4 $< 10\%$, and T-cell proliferation absent, defines a group of patients who can be considered as combined immunodeficiency (CID). HGUS was

TABLE I. Definitions according to ESID/PAGID 1999, ESID 2014, and DEFI 2015

Diagnosis		ESID/PAGID 1999	ESID 2014	DEFI 2015
IPH/HGUS		Not defined	Marked decrease (at least 2 SD below the mean for age) in IgG Or a marked decrease in one of the major IgG subclasses (IgG1, IgG2, IgG3) And not fulfilling ESID 2014 CVID diagnosis (XLA, Good syndrome and selective IgA, IgM deficiency, and hyper-IgM are excluded)	Marked decrease (at least 2 SD below the mean for age) in IgG Or marked decrease in one of the major IgG subclasses (IgG1, IgG2, IgG3) And not fulfilling DEFI 2015 CVID diagnosis (XLA, Good syndrome and selective IgA, IgM deficiency, and hyper-IgM are excluded)
CVID	Immunoglobulin levels	Marked decrease of IgG (at least 2 SD below the mean for age) And marked decrease in at least IgM or IgA	Marked decrease of IgG And a marked decrease of IgA with or without low IgM levels (measured twice; < 2 SD of the normal levels for age)	Marked decrease of IgG And marked decrease of IgA with or without low IgM levels (measured twice; <2 SD of the normal levels for age)
	Age of diagnosis	And onset at > 2 y of age	And diagnosis after the fourth year of life	And diagnosis after the fourth year of life
	Biological features	And absent isohemagglutinins or poor response to vaccines	And at least one of the following: poor antibody response to vaccines (or absent isohemagglutinins), low switched memory B cells (<70% of age-related normal value) And no evidence of profound T-cell deficiency, defined as 2 of the following: CD4 < 200/μL, naive CD4 < 10%, T-cell proliferation absent	And low switched memory B cells (<10%)
	Clinical features		At least one of the following: increased susceptibility to infection, autoimmune manifestations, granulomatous disease, polyclonal lymphoproliferation, affected family member with antibody deficiency	And no evidence of profound T-cell deficiency, defined as: naive CD4 < 20/μL Or opportunistic infection
	Exclusion criteria	And defined causes of hypogammaglobulinemia have been excluded	And secondary causes of hypogammaglobulinemia have been excluded	And secondary causes of hypogammaglobulinemia have been excluded
LOCID/CID		Not defined	CVID with profound T-cell defect defined as 2 of the following: • CD4 < 200/μL • Naïve CD4 < 10% • T-cell proliferation absent	CVID with profound T-cell defect defined as: Naive CD4 < 20/μL Or opportunistic infection

CID, Combined immunodeficiency; *CVID*, common variable immune deficiency; *ESID*, European Society for Immunodeficiency; *HGUS*, hypogammaglobulinemia of undetermined significance; *IPH*, idiopathic primary hypogammaglobulinemia; *LOCID*, late onset combined immunodeficiency; *PAGID*, Pan-American Group for Immune Deficiency; *SD*, standard deviation; *XLA*, X-linked agammaglobulinemia.

TABLE II. CVID patient characteristics

	CVID ESID/PAGID 1999	CVID ESID 2014	Δ 1999-2014
Population (n)	351	289	62
Age (y)			
at diagnosis	36 (25-48)	35 (25-46)	42 (24-56)
at first symptoms	21 (11-37)	20 (10-35)	25 (13-47)
at inclusion	45 (33-56)	43 (33-54)	49 (34-62)
Male gender	148 (42%)	121 (42%)	27 (44%)
Consanguinity	16 (5%)	16 (6%)	0
Familial	68 (19%)	56 (19%)	12 (19%)
Clinical features			
Infections only	203 (58%)	157 (54%)	46 (74%)
Disease-related complications	148 (42%)	132 (46%)	16 (26%)
Pneumonia	194 (55%)	166 (57%)	28 (45%)
Bronchiectasis	110 (31%)	99 (34%)	11 (18%)
Granuloma	51 (15%)	47 (16%)	4 (6%)
Autoimmune cytopenia	64 (18%)	57 (20%)	7 (11%)
Enteropathy	21 (6%)	20 (7%)	1 (2%)
Lymphoma	12 (3%)	11 (4%)	1 (2%)
Biology			
IgG, g/L	2.1 (0.9-3.6)	1.9 (0.8-3.4)	3.6 (2.0-4.1)
IgA, g/L	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.3 (0.2-0.7)
IgM, g/L	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.2-0.4)
CD19+ B-cell count			
$\times 10^6$/L	101 (48-181)	96 (46-187)	114 (58-173)
SmB-cell count			
$\times 10^6$/L	2 (1-6)	2 (1-4)	13 (5-24)
Percentage	2.0 (0.9-5.0)	1.8 (0.7-3.0)	12.0 (7.0-20.0)
CD4+ T-cell count			
$\times 10^6$/L	559 (391-785)	554 (396-770)	603 (305-911)
Percentage	41.0 (34.0-51.0)	41.0 (33.0-51.0)	43.0 (36.0-49.0)
Naive CD4+ T-cell count			
$\times 10^6$/L	102 (40-253)	94 (39-234)	154 (76-387)
Percentage	23.0 (9.0-38.0)	21.0 (8.0-36.0)	31.0 (17.0-40.0)

