Joint Bone Spine 78 (2011) 241–245

Available online at ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Review

Diagnostic strategy for patients with hypogammaglobulinemia in rheumatology

Maxime Samson[a,b], Sylvain Audia[a,b], Daniela Lakomy[b,c], Bernard Bonnotte[a,b], Christian Tavernier[d], Paul Ornetti[d,*,e]

[a] Department of Internal Medicine and Clinical Immunology, Dijon University Hospital, 21079 Dijon, France
[b] CR Inserm U866, Lipids Nutrition Cancer, 21000 Dijon, France
[c] Laboratory of Immunology, Dijon University Hospital, 21079 Dijon, France
[d] Department of Rheumatology, hôpital général, Dijon University Hospital, 3, rue du Faubourg-Raines, 21000 Dijon, France
[e] Inserm U887, 21078 Dijon, France

ARTICLE INFO

Article history:
Accepted 4 August 2010
Available online 30 October 2010

Keywords:
Hypogammaglobulinemia
Chronic inflammatory rheumatism
Primary immunodeficiency
Diagnosis
Etiologies

ABSTRACT

The discovery of hypogammaglobulinemia, which is defined as a plasmatic level of immunoglobulin (Ig) under 5 g/L is rare in clinical practice. However, the management of immunodepressed patients in rheumatology, sometimes due to the use of immunosuppressive treatments such as anti-CD20 in chronic inflammatory rheumatisms, increases the risk of being confronted to this situation. The discovery of hypogammaglobulinemia in clinical practice, sometimes by chance, must never be neglected and requires a rigorous diagnosis approach. First of all, in adults, secondary causes, in particular lymphoid hemopathies or drug-related causes (immunosuppressors, antiepileptics) must be eliminated. A renal (nephrotic syndrome) or digestive (protein-losing enteropathy) leakage of Ig is also possible. More rarely, it is due to an authentic primary immunodeficiency (PID) discovered in adulthood: common variable immunodeficiency (CVID) which is the most frequent form of PID, affects young adults between 20 and 30 years and can sometimes trigger joint symptoms similar to those in rheumatoid arthritis; or Good syndrome, which associates hypogammaglobulinemia, thymoma and recurrent infections around the age of 40 years. In most cases, after confirming hypogammaglobulinemia on a second test, biological examinations and thoracic-abdominal-pelvic CT scan will guide the diagnosis, after which the opinion of a specialist can be sought depending on the findings of the above examinations. At the end of this review, we provide a decision tree to guide the clinician confronted to an adult-onset hypogammaglobulinemia.

The discovery of hypogammaglobulinemia (< 5 g/L) during a check-up or the follow-up of a patient with chronic inflammatory rheumatism is a rare but not exceptional situation in everyday clinical practice. This biological abnormality is a real diagnostic challenge for practitioners. Indeed, a deficit in immunoglobulins (Ig) brings into question the management of the rheumatism (iatrogenic effect of immunosuppressors, hematological complication of the chronic arthritis, or possibly polyarthritis directly related to Ig deficiency). All of these etiologies must be considered when complementary examinations are conducted to guide the diagnosis in cases of hypogammaglobulinemia.

The first question that needs to be answered is the possible iatrogenic cause of the hypogammaglobulinemia, in particular when a patient with inflammatory rheumatism is treated by immunosuppressors. The growing use of anti-CD20 antibodies in rheumatology, such as rituximab and soon ocrelizumab, has increased the risk of hypogammaglobulinemia occurring during the follow-up, with the subsequent risk of infectious complications [1]. The second question concerns the possible neoplastic complication of the chronic inflammatory rheumatism (rheumatoid arthritis (RA), Gougerot-Sjögren syndrome, systemic lupus erythematosus), notably lymphoma. The third question concerns a possible link between polyarthralgia presented by the patient and primary immunodeficiency (PID), even though the occurrence of PID in the form of inflammatory rheumatism in adulthood is rather exceptional.

All things considered, the discovery of hypogammaglobulinemia requires a coherent diagnostic approach to determine the origin, so that an appropriate etiological treatment and if necessary polyvalent Ig replacement therapy can be implemented.

After a short reminder about the physiopathology, this review will describe in the first part the different etiologies that should be considered in cases of hypogammaglobulinemia, focusing on the most frequently causes seen in the field of rheumatology. In the second part, a diagnostic decision tree is proposed to help practitioners confronted to this unusual clinicobiological situation in order to guide the choice of complementary examinations, before seeking the opinion of a specialist.

* Corresponding author. Tel.: +33 3 80 29 37 45; fax: +33 3 80 29 36 78.
E-mail address: paul.ornetti@chu-dijon.fr (P. Ornetti).

1297-319X/$ – see front matter © 2010 Société française de rhumatologie. Published by Elsevier Masson SAS. All rights reserved.
doi:10.1016/j.jbspin.2010.09.016

Table 1
Function, molecular weight, serum levels, roles and half-life of the different immunoglobulins in adults.

	IgG_1	IgG_2	IgG_3	IgG_4	IgM	IgA_1	IgA_2	IgD	IgE
Heavy chain	γ1	γ2	γ3	γ4	μ	α1	α2	δ	ε
Molecular weight (kDa)	146	146	165	146	970[a]	160	160	184	188
Serum level (g/L) in adults	9	3	1	0.5	1.5	3.0	0.5	0.03	5×10^{-5}
Half-life in serum (days)	21	20	7	21	10	6	6	3	2
Activation of classical complement pathway	++	+	+++	–	++++	–	–	–	–
Activation of alternative complement pathway	–	–	–	–	–	+	–	–	–
Placental transfer	+++	+	++	+/–	–	–	–	–	–
Binding to Fc receptors	+	–	+	+/–	–	+	+	–	+
High affinity binding to mastocytes and basophils	–	–	–	–	–	–	–	–	+++

[a] Molecular weight of the pentamer.

