Common variable immunodeficiency. Old questions are getting clearer

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ABSTRACT

Common variable immunodeficiency (CVID) is a heterogeneous entity characterized by an impaired ability to produce antibodies. The failure is localized in partially mature B lymphocytes, though T lymphocyte abnormalities are occasionally present. This deficiency affects antibody synthesis and class switch from IgD and IgM, to IgG and IgA. CVID is related to selective IgA deficiency, and both abnormalities may coincide in one same family, and evolve from one to another in the same patient. The symptoms generally manifest in adults, but can occur at any age, even in infancy. Recurrent bacterial infections or pneumonias are frequent, and may be complicated by gastrointestinal problems, granulomas, autoimmune disorders or malignancies. A defect in memory B cells seems to condition the clinical severity. Recently, several mutations in genes encoding for molecules (CD19, TACI, ICOS) involved in B cell survival and isotype switch have been identified in patients with CVID. Nevertheless, genetic abnormalities have been found in less than 25 % of cases with CVID; the underlying mechanism thus remains unknown in the majority of CVID patients, and research in this field must continue.

Key words: Antibody class switch. Autoimmunity. Common variable immunodeficiency. B cells. CD19. ICOS. TACI.

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Common variable immunodeficiency (CVID) is classified as a predominantly antibody deficiency[1] (table I). It comprises a heterogeneous group of alterations all characterized by deficient antibody synthesis[2-4]. In the past it was known as late-onset hypogammaglobulinemia, and earlier still was referred to as Giedion-Scheidigger deficiency or dysgammaglobulinemia – due to the multiple combinations of immunoglobulin levels involved. CVID is related to selective IgA deficiency, and both abnormalities may often coincide in one same family[3]. CVID can manifest at any age as recurrent bacterial infections, and is characterized by the presence of hypogammaglobulinemia with failure in the production of antibodies in response to different antigens. The number of B and T lymphocytes tends to be normal or almost normal, though important reductions in cell count are sometimes observed[5]. The incidence of CVID ranges from 1/25,000 to 1/66,000 inhabitants, though the more milder cases probably go undetected[6]. Although selective IgA deficiency is much more common, it is also frequently asymptomatic; conse-

Table I

Immunodeficiencies of antibody synthesis with special attention to CVID (From the Primary Immunodeficiency Diseases Classification Committee of IUIS. Budapest 2005)

1. Severe reduction in all serum Ig isotypes with absent B cells (Six variants are accepted. The prototype is the X-linked agammaglobulinemia)
2. Severe reduction in at least 2 serum Ig isotypes with normal or low numbers of B cell
   - *a.* Common variable immunodeficiency disorders (CVID)
   - *b.* ICOS deficiency
   - *c.* CD19 deficiency
   - *d.* TACI deficiency
   - *e.* BAFF receptor deficiency
3. Severe reduction in serum IgG and IgA with increased IgM and normal numbers of B cells (Two variants are accepted: AID deficiency and UNG deficiency)
4. Isotypes or light chain deficiencies with normal numbers of B cells (Four variants are accepted with different IgG subclasses and IgA deficiency)
5. Specific antibody deficiency with normal Ig concentrations and number of B cells (Variable inheritance and unknown genetics)
6. Transient hypogammaglobulinemia of infancy (Serum IgG and IgA decreased. Variable inheritance and unknown genetics)

quently, CVID is considered to be the most frequent immune deficiency requiring patient treatment.

PATHOGENESIS

The defect underlying CVID is located in the terminal maturation phase of the B lymphocytes, affecting the production of antibody-generating plasma cells or the immunoglobulin class switch from IgM to IgG. The effect is generally intrinsic to the B cell population, though in some cases regulatory T cell function fails, with or without primary B cell deficiency. IL-2, IL-4, IL-5 and IFN-γ deficiency may be associated, and in some cases a CD40 ligand (CD40L) defect is observed – though this appears to constitute a secondary alteration. Genetic and molecular studies have shown the coincidence in one same family, and even within one same individual, of cases of CVID and of selective IgA deficiency. It is believed that the carriers of certain mutations, depending on exogenous factors or complementary genes, develop isolated IgA deficiency in some instances and CVID in others, with different intensities and at different times – even in adults. Thus, some of these families present mutations in genes of the HLA-III system, e.g., C2 and C4 factors, or TNF.

Immune alterations in CVID

Patients with CVID usually present hypogammaglobulinemia[7], and IgG and IgA are more affected than IgM, though there are multiple possible levels and combinations. It should be pointed out that immunoglobulin normality does not rule out CVID, and the definitive diagnosis requires confirmation of the lack of specific antibody response following protein and/or polysaccharide antigen challenge[8-10].

The B lymphocyte count is usually normal or almost normal, with a mature B phenotype, though in contrast the plasma cells of the lymphoid tissues are diminished in number. Nevertheless, imbalances in some B cell subpopulations have been found, such as the immature forms[11], and such populational anomalies may increase with patient age[12]. The most relevant observation has been the detection of anomalies in the memory B cells, which serves to classify the different forms of CVID and to predict the course of the disorder in each patient[13-16] (table II). The reduction in memory B cells (CD19 + CD27 + IgD–) is associated in both children and in adults to severe forms, with bronchiectasis and/or splenomegalia[17], though not so the immunoglobulin levels, which lack prognostic value[18]. In contrast to what was expected, the situation in terms of the memory B lymphocytes was not seen to correlate to the genetic mutations recently described in CVID[18].

The T cells are seen to be normal in some patients, though other affected individuals present anomalies in proliferation or cytokine synthesis in response to different stimuli. T-B lymphocyte cooperation is particularly affected[7]. Patients with serious complications tend to present a low CD4/CD8 ratio due to an increase in activated CD8 + lymphocytes (CD8 + HLA-DR +)[19]. High counts of large granular lymphocytes (LGL) have also been reported[20].

Recently new anomalies have been described in CVID, though their relationship to the pathogenesis and clinical severity of the disease remains the subject of research, since they appear to manifest in some but not in all patients. These anomalies include innate immune defects, particularly in relation to the activation, development and function of the dendritic cells of monocytic origin[21,22]. In some cases the defect is accompanied by variable alterations in the production of IL-12[23,24], which causes secondary anomalies in T cell activation, though no significant Th2 > Th1 predominance has been demonstrated[25]. A defect in IL-7 synthesis has also recently been published that appears to be relevant, since it occurred in a subgroup of patients with CVID complicated by splenomegalia, autoimmune disorders and