

REVIEW

Current perspectives on common variable immunodeficiency (CVID)

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Introduction

Common variable immunodeficiency (CVID) is the commonest symptomatic primary antibody deficiency syndrome, and Scandinavian data suggest a prevalence of 1 per 50 000 [1]. Data collected in the UK indicate that a substantial number of patients remain undiagnosed if this figure applies to the UK. There is still a major awareness problem among clinicians, especially general practitioners, adult general physicians and chest physicians and ENT surgeons, to whom patients are most likely to present in the first instance.

The diagnosis of antibody deficiency can usually be made fairly easily once the question has been raised, although immunoglobulin levels are variable and the precise immunological classification may require more detailed immunological and genetic studies. CVID is closely related to selective IgA deficiency, IgG subclass deficiencies and specific antibody deficiency, where there is a lack of humoral immune responsiveness to specified antigens, particularly bacterial capsular polysaccharides. There is some anecdotal evidence that CVID may represent the end stage of the evolution of a progressive humoral immune deficiency.

Distinction between primary and secondary antibody deficiency becomes increasingly difficult with increasing age. CVID may present at any age, from childhood through to post-retirement, although the peak of presentation is in childhood and early adult life. In almost all cases the disease once established is irreversible, although there have been sporadic reports of spontaneous cure, or paradoxical improvement of immune function following viral infections such as HIV and hepatitis C virus (HCV).

Definition and classification

The principle presentation of antibody deficiency is with

recurrent upper and lower respiratory tract infections. However, initial presentation of CVID may include thrombocytopenia and other autoimmune phenomena, bowel infections such as chronic giardiasis, malabsorption and granulomatous disease affecting spleen, lymph nodes and lung (mimicking sarcoidosis) [2–5].

X-linked agammaglobulinaemia (XLA) was described in 1952 and the first cases of CVID were described the following year. Initial definitions of XLA depended on the demonstration of complete absence of B lymphocytes with absent serum immunoglobulins. It is now recognized that not all patients with XLA lack B cells, and conversely many patients with CVID have low B cell numbers [6,7]. It is therefore difficult to distinguish between CVID and XLA in young male children. In older patients, it is essential to exclude secondary causes of hypogammaglobulinaemia prior to making a diagnosis of CVID. Secondary causes would include drugs, especially anti-convulsants such as phenytoin [8], primary protein losing enteropathy, which obviously presents difficulties in diagnosis, as malabsorption may also be a feature of CVID, nephrotic syndrome, and lymphoproliferative disease. The latter presents a significant problem, as there is now evidence that a significant humoral immune deficiency often accompanies non-Hodgkin's lymphoma [9], and this may persist long-term even following apparently successful chemotherapy and autologous transplantation. Further complication is added by the abnormal lymphoid histology seen in patients with CVID [10,11], which may of its own right be mistaken for lymphoma. Genetic tests are available for XLA and XL-HIGM, which will assist in the diagnosis at least of the inherited antibody deficiencies, although the tests are neither easily available nor cheap in the UK.

To a large extent therefore, the diagnosis of CVID is based on exclusion of other more robustly defined diseases, there being no unique operational or immunological definition of CVID, despite attempts to produce one. It is likely that CVID as presently identified comprises more than one disease condition, and certainly older series

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undoubtedly contain milder variants of XLA and also X-linked and autosomal recessive forms of hyper-IgM syndrome. Rarer immunodeficiencies such as μ -chain deficiency, light chain deficiency and *blnk* deficiency may also be hidden within the global diagnosis of CVID [12–14]. Extreme lyonization may give rise to females with 'X-linked' conditions [15].

Multiple attempts have been made to classify the disease, usually based on *in vitro* immunological abnormalities. Using flow cytometry to define the subpopulations of lymphocytes present and cross-linking anti- μ + IL-2 as a B lymphocyte stimulus, with antibody production as the read-out, it is possible to classify 'CVID' into four groups [16,17], dependent on the amount of IgG and IgM produced. The importance of this type of approach is that it allows the comparison of immunologically equivalent patients and allows a more realistic attempt to evaluate the underlying aetiology. However, this work was undertaken before the discovery of more recent genetically defined B cell deficiencies [12–14], and requires repeating with exclusion of patients with genetic defects.

Diagnosis

The most important aspect of diagnosis is to suspect the disorder and undertake immunological testing. Many patients are still presenting to immunologists late with established structural lung damage, which is not reversible to any significant degree by IVIG therapy. Part of the problem lies in the lack of correlation between clinical symptoms and total immunoglobulin levels, although in many patients even grossly reduced immunoglobulins are not identified simply because the appropriate (inexpensive) tests have not been requested.

Investigation therefore begins with measurement of serum immunoglobulins. It is critical in children that the values are compared with age-matched ranges; equally in adults there are sex-related differences in the ranges for IgM. Normal or high IgM levels with low IgG and IgA should suggest the hyper-IgM syndrome: not all such patients have raised IgM at presentation [18]. Normal serum immunoglobulins do not, however, exclude a humoral immune deficiency, and measurement of specific antibody production is required as a test of humoral function. This should include as a baseline antibodies to pneumococcal polysaccharide, *Haemophilus influenzae* type b polysaccharide, tetanus toxoid, and viral antigens such as measles, mumps, rubella, polio and Epstein–Barr virus (EBV). The results need to be correlated with the infection and immunization history. More importantly, test immunization with protein and polysaccharide antigens allows formal evaluation of *in vivo* responsiveness (expecting a 3-week post-immunization level within the

protective range and at least a four-fold rise from baseline). There is concern over the validity of some assays for specific antibodies, and EQA results show poor correlation between different methodologies.

Rare individuals may give a good initial response to immunization, but the response may decay away within months; repeated immunization gives the same short-lived response on each occasion. These patients may also be at risk of recurrent infections. At present we have little evidence of whether alterations in the affinity and avidity of antibodies play a significant role in clinical immunodeficiency. Suspected immunodeficient patients should not be given live vaccines, such as polio, because they may fail to clear the vaccine: cases of paralytic polio have been reported in antibody deficiency [19].

The value of IgG subclass measurements is debatable and they certainly give less useful information in defining immune function than the dynamic tests. IgG subclass deficiency due to deletion of the relevant coding sequences may be compatible with a lack of clinical symptoms [20,21] and entirely normal humoral immune function, when dynamic testing is carried out.

It is essential to analyse lymphocyte subpopulations in the peripheral blood and this must include B cell and T cell subsets. Reduction in CD4⁺ T cells is often seen in CVID, but is not present in XLA [7]. The reduction in CD4⁺ T cells is predominantly in the CD45RA population [