Δ, Difference; *CVID*, common variable immunodeficiency; *Enteropathy*, unexplained enteropathy with villous atrophy; *ESID*, European Society for Immunodeficiency; *Naive CD4+ T cell*, (CD4+ CD45RA+ CCR7+) T cells; *PAGID*, Pan-American Group for Immune Deficiency; *SmB*, (CD19+, IgD-, CD27+) switched memory B cells.
Number (%) and median (interquartile range).

defined by primary hypogammaglobulinemia not fulfilling CVID diagnosis but with a marked decrease (at least 2 SD below the mean for age) in IgG or in one of the major IgG subclasses (IgG1, IgG2, IgG3). XLA, Good syndrome, selective IgA or IgM deficiency, and hyper-IgM syndrome were excluded.

The DEFI 2015 CVID definition. It differs from the ESID 2014 as the presence of clinical symptoms and antibody response to vaccine are no more mandatory; the cutoff for SmB-cell defect is fixed to 10% of B cells. The definition of T-cell defect is less restrictive: occurrence of opportunistic infection or naive CD4 cell count below 20×10^6/L. The presence of the T-cell defect defines a group of patients with LOCID.

Statistical analysis

All patients included in the DEFI study with full complete dataset were included in the analysis. Descriptive statistics were reported as medians (interquartile range) or numbers (%). The follow-up began on the inclusion date in the DEFI study and ended in June 2014. To avoid selection bias, OS was calculated from inclusion in the DEFI study until June 2014 or death from any cause. Survivals were estimated using the Kaplan-Meier product-limit method, and compared using a log-rank test. Statistical analysis was conducted using STATA Statistical Software version 11.1 (StataCorp., College Station, Tex).

RESULTS

At the time of analysis, 595 patients included in the DEFI study had been followed for a median of 7.4 years (95% confidence interval [CI], 5.4-8.4). Of them, 62 were excluded because of incomplete data and 12 because of lymphoma at CVID diagnosis or during the following 6 months. Therefore, 521 patients were analyzed.

In the DEFI database, 351 patients fulfilled the ESID/PAGID 1999 criteria for CVID. The median age at diagnosis was 36 years and 58% were female. Patients with infection only had a better prognosis than patients with disease-related complications, with a 5-year OS of 97% versus 87%, respectively ($P = .0006$).

TABLE III. Patient characteristics according to the ESID 2014 definition

	ESID 2014 CVID			
	Total	IO phenotype	DRC phenotype	CID
Population (n)	289	157	132	6
Age (y)				
at diagnosis	35 (25-46)	34 (25-45)	35 (25-48)	39 (10-53)
at first symptoms	20 (10-35)	19 (11-30)	22 (10-36)	26 (8-38)
at inclusion	43 (33-54)	40 (30-53)	47 (35-56)	46 (30-68)
Male gender	121 (42%)	64 (41%)	57 (43%)	5 (83%)
Consanguinity	16 (6%)	7 (4%)	9 (7%)	0
Familial	56 (19%)	34 (22%)	22 (17%)	2 (33%)
Clinical features				
Infections only	157 (54%)	157 (100%)	0 (0%)	0
Disease-related complications	132 (46%)	0 (0%)	132 (100%)	6 (100%)
Pneumonia	166 (57%)	88 (56%)	78 (59%)	5 (83%)
Bonchiectasis	99 (34%)	50 (32%)	49 (37%)	2 (33%)
Granuloma	47 (16%)	0 (0%)	47 (36%)	2 (33%)
Autoimmune cytopenia	57 (20%)	0	57 (43%)	3 (50%)
Enteropathy	20 (6%)	0	20 (15%)	0
Lymphoma	11 (4%)	0	11 (8%)	1 (17%)
Opportunistic infections	15 (5%)	5 (3%)	10 (8%)	2 (33%)
Immunoglobulin substitution	233 (77%)	115 (73%)	102 (82%)	4 (67%)
Biology				
IgG, g/L	1.9 (0.8-3.4)	2 (0.8-3.4)	1.8 (0.8-3.4)	2.9 (1.2-4.3)
IgA, g/L	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.2)	0.3 (0.1-0.3)
IgM, g/L	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.2 (0.1-0.4)	0.2 (0.2-0.3)
CD19+ B-cell count				
$\times 10^6$/L	96 (46-187)	102 (51-190)	89 (41-171)	39 (1-158)
SmB-cell count				
$\times 10^6$/L	2 (1-4)	1 (1-4)	1 (0-4)	1 (0.3-3)
Percentage	1.8 (0.7-3.0)	1.9 (1.0-3.0)	1.3 (0.5-3.1)	0.4 (0.3-2.0)
CD4+ T-cell count				
$\times 10^6$/L	554 (396-770)	569 (414-771)	541 (377-767)	145 (109-182)
Percentage	41.0 (33.0-51.0)	40.4 (33.0-49.0)	41.0 (34.0-52.0)	18.0 (16.2-23.0)
Naive CD4+ T-cell count				
$\times 10^6$/L	94 (39-234)	151 (69-279)	52 (16-133)	5 (1-7)
Percentage	21.0 (8.0-36.0)	29.3 (17.2-42.6)	11.0 (4.0-25.0)	3.9 (1.8-5.0)
Outcome				
Deaths	18 (6.2%)	3 (2%)	15 (11.4%)	4 (66.6%)
5-y OS	92.2%	97.0%	87.6%	50.0%
95% CI	87.2-95.4	91.1-99	78.6-93	11.0-80.3

