Abbreviations used
AIE- autoimmune enteropathy
AIHA- autoimmune hemolytic anemia
CID- combined immunodeficiency
CT- computed tomography
CVID- common variable immunodeficiency disorders
HSCT- hemopoietic stem cell therapy
ITP- immune thrombocytopenic purpura
IVIG- intravenous immunoglobulin
LOCID- late-onset combined immune deficiency
SCIG- subcutaneous immunoglobulin
SNP- single nucleotide polymorphism
TREC- T-cell receptor excision circle

1. Onset of immunodeficiency at greater than 2 years of age
2. Absent isohemagglutinins and/or poor response to vaccines
3. Defined causes of hypogammaglobulinemia have been excluded according to a list of differential diagnosis (Table I).

As will be discussed further below, CVID encompasses a group of heterogeneous primary antibody failure syndromes characterized by hypogammaglobulinemia. The number of potential distinct entities within this group is still unknown, and the diagnosis remains one of exclusion. Monogenic forms have been described, but polygenic inheritance is likely in most cases.[4-6] Despite the fact that several monogenic defects underlying apparent CVID have been defined, because of the rarity of each defect and the lack in most cases of significant impact on management, as well as the cost of testing, genetic studies are not considered appropriate for routine use in patients with CVID at this time.

The onset of the varied clinical manifestations and laboratory abnormalities do not necessarily coincide, and may occur at any age from early childhood to old age. Given (1) the broad differential diagnosis of hypogammaglobulinemia (Table I),[7] (2) the challenge of differentiating some of these in early childhood (particularly regarding definitive assessment of vaccine responses), and (3) that CVID is considered a diagnosis of exclusion, it is best not to confer this diagnosis before at least age 4 years.

Antibody production is always disturbed in CVID. This is often the result of B-cell dysfunction, but may also result primarily from impairment of T-cell function and lack of sufficient help for antibody production. Infection susceptibility is mainly to encapsulated extracellular bacteria in the respiratory tract, but there may also occur various other clinical manifestations affecting many organ systems. The phenotype is very broad, ranging from only bacterial infections, to progression from a CVID-like condition to severe disease similar to a combined immunodeficiency, possibly having a different etiology.[8,9] Some patients may also have distinct initial presentations, such as autoimmune disease, granulomatous disease, or enteropathy without recurrent infections (discussed in detail below).[10,11]

The normal range of IgG serum levels varies in different age groups; therefore, it is critical that this be defined according to the age-adjusted reference range for the population. An absolute lower limit value of IgG at 4.5 g/L for adults has been proposed, because nearly 95% of the patients with CVID in a European cohort fulfilled this criterion.[12] However, it is recognized that some patients with CVID have relatively high residual IgG levels (up to 6 g/L) at diagnosis while still showing impaired specific antibody formation.[13] Furthermore, the normal range of IgG levels may also vary according to race or ethnicity.[14] Thus, for practical purposes, the definition of hypogammaglobulinemia depends on the local or regional reference range applicable to the patient. In addition to a low IgG level, IgA or IgM level must be low for a definite diagnosis of CVID.[15] Note that not all clinical immunologists agree regarding these laboratory criteria. Some do not confer a diagnosis of CVID if the IgA level is normal. We publish the less stringent criteria here because it is an accepted standard for many practitioners. It is of critical importance that all immunoglobulin measurements be interpreted according to

TABLE I. Differential diagnosis of hypogammaglobulinemia

Drug induced
Antimalarial agents
Captopril
Carbamazepine
Glucocorticoids
Fenclofenac
Gold salts
Penicillamine
Phenytoin
Sulfasalazine
Anti-CD20 mAbs (rituximab)
Single gene and other defects
Ataxia telangiectasia
Autosomal-recessive forms of SCID and other forms of combined immunodeficiency
Hyper-IgM syndromes
Transcobalamin II deficiency and hypogammaglobulinemia
X-linked agammaglobulinemia
X-linked lymphoproliferative disorder (EBV-associated)
X-linked SCID
Some metabolic disorders
Chromosomal anomalies
Chromosome 18q- syndrome
Monosomy 22
Trisomy 8
Trisomy 21
Infectious diseases
HIV
Congenital infection with rubella virus
Congenital infection with cytomegalovirus
Congenital infection with *Toxoplasma gondii*
EBV
Malignancy
Chronic lymphocytic leukemia
Immunodeficiency with thymoma
Non-Hodgkin lymphoma
Monoclonal gammopathy (mutiple myeloma, Waldenstrom macroglobulinemia)
Other systemic disorders
Immunodeficiency caused by excessive loss of immunoglobulins (nephrosis, severe burns, lymphangiectasia, protein-losing enteropathy)

SCID, Severe combined immunodeficiency.