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Original Article

Should mild hypogammaglobulinemia be managed as severe hypogammaglobulinemia? A study of 389 patients with secondary hypogammaglobulinemia

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ABSTRACT

Background: Although secondary hypogammaglobulinemia is more frequent than primary hypogammaglobulinemia, its etiology and management are poorly described, particularly for mild hypogammaglobulinemia.
Methods: This retrospective observational study included all adult patients with a gammaglobulin level <6.4 g/L on serum electrophoresis identified at Dijon teaching hospital between April and September 2012. Clinico-biological features, etiologies and infectious complications were collected at inclusion and compared between group 1 (gammaglobulin <5 g/L, severe hypogammaglobulinemia), and group 2 (gammaglobulin <6.4 and ≥5 g/L, mild hypogammaglobulinemia).
Results: Among the 4011 serum electrophoreses, 570 samples from 389 patients had gammaglobulin levels below 6.4 g/L: 156 (40%) in group 1 and 233 (60%) in group 2. Mean age ± SD was 67 (15) years, and sex ratio was 1.04 (M/F) with no difference between the two groups. An etiology was identified in 79% and 58% of patients in groups 1 and 2, respectively ($p < 0.0001$). The main etiologies were similar in both groups and included malignant hemopathy treated with cytostatic agents (n = 129, 33%), smoldering or newly-diagnosed hemopathy without treatment (n = 49, 13%) and immunosuppressive treatment (n = 91, 23%). The incidence of hypogammaglobulinemia-related infections was 22/100/year, with no significant difference between the two groups ($p = 0.17$). Vaccination coverage against pneumococcus was 33%, and higher in group 1 (46% vs. 24%; $p < 0.0001$). When no cause was known at inclusion, an etiology was discovered in 22/130 patients (17%), 11 in each group.
Conclusions: Though mild hypogammaglobulinemia does not meet the classical criteria for hypogammaglobulinemia (<5 g/L), the etiology and infectious risk are similar. It therefore requires investigation and vaccination.

1. Introduction

Hypogammaglobulinemia diagnosed on serum protein electrophoresis (SPE) is a diagnostic challenge for clinicians. After confirmation on a second electrophoresis, it is essential to identify a cause and prescribe a treatment when possible [1,2]. Hypogammaglobulinemia can be due to a variety of conditions, which can be divided into immunoglobulin production diseases such as lymphoid hemopathies (most commonly chronic lymphocytic leukemia (CLL) and multiple myeloma (MM)), infections (human immunodeficiency virus (HIV), parvovirus B19, Epstein–Barr virus (EBV), cytomegalovirus (CMV)) [1,2], medications (mainly antiepileptic and immunosuppressive therapies (IST)) and immunoglobulin loss diseases such as enteropathies or renal amyloidosis. When no cause is identified, a diagnosis of primary immune deficiency, most frequently common variable immunodeficiency (CVID) or Good syndrome in adults, has to be made [1,2].

While the incidence, findings and infectious consequences of CVID are well documented [3,4], little is known about the epidemiology, management and complications of secondary hypogammaglobulinemia, although these conditions are more frequent than primary hypogammaglobulinemia. Secondary hypoglobulinemia is found in 27% to 52% of CLL, depending on the definition of hypogammaglobulinemia and the stage and duration of CLL [5,6]. Under anti-CD20 therapy,

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38.5% of patients has transient hypogammaglobulinemia, essentially depending on the duration of treatment [7]. However, hypogammaglobulinemia may promote infections. About 38% of patients suffering from invasive encapsulated *Streptococcus pneumoniae* or *Haemophilus influenzae* infections presents hypogammaglobulinemia [8]. Therefore patients with hypogammaglobulinemia should be vaccinated against *S. pneumoniae* and influenza [9]. Intra-venous immunoglobulin (IVIg) therapy may be administered in secondary hypogammaglobulinemia only when severe and recurrent infections occur, especially in CLL and MM, even if this treatment is still debated [10,11].

Furthermore, the definition of hypogammaglobulinemia is still discussed even though a serum level of immunoglobulin (Ig) under 5 g/L has been arbitrarily defined for CVID diagnosis [2,12]. However, the lower limit of normal for gammaglobulin (γGb) on SPE is usually higher, around 7 g/L, depending on the manufacturer of the SPE kit [6,7]. In addition, little is known about patients who present mild hypogammaglobulinemia, and there is still no consensus on how such patients should be managed.

In this study, we compared etiologies, infectious complications and management (diagnostic strategy and vaccination coverage) of hypogammaglobulinemia in group 1 (severe hypoγGb under 5 g/L) and in group 2 (mild hypoγGb from 5 to 6.4 g/L).

2. Methods

2.1. Study design

A retrospective, single-center, observational study of all adults with hypogammaglobulinemia under 6.4 g/L, which was the main French national threshold, recorded between April 1st and September 31st 2012 in the biochemistry laboratory of a 1772-bed teaching hospital (Dijon CHU—France) was performed. A second electrophoresis was recorded when available. Clinical and biological data as well as the etiologies of the hypogammaglobulinemia were collected at the time of inclusion. Patients diagnosed with primary immunodeficiency or "false" hypogammaglobulinemia (cryoglobulinemia, hemodilution) were excluded. Serum levels of γGb were analyzed by SPE in the immunology laboratory of Dijon CHU on a Sebia Hydrasys system (Sebia, Evry, France) with agarose gel reagents (Hygragel ref 4140, Sebia). Total protein concentrations were assessed using a modified biuret reaction on a Dimension Vista analyzer (Siemens Healthcare Diagnostics, Deerfield USA).

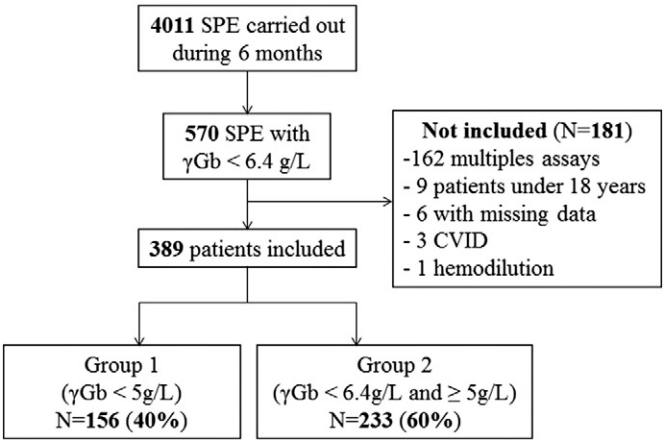

Fig. 1. Flow chart showing the selection of patients with secondary hypogammaglobulinemia.

2.2. Data collection

Common causes of hypogammaglobulinemia such as hematological diseases (MM, CLL, B-cell lymphoma, AL amyloidosis, monoclonal gammopathy of unknown significance (MGUS)), drugs, Ig leakages (nephrotic syndrome, protein-losing enteropathy, capillary leakage), and infections (HIV, EBV, CMV, parvovirus B19) [1,2,13] were identified. Demographic data, biological findings, vaccination against *S. pneumoniae* and intravenous Ig (IVIg) therapy were recorded. Infections that occurred during the year before the inclusion were analyzed and ear nose throat (ENT), respiratory or meningeal infections were considered related to the hypogammaglobulinemia. For patients for whom no etiology of hypogammaglobulinemia was identified, the initial clinical, biological presentation and complementary investigations that were performed to find a cause were collected. Blood tests (albumin, creatinine, calcemia, hemoglobin count, SPE, immunoglobulin test, serum immunofixation electrophoresis (IFE), kappa/lambda light chain ratio, lymphocyte immunophenotyping), urinary exams (proteinuria (g/day), urinary electrophoresis and IFE), medullogram, osteomedular biopsy and imaging (tomodensitometry and positron emission tomography scan) were collected. Data from the two groups were compared: patients with γGb level <5 g/L (group 1: severe hypogammaglobulinemia) and those with γGb level ≥5 and <6.4 g/L (group 2: mild hypogammaglobulinemia). The study was outside the Huriet act, and in accordance with the local ethics committees of Dijon University Hospital.

2.3. Statistics

Continuous variables were expressed with means ± standard deviations (SD), and categorical variables with frequencies and

Table 1
Demographic data and spectrum of etiologies of 389 adult patients with hypogammaglobulinemia: comparison of group 1 (gammaglobulin level <5 g/L) and group 2 (gammaglobulin level ≥5 g/L and <6.4 g/L).

	Total	Group 1	Group 2	p values
	n = 389	n = 156	n = 233	
Demographic data				
Age, mean (SD)	67 (15)	68 (13)	67 (16)	0.87
Male	198 (51)	81 (52)	117 (50)	0.74
Known etiology	259 (67)	123 (79)	136 (58)	<.0001
Etiology discovered after investigation	22 (6)	11 (7)	11 (5)	0.33
No etiology	108 (28)	22 (14)	86 (37)	<.0001
Hemopathy without IST	49 (13)	24 (15)	25 (11)	0.18
Multiple myeloma	16 (4)	9 (6)	7 (3)	0.18
Lymphoma	12 (3)	5 (3)	7 (3)	1.0
Chronic lymphocytic leukemia	9 (2)	7 (5)	2 (1)	0.03
MGUS	9 (2)	2 (1)	7 (3)	0.33
Others	3 (1)	1 (1)	2 (1)	1.0
Hemopathy with chemotherapy or IST	129 (33)	74 (47)	55 (24)	<0.0001
Treated multiple myeloma	89 (23)	51 (33)	38 (16)	<0.0001
Treated lymphoma	21 (5)	9 (6)	12 (5)	0.79
Treated chronic lymphocytic leukemia	10 (3)	8 (5)	2 (1)	0.02
Treated AL amyloidosis	6 (2)	4 (3)	2 (1)	0.22
Others	4 (1)	2 (1)	2 (1)	1.0
Drug	92 (24)	28 (18)	64 (28)	0.03
Corticoid only	40 (10)	14 (9)	26 (11)	0.49
IST in association	46 (12)	11 (7)	35 (15)	0.02
Cancer chemotherapy	5 (1)	3 (2)	2 (1)	0.39
Anti-epileptic drug	1	0	1	
Leakage of immunoglobulin				
Nephrotic syndrome	8 (2)	6 (4)	2 (1)	0.06
Protein-losing enteropathy	1	1	0	
Infection				
HIV	1	1	0	
EBV	1	0	1	

All data are represented as number (%), except age: mean (SD). Abbreviations: MGUS: monoclonal gammopathy of undetermined significant; IST: immunosuppressive therapies; HIV: human immunodeficiency virus; EBV: Epstein–Barr virus.