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# Diagnostic criteria of hypogammaglobulinemia in infancy

V. Lougaris
A. Soresina
A. Meini
E. Vettore
G. Cattaneo
A. Plebani

Department of Pediatrics and Istituto di Medicina Molecolare A. Nocivelli, Spedali Civili, Brescia, Italy

Of all of the primary immunodeficiency diseases, those affecting B cell function are the most frequent. Selective absence of serum and secretory IgA is the most common defect, with rates ranging from 1/333 persons to 1/16.000 among different race. By contrast, it has been estimated that hypo/agammaglobulinemia occurs with a frequency of only 1/50.000 persons. Patients with antibody deficiency are usually recognized because they have recurrent infections with encapsulated bacteria or a history of failure to respond to antibiotic treatment, but some individuals, mainly those affected by IgA deficiency or transient hypogammaglobulinemia of infancy, may have few or no infections. Quantitative determination of serum IgG, IgA and IgM is the most useful laboratory analysis for the identification of patients with hypogammaglobulinemia. Quantitative Ig assays are recommended, since immunoelectrophoresis or plasma electrophoresis do not provide exact information about the levels of individual Igs. The Ig levels must be interpreted with care because of marked alterations with each age. All infants aged 3 to 6 months are hypogammaglobulinemic if adult normal values are used. Therefore, comparison of each Ig value with its age matched control is essential. An Ig level within two standard deviations of the mean for age is considered normal.

At birth immunoglobulins (IgG) of the newborn are virtually all maternally derived and explain the reason why the serum IgG level in term infants is comparable to that in the mother. After birth the levels of maternally derived IgG decline rapidly, and serum IgG levels reach their lowest point at 6 months of age, when the infant's own IgG production is not fully developed. This sequence of events is accepted as normal *physiological* hypogammaglobulinemia; extension beyond 6 months of age is frequently termed transient hypogammaglobulinemia of infancy. This condition likely represents a heterogeneous group of functional *non biologically-relevant errors* in the immune system, and the distinction between transient hypogammaglobulinemia of infancy and other humoral genetic primary immunodeficiencies (i.e. common variable immunodeficiency, X- or autosomal recessive forms of agammaglobulinemia) may be difficult to ascertain at early age. This differential diagnosis is made even more difficult by the fact that the primary vaccination cycle is concluded only after the first years of life; this means that, as the antibody response against vaccine antigens is considered a crucial parameter in the differential diagnosis between transient hypogammaglobulinemia of infancy and common variable immunodeficiency (both these conditions are characterized by normal number of circulating B cells), the differential diagnosis between these two conditions can not be made with certainty before 2-3 years of age. In this case the presence of a positive family history for immunodeficiencies can be helpful.

In the differential diagnosis of hypogammaglobulinemia condition, besides immunoglobulin assessement, determination of circulating B cells is a usefull tool: absence of circulating B cells is compatible with X-linked or autosomal recessive forms of agammaglobulinemia, and allows to perform a differential diagnosis between these two conditions from common variable immunodeficiency.

Hypoagammaglobulinemia is an immunological feature which is also associated with cellular immunodeficiencies (i.e. combined immunodeficiencies). In this case, the complete blood cell count, including differential count, is the most simple, low cost, and practical laboratory analysis for distinguishing the *pure* humoral immunodeficiencies from the combined immunodeficiencies (defect in T or T/B cell compartment), as the presence of lymphopenia is more compatible with the latter. Thus the total lymphocyte count should be calculated; the nor-

mal lymphocyte count is 2000 to 6000 cells/μL. Lymphopenia is suggested if the lymphocyte counts is less than 2000 cells/μL and is present if the count is less than 1500 cells/μL. Persistent lymphopenia, generally associated with a paucity of small lymphocytes on the peripheral smear, is present in many cellular immunodeficiencies. Lymphopenia in a newborn or an infant is a special cause for concern because babies normally have high levels of total lymphocytes. A diagnosis of combined immunodeficiencies should be suspected in all infants with a low lymphocyte count.

The identification of the type of combined immunodeficiency, firstly suggested by the occurrence of persistent lymphopenia, relies on the enumeration of the total number of T cells ($CD3^+$ cells) and major T-cell subsets ($CD3^+$ and $CD8^+$ cells) in the peripheral blood. Both the percentage and absolute number of these cells should be recorded and the ratio between CD4 and CD8 cells calculated. The percentages and the CD4/CD8 ratio tends to be more constant over time and is of particular value in determining long-term trends. Absolute numbers of T cells, although dependent on the total white blood cell count, better reflect the degree of T cell immunodeficiency.

The enumeration of T cell subsets is a usefull tool for the identification of some forms of combined immunodeficiencies presenting with normal lymphocyte count; this can occur in the presence of maternal engrafment or in the case of immunodeficiencies with B and/or NK cells (T- B+; T- NK+ combined immunodeficiencies.

The evaluation of the ability of the patient's lymphocytes to proliferate in vitro under the influence of antigens, allogeneic cells, mitogens such as PHA, PMA+ ionomycin) can be an additional laboratory test useful for the identification of cellular immunodeficiencies characterized by defective signal transduction, mainly in the forms in which lymphopenia is not present and T cell subset only partially affected.

These very simple immunological tools which are currently available among the majority of the regional hospital are sufficient, if correctly interpreted, to perform, an early diagnosis of the most common forms of primary immunodeficiencies. The identification of the genetic defect by gene sequence analysis is a more complex analysis which can be done only in experienced laboratories. It is important to underline that the identification of the genetic defect, does not add anything substantial to the clinical management of these patients, with the exception of the genetic counselling. Thus once identified by simple immunological assays, do not waste time in order to perform genetic sequence analysis, but address the patient to the experienced center for the correct clinical management.