CI, Confidence interval; *CID*, combined immunodeficiency; *CVID*, common variable immunodeficiency; *DRC*, disease-related complications; *Enteropathy*, unexplained enteropathy with villous atrophy; *ESID*, European Society for Immunodeficiency; *IO*, infection only; *Naive CD4+ T cell*, (CD4+ CD45RA+ CCR7+) T cells; *OS*, overall survival; *SmB*, (CD19+, IgD-, CD27+) switched memory B cells.
Number (%) and median (interquartile range). Immunoglobulin substitution was evaluated at inclusion.

ESID 2014 CVID definition excluded 62 patients (18%) from the CVID group defined with the ESID/PAGID 1999 definition

The new ESID 2014 definition defined 3 groups of patients: a CVID group of patients who fulfill the new criteria (n = 289), a CID group defined by severe T-cell defect criteria that excluded them from a CVID diagnosis (n = 6), and a third group of patients considered as HGUS as presenting with primary hypogammaglobulinemia but not fulfilling the criteria for a CVID diagnosis (n = 226). Detailed descriptions of patients' characteristics are provided in Tables II and III.

ESID 2014 CVID patient. The median age at diagnosis was 35 years, but 23 patients (8%) were diagnosed before the age of 15 years. The infection only group (n = 157) represented 54% of the population, whereas the disease-related complications group (n = 132) represented the remaining 46%. The median naive CD4+ T-cell count was lower in the disease-related complications group than in the infection only group (52×10^6/L vs 151×10^6/L, respectively, $P < 10^{-4}$). Patients with infection only had a better prognosis than patients with disease-related complications, with a 5-year OS of 97% (95% CI, 91.1-99) versus 87.6% (95% CI, 78.6-93), respectively ($P = .004$). In

TABLE IV. Major characteristics of patients with HGUS

	ESID/PAGID 1999	ESID 2014	DEFI 2015
Population (n)	191	226	215
Age (y) at diagnosis	37 (23-55)	38 (23-54)	38 (23-55)
Male gender	82 (43%)	91 (40%)	98 (42%)
Consanguinity	7 (4%)	7 (3%)	7 (3%)
Familial	45 (24%)	55 (22%)	55 (23%)
Clinical features			
Infection only	166 (87%)	195 (86%)	204 (86%)
Disease-related complications	25 (13%)	31 (14%)	32 (14%)
Pneumonia	72 (38%)	85 (38%)	91 (39%)
Bronchiectasis	36 (19%)	43 (19%)	42 (18%)
Granuloma	8 (4%)	9 (4%)	10 (4%)
Autoimmune cytopenia	16 (8%)	17 (7%)	18 (8%)
Lymphoma	4 (2%)	4 (2%)	4 (2%)
Opportunistic infections	0	0	0
Immunoglobulin substitution	91 (48%)	119 (53%)	112 (52%)
Biology			
IgG, g/L	5.8 (4.8-7.7)	5.2 (3.9-6.9)	5.4 (4.1-6.9)
IgA, g/L	0.9 (0.4-1.7)	0.8 (0.3-1.5)	0.8 (0.3-1.6)
IgM, g/L	0.6 (0.4-1.1)	0.6 (0.3-1.0)	0.6 (0.3-1.0)
CD19 + B-cell count			
$\times 10^6$/L	136 (62-215)	135 (70-205)	135 (62-205)
SmB-cell count			
$\times 10^6$/L	12 (5-26)	12 (5-25)	13 (6-27)
Percentage	11.0 (5.0-17.0)	11.2 (5.0-18.0)	12.0 (6.0-19.0)
CD4+ T-cell count			
$\times 10^6$/L	811 (176-510)	771 (508-1043)	777 (508-1057)
Percentage	45.0 (37.3-52.0)	44.2 (38.0-52.0)	44.2 (38.0-51.7)
Naive CD4+ T-cell count			
$\times 10^6$/L	327 (176-510)	286 (144-487)	292 (150-491)
Percentage	42.2 (28.0-51.0)	38.5 (25.7-50.3)	39.6 (24.3-50.2)
Outcome			
Deaths	7 (3.2%)	7 (3.2%)	7 (3.2%)
5-y OS	98.0%	94.9%	94.5%
95% CI	93.8-99.3	87.6-97.9	86.8-97.8

Enteropathy, unexplained enteropathy with villous atrophy; *ESID*, European Society for Immunodeficiency; *HGUS*, hypogammaglobulinemia of undetermined significance; *Naive CD4+ T cell*, (CD4+ CD45RA+ CCR7+) T cells; *OS*, overall survival; *PAGID*, Pan-American Group for Immune deficiency; *SmB*, (CD19+, IgD-, CD27+) switched memory B cells.
Immunoglobulin substitution was evaluated at inclusion.

this CVID group, 15 patients (6%) had developed opportunistic infection and only 4 of them had a CD4+ T-cell count below 200×10^6/L.

ESID 2014 CID patients. The CID group that was defined by the presence of a severe T-cell defect remains very small accounting for only 6 patients (2%). Age at diagnosis was not different from that observed in patients with CVID. The clinical phenotype was more severe with a high frequency of pneumonia (83%) and all 6 patients had disease-related complications. Global T-cell lymphopenia was demonstrated in most patients with a severe defect in CD4+ and naive CD4+ T cells. In addition, the median B-cell count was markedly low 39×10^6/L (interquartile range [IQR], 1-158) and 3 of the 6 patients had a CD19+ B-cell count below 1%.

ESID 2014 HGUS patients. This group included 226 patients with moderate hypogammaglobulinemia (n = 127), IgA deficiency + IgG subclass deficiency (n = 31), IgM deficiency + IgG subclass deficiency (n = 12), and isolated IgG subclass deficiency (IgG1 and/or IgG2 and/or IgG3) (n = 56). Disease-related complications (14%) were less frequent than in patients with CVID. However the frequency of pneumonia and bronchiectasis remained high in this patient population, 38% and 19%, respectively (Table IV).

Patients with CVID excluded with the new ESID 2014 definition. We did not observe major differences in the clinical and biological phenotypes between the patients with CVID selected with the ESID/PAGID 1999 and the ESID 2014 definitions. Sixty-two patients (18%), who fulfilled the

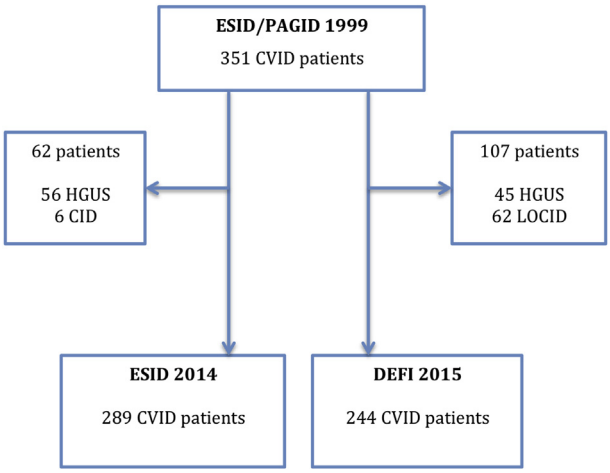


FIGURE 1. Flowchart of patients with common variable immunodeficiency (CVID) according to definitions.

ESID/PAGID 1999 CIVD definition, were no more considered as CVID when using the new ESID 2014 definition (Figure 1). The reasons for exclusion were as follows: age at diagnosis below 4 years in 5 patients, normal IgA levels in 34 patients, SmB cells $\geq$ 10% in 42 patients, and severe T-cell defect (CD4+ count $<$ 200 $\times$ 10^6/L and naive CD4+ T cells $<$ 10%) in 6 patients. None were excluded because of a lack of clinical symptoms. Therefore, 56 patients were reclassified as HGUS and 6 as CID.

Survival. The OS appeared to be very similar in patients with HGUS or CVID whatever the definition used with an estimate 5-year OS above 92% (Figure 2). In contrast, the 6 patients defined as CID with the ESID 2014 definition had a very poor prognosis as 4 died providing a 5-year OS around 50% (Figure 2).

The DEFI 2015 CVID definition defines a larger group of patients with severe T-cell defect and poor outcome

DEFI 2015 CVID patients. The DEFI 2015 definition selected 244 patients fulfilling the criteria. The median age at diagnosis was 34 years and 60% were female. Among this population, 18 (7%) patients were aged below 15 years at diagnosis. At evaluation, 19 (8%) patients were treated with low-dose steroids and 19 (8%) patients with immunosuppressive therapy. Patients with infection only and patients with disease-related complications were very similar in terms of frequency of pneumonia, bronchiectasis, and regarding B- and T-cell phenotypes (Table V). Even after excluding the patients with the lowest naive CD4 cell count (LOCID group), the naive CD4+ T-cell count was still lower in the disease-related complications group (median: 96 $\times$ 10^6/L; IQR, 41-200) than in the infection only group (median: 172 $\times$ 10^6/L; IQR, 78-291; P = .0001). However, the OS was not different in patients with infection only, 98.9% (95% CI, 92.4-99.8), and in patients with disease-related complications, 96.9% (95% CI, 87.8-99.2) (P = .09).

DEFI 2015 LOCID patients. When we used opportunistic infections and naive CD4+ T cells to define the LOCID group, 62 patients fulfilled the definition. The age at onset of symptoms

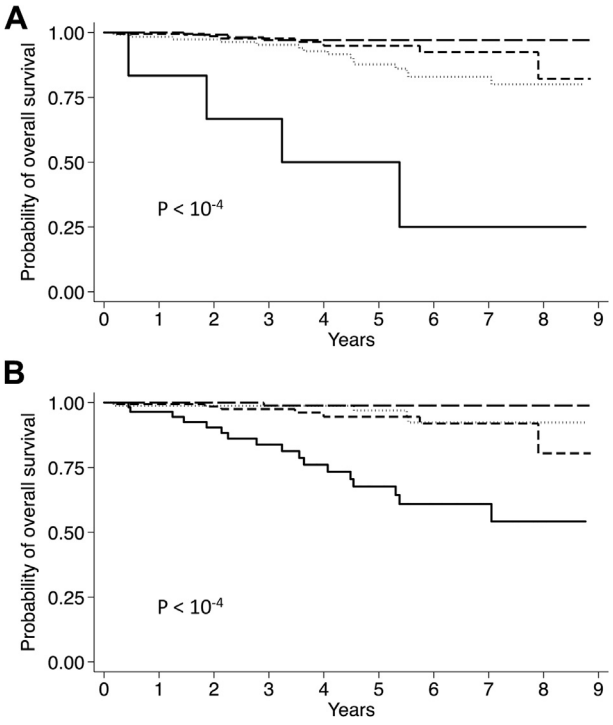


FIGURE 2. Kaplan-Meier plot (comparison using a log-rank test) of overall survival (OS) in patients with primary hypogammaglobulinemia. OS of patients with LOCID (plain line), HGUS (dashed line), infection only CVID (long dashed line), and CVID with disease-related complications (dotted line). ESID 2014 definition (**A**): HGUS vs CVID IO (P = .22), HGUS vs CVID DRC (P = .10), CVID IO vs CVID DRC (P = .004), LOCID vs HGUS ($P < 10^{-4}$), LOCID vs CVID IO ($P < 10^{-4}$), LOCID vs CVID DRC ($P < 10^{-4}$). DEFI 2015 definition (**B**): HGUS vs CVID IO (P = .03), HGUS vs CVID DRC (P = .56), CVID IO vs CVID DRC (P = .09), LOCID vs HGUS ($P < 10^{-4}$), LOCID vs CVID IO ($P < 10^{-4}$), LOCID vs CVID DRC ($P < 10^{-4}$). *CVID*, Common variable immunodeficiency; *DRC*, disease-related complications; *ESID*, European Society for Immune Deficiency; *HGUS*, hypogammaglobulinemia of undetermined significance; *IO*, infection only; *LOCID*, late onset combined immunodeficiency.

was not different from that observed in patients with CVID: median, 22 years versus 20 years, respectively. Familial consanguinity was observed in 7 patients (12%). Among these patients, 17 presented with at least 1 opportunistic infection: 8 with invasive mycoses (aspergillosis in 3, candidiasis in 3, cryptococcosis in 1, and pneumocystosis in 1), 4 with cytomegalovirus-associated disease, 1 with adenovirus, 1 with Kaposi sarcoma, 2 with toxoplasmosis, and 1 with cryptosporidiosis. Interestingly, the median CD4+ T-cell count was quite high (398 $\times$ 10^6/L) in this population but 5 patients had a naive CD4+ T-cell count below 20 $\times$ 10^6/L, all of them presenting with invasive fungal infection. Besides opportunistic infections, these patients had a severe disease with a high frequency of pneumonia (71%) and bronchiectasis (42%), a very high proportion of disease-related complications (81%), and a poor outcome with an estimate 5-year OS of 67.6% (95% CI, 51.1-79.7), significantly different from the 98.0% (95% CI, 93.8-99.3) observed in the CVID

TABLE V. Patient characteristics according to the DEFI 2015 definition

	DEFI 2015 CVID			
	Total	IO phenotype	DRC phenotype	LOCID
Population (n)	244	153	91	62
Age (y)				
at diagnosis	34 (23-46)	35 (25-46)	34 (21-46)	39 (27-53)
at first symptoms	20 (11-34)	20 (11-33)	21 (10-35)	22 (9-42)
at inclusion	41 (31-53)	40 (31-53)	42 (33-53)	52 (39-61)
Male gender	98 (40%)	61 (40%)	37 (41%)	34 (55%)
Consanguinity	9 (4%)	5 (3%)	4 (4%)	7 (12%)
Familial	48 (20%)	31 (20%)	17 (19%)	10 (16%)
Clinical features				
Infection only	153 (63%)	153 (100%)	na	12 (19%)
Disease-related complications	91 (37%)	na	91 (37%)	50 (81%)
Pneumonia	131 (54%)	83 (54%)	48 (53%)	44 (71%)
Bronchiectasis	78 (32%)	49 (32%)	29 (31%)	26 (42%)
Granuloma	28 (11%)	0	28 (31%)	21 (34%)
Autoimmune cytopenia	40 (16%)	0	40 (44%)	22 (35%)
Enteropathy	11 (4.5%)	0	11 (12%)	9 (14.5%)
Lymphoma	4 (2%)	0	4 (4%)	8 (13%)
Opportunistic infections	0	0	0	17 (27%)
Immunoglobulin substitution	180 (74%)	111 (62%)	69 (38%)	54 (87%)
Biology				
IgG, g/L	2.0 (0.9-3.5)	2.1 (0.8-3.4)	2.0 (1.1-3.6)	1.8 (0.9-2.9)
IgA, g/L	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.3)	0.1 (0.1-0.3)
IgM, g/L	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.4)	0.2 (0.1-0.3)
CD19+ B-cell count				
$\times 10^6$/L	105 (59-196)	110 (56-194)	94 (59-203)	48 (6-108)
SmB-cell count				
$\times 10^6$/L	2 (1-5)	2 (1-5)	2 (0.3-5)	1 (0.2-2)
Percentage	2.0 (0.9-4.0)	2.0 (1.0-4.0)	2.0 (0.6-4.0)	0.9 (0.4-2.0)
CD4+ T-cell count				
$\times 10^6$/L	583 (422-787)	594 (437-778)	559 (391-811)	383 (245-603)
Percentage	41.0 (34-49.9)	41.0 (33.0-49.0)	41.2 (36.0-52.0)	39.0 (29.0-51.0)
Naive CD4+ T-cell count				
$\times 10^6$/L	137 (67-270)	172 (78-291)	96 (41-200)	11 (6-17)
Percentage	26.4 (14.0-39.5)	31.6 (20.2-43.4)	19.1 (9.6-32.9)	2.9 (1.5-5.8)
Outcome				
Deaths	5 (2.0%)	1 (0.6%)	4 (4.4%)	17 (27.4%)
5-y OS	98.0%	98.9%	96.9%	67.6%
95% CI	93.8-99.3	92.4-99.8	87.8-99.2	51.1-79.7

CI, Confidence interval; *CVID*, common variable immunodeficiency; *DRC*, disease-related complications; *Enteropathy*, unexplained enteropathy with villous atrophy; *IO*, infection only; *LOCID*, late onset combined immunodeficiency; *Naive CD4+ T cell*, (CD4+ CD45RA+ CCR7+) T cells; *OS*, overall survival; *SmB*, (CD19+, IgD-, CD27+) switched memory B cells.

Number (%) and median (interquartile range). Immunoglobulin substitution was evaluated at inclusion.

patients group ($P < .001$; Figures 2 and 3). The global T-cell count was very low in this population and the B-cell count was also severely depressed, with a median CD19+ cell count of 48 $\times$ 10^6/L and SmB cells almost absent in all patients (Table V).

DISCUSSION

In the absence of specific genetic markers, the definition of CVID has always been challenging and mainly a diagnosis of exclusion. In 1999, a consensus was reached and since that date a single definition was used both for scientific and clinical purposes. However, there are still some issues when using this definition: (1) the use of isohemagglutinins and antibody response to vaccination are associated with difficulties in results interpretation in the absence of consensual techniques and therefore often not used in the initial evaluation of primary hypogammaglobulinemia in a common practice[9]; (2) the clinical spectrum of CVID is very heterogeneous with different subgroups associated with different outcomes[12]; (3) some patients present with evidence of associated T-cell defect and could be considered as LOCID but still fulfilled the criteria for CVID[6]; (4) in a few patients, a congenital genetic abnormality can be demonstrated and these patients can be considered

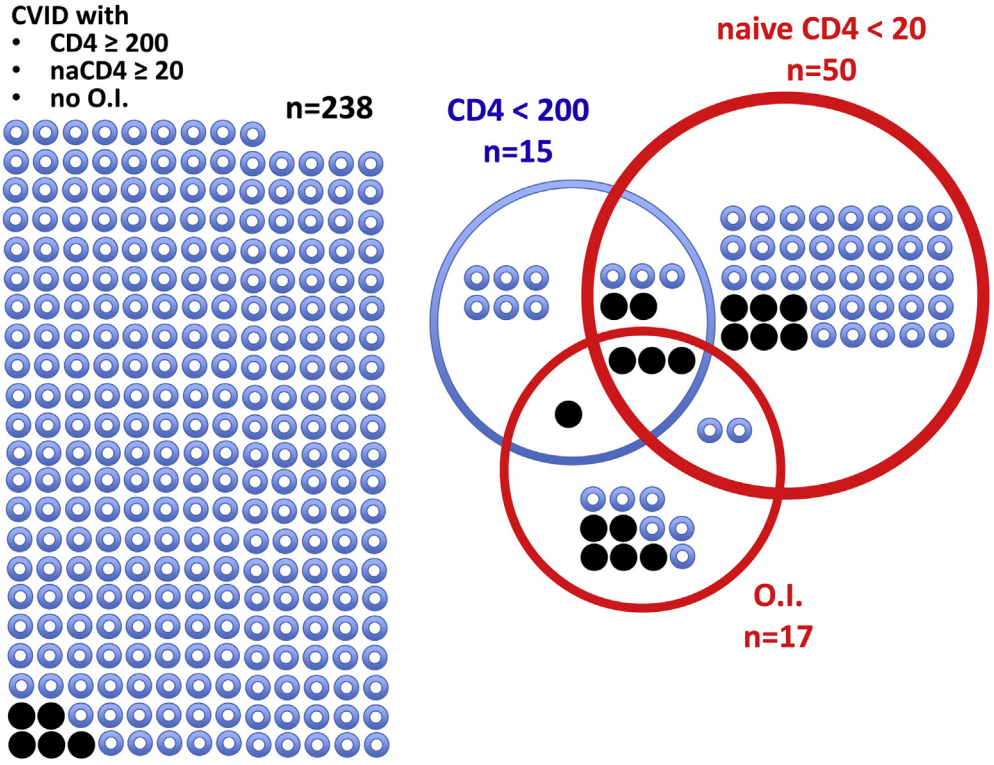


FIGURE 3. Distribution of the patients according to DEFI 2015 criteria: 244 patients with CVID and 62 patients with LOCID (red circles). After 7-year follow-up, 284 patients were alive (blue dots) and 22 patients had died (black dots). *CVID*, Common variable immunodeficiency; *LOCID*, late onset combined immunodeficiency.

separately on a scientific basis but still, for clinical care, belong to the CVID group.

In 2014, to improve CVID definition, ESID proposed new criteria. The major differences are the inclusion of clinical features, a minimum age of 4 years for diagnosis, IgA deficiency mandatory, defect in SmB cells that can be used instead of isohemagglutinins and antibody response to vaccines, and no evidence for severe T-cell defect.[13] To assess the new ESID 2014 criteria for CVID, we have used the French DEFI database to test both definitions. As expected with the more restrictive 2014 definition, less patients fulfilled the new criteria. The new definition led to the exclusion of 18% of the patients previously considered as CVID. This did not affect the demographic characteristics of the CVID population. We did not find significant differences in both clinical and biological markers. Survival was not different in the 2 groups ($P = .09$). Most of the excluded patients presented with higher serum immunoglobulin levels and higher SmB-cell counts and were reclassified as HGUS. These patients had a less severe disease with a more frequent infection only phenotype. However, most of them were symptomatic with pneumonia and/or bronchiectasis and most of them were yet receiving immunoglobulin substitution at entry into the DEFI study.

The ESID 2014 definition of severe T-cell defect was very restrictive and only 2% of the initial CVID population was excluded because of these criteria. These patients represent the most severe aspect of the disease and obviously should be considered as patients with CID. Most of these patients present both severe B- and T-cell defect, but in opposition with classical CID, the onset of the disease is usually delayed to early adulthood (median, 26 years), which is similar to what is observed in the other patients with CVID (median, 20 years). However, first symptoms suggesting a CVID-like phenotype may occur during childhood and most of the genetic disorders have been discovered in kindreds with symptomatic children, suggesting that pediatricians should keep looking at possible known gene defects in children presenting with a CVID-like phenotype.

Within a median follow-up of 7.4 years (95% CI, 5.4-8.4), 4 of the 6 patients died, providing an estimate 5-year OS around 50%. By using this definition, we still observe a difference in the prognosis of patients with CVID with infection only (5-year OS: 97%; 95% CI, 91.1-99) and disease-related complications (5-year OS: 87.6%; 95% CI, 78.6-93) ($P = .004$). Some of these patients, just as children diagnosed with CID, may require bone marrow transplantation, whereas patients with CVID usually only require immunoglobulin replacement therapy.

As we had previously shown that a larger proportion of patients may present with LOCID associated with poor prognosis, we evaluated an alternate definition that is very similar to the ESID 2014 definition excepted for the T-cell defect criteria. We defined new surrogate markers for T-cell defect associated with poor outcome.[6] With this perspective the CD4-cell count did not appear to be such an accurate prognostic marker, at least on survival. The median CD4-cell count in patients who developed opportunistic infections was not severely depressed (398×10^6/L). In addition, among the

7 patients with a CD4-cell count below 200 × 10^6/L and naive CD4 T cells above 20 × 10^6/L, only 1 had developed opportunistic infection and died. In contrast, the occurrence of opportunistic infections or a very low level of naive CD4+ T cells was clearly associated with typical features of CID and poor prognosis. Using these markers we defined a population that represented 20% of the initial CVID population by increasing the number of patients with a severe T-cell defect from 6 to 62. This population not only exhibited a severe T-cell defect but also a more profound B-cell defect and a poor outcome. Interestingly, the demographics of this LOCID population is not very different from that of the patients with CVID with similar age for onset of symptoms and diagnosis, similar proportion of familial cases, and slightly higher rate of consanguinity (Table V). The systematic detection of a severe defect in naive CD4+ T cells is therefore pivotal to diagnose these patients even before the occurrence of an opportunistic infection.

A diagnosis of LOCID (vs CID) may be used in patients with onset of symptoms or diagnosis in late childhood or adulthood, that is, in patients initially considered with a CVID-like phenotype.

These patients had a very high frequency of disease-related complications, and once they were excluded from the CVID group, patients with infection only phenotype and patients with disease-related complications shared a very similar outcome with a 5-year OS of 98.9% versus 96.9%, respectively ($P = .09$). These data suggest that the poor outcome that had been observed in patients with disease-related complications from several cohorts was in fact related to the presence of a subgroup of patients with associated severe T-cell deficiency. According to these data and in addition to the classical care including immunoglobulin replacement therapy, these patients with LOCID deserve a specific attention not only for genetic studies but also for daily care.

On the other hand, we used the same criteria as ESID regarding the B-cell defect and therefore excluded the same patients with mild B-cell defect and reclassified them in the HGUS group. The acronym HGUS, by referring to the patients with monoclonal gammopathy of undetermined significance, was preferred to IPH as IPH does not say more or less than CVID, and because HGUS suggests that the diagnosis may evolve and that some patients with HGUS may, over time, fulfill CVID criteria. The HGUS group enlarged when using the new CVID definitions. However, although presenting with a milder immune deficiency, most of these patients were symptomatic with a high prevalence of pneumonia and bronchiectasis but with very few disease-related complications. Most of these patients (86%) exhibited an infection only phenotype and should have access to immunoglobulin substitution.

CONCLUSIONS

The new ESID criteria definitely improve the definition of CVID. However, when testing this definition against the older one within a single national cohort, 2 limitations could be disclosed: (1) a significant proportion (16%) of the patients were excluded from a CVID diagnosis and reclassified as HGUS; (2) only the most severe patients (2%) with profound T-cell defect were excluded and reclassified as CID.

Most of the patients with HGUS from our study were symptomatic and required immunoglobulin substitution. One should be caution when reclassifying a patient from CVID to HGUS in terms of possible access to immunoglobulin therapy.

On the other hand, the definition used to define patients with T-cell defect appeared too restrictive. We propose to keep the new criteria regarding the B-cell defect and to propose a definition of the T-cell defect based on the prognostic value of clinical and biological markers of this defect. Using opportunistic infections and naive CD4+ T-cell count, we could define a group of patients with LOCID representing 20% of the initial CVID population and accounting for 77% of the deaths observed in this population. These patients definitely require specific genetic studies, management, and clinical care. Moreover, once these patients with LOCID are excluded from the diagnosis of CVID, the CVID group appeared much more homogeneous in terms of prognosis as patients with infection only and patients with disease-related complications phenotypes experienced similar OS.

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Coordination: E. Oksenhendler, Hôpital Saint Louis, Paris.

Clinical centers: Hôpital Saint Louis, Paris: C. Fieschi, M. Malphettes, L. Galicier, D. Boutboul, J. P. Fermand. Bordeaux: J. F. Viallard. Limoges: A. Jaccard. Tours: C. Hoarau, Y. Lebranchu. Hôpital Cochin, Paris: A. Bérezné, L. Mouthon. HEGP, Paris: M. Karmochkine. Marseille: N. Schleinitz. Lyon Sud: I. Durieu, R. Nove-Josserand. Clermont-Ferrand: V. Chanet. Montpellier: V. Le-Moing. Roubaix: N. Just. Hôtel-Dieu, Paris: C. Salanoubat. Reims: R. Jaussaud. Hôpital Necker, Paris: F. Suarez, O. Hermine. Le Mans: P. Solal-Celigny. Lille: E. Hachulla. Perpignan: L. Sanhes. Angers: M. Gardembas, I. Pellier. Troyes: P. Tisserant. Lyon Armée: M. Pavic. Dijon: B. Bonnotte. Pitié-Salpêtrière, Paris: J. Haroche, Z. Amoura. Toulouse: L. Alric, M. F. Thiercelin, L. Tetu, D. Adoue. Nancy Vandoeuvre: P. Bordigoni. Lyon Croix Rousse: T. Perpoint. Lyon Hotel-Dieu: P. Sève. Besançon: P. Rohrlich. Strasbourg: J. L. Pasquali, A.S. Korganow, P. Soulas. Hôpital Foch, Suresnes: L. J. Couderc, E. Catherinot. Montauban: P. Giraud. Hôpital Saint-Louis, Pédiatrie, Paris: A. Baruchel. Clermont-Ferrand 2: I. Deleveau. Kremlin-Bicêtre: F. Chaix. Hôpital Trousseau, Paris: J. Donadieu. Rouen: F. Tron. Bobigny: C. Larroche. Aix: A. P. Blanc. Nantes: A. Masseau, M. Hamidou. Nancy: G. Kanny, M. Morisset. Poitiers: F. Millot. Bondy: O. Fain. Hôpital Bichat, Paris: R. Borie. Rennes: A. Perlat. CHU de Caen: B. Bienvenue.

Labs:

Pitié-Salpêtrière, INSERM U543, Paris: B. Autran, G.Gorochov, JL. Garnier.

Saint-Louis, Immunologie, Paris: H. Moins, G. Maki.

Inserm U1126, Saint-Louis, Paris: C. Fieschi, M. Malphettes, D. Boutboul.

Data management and statistics: L. Gérard.

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