1. Physiopathogenic aspects

Igs are glycoproteins encountered either as membranous receptor (BCR) on B cells or produced by plasma cells as soluble molecules, called "antibodies" (Ab) and present in the serum and extracellular fluids. There are different classes of Ig: IgG_1 to IgG_4, IgA_1 and IgA_2, IgM, IgD and IgE, the function and half-life of which are very different, from several hours to several weeks (Table 1) [2]. Only IgG, IgA and IgM play a role in anti-infectious immunity [3], through different mechanisms: neutralization of the antigen, bactericidal effect by activation of the classical pathways of complement (complement dependent cytotoxicity [CDC]), bactericidal effect via mechanisms of Ab-dependent cytotoxicity (antibody-dependent-cell-mediated cytotoxicity [ADCC]), opsonization of rapidly developing extracellular bacteria such as Gram positive cocci and enterobacteria, thus facilitating phagocytosis.

Concerning other classes of Ig, IgM are the predominant antibodies during the primary immune response and are essentially confined to the intravascular compartment. IgM are powerful activators of classical complement pathway. IgG are the most abundant Ig and are equally distributed in the vascular and extravascular compartments. IgG interact with various receptors of the Fc fragment (FcγR) expressed by various subsets of immune cells, especially from the myeloid lineage such as monocytes or macrophages. IgG_1 and IgG_3 are also able to activate complement. The main role of IgA is to inhibit the adherence of bacteria on the mucosa of the respiratory, gastrointestinal and genital tracts.

On serum protein electrophoresis (SPE), Ig migrate mainly in the zone of gammaglobulins. Normal levels vary with age. They range from 8 to 12 g/L in healthy adults. Hypogammaglobulinemia is defined by a level less than 5 g/L. The term agammaglobulinemia describes situations that associate a level of gammaglobulins below 1 g/L and the absence of circulating B lymphocytes. As well as the fall in the level of gammaglobulins, other elements must be searched for on the SPE to begin the etiological investigation: a monoclonal peak or hypoalbuminemia. The latter could suggest a renal or digestive leakage of Ig.

2. Principal causes of hypogammaglobulinemia

2.1. Context of discovery

The most frequent context of discovery in everyday practice is chance. A variety of clinical manifestations frequent in rheumatology (described as follows) may also lead to a prescription of SPE to screen for hypogammaglobulinemia.

2.1.1. Infection

The main risk of a deficit in Ig, whether primary or secondary, is an increased susceptibility to infections by encapsulated germs, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* but also other Streptococci, Staphylococci or enterobacteria [4–6]. The infections are mainly recurrent and/or severe and concern the ENT or airways. In clinical practice, the onset of more than two episodes of sinusitis or pneumopathy in a year, or more than eight episodes of acute middle-ear otitis should bring to mind immune deficiency.

2.1.2. Autoimmune manifestations

Autoimmune cytopenia [7], polyarthritis [8] or any other manifestation of immune dysfunction must lead to an SPE. However, no studies have validated the interest of the systematic prospective SPE in the onset of inflammatory rheumatism of unknown origin.

2.1.3. Peripheral lymphadenopathy, hepatomegaly and splenomegaly

This clinical picture should lead to systematic SPE, since there is a question of hemopathy.

In the majority of cases, the rheumatologist is faced with hypogammaglobulinemia with no clinical signs to help guide the diagnosis. It is this embarrassing clinical situation for the clinician that led us to propose the diagnostic decision tree in the next section. Simple biological surveillance is not recommended because the etiology needs to be found quickly. Indeed, the therapeutic approach may be totally different depending on the cause: interruption of an immunosuppressive treatment in case of iatrogenic hypogammaglobulinemia or implementation of a cytotoxic treatment in case of lymphoid hemopathy.

2.2. Etiologies

It is possible to distinguish between primary causes (PID) and secondary causes of hypogammaglobulinemia with a wide variety of etiologies, which must be immediately searched for in adults.

2.2.1. Medication

Many medicines can induce hypogammaglobulinemia, among which some are widely prescribed by rheumatologists (Table 2). Among the medicines on this list, all of which require a pharmacovigilance investigation, we can focus on the following:

- antiepileptics and in particular carbamazepine (Tegretol®), phenytoin (Dihydan®, Dilantin®) and clonazepam (Rivotril®). The deficiency affects all classes of Ig and is usually reversible and disappears with cessation of the treatment [9–11]. Complications due to infections are generally rare [12–16];
- disease modifying treatments for chronic inflammatory rheumatism, in particular D-penicillamine (Trolovol®), gold salts and sulfasalazine (Salazopyrine®). They principally cause IgA deficiency, but hypogammaglobulinemia has also been described, often with no clinically important consequences [17–22]. Some observations have suggested that methotrexate may also cause such deficiencies, but the risk seems to be lower in comparison with the treatments above [23];
- targeted biotherapies, employed in oncohematology and more recently in the treatment of immune dysfunction, in particular anti-CD20, such as rituximab (Mabthera®). The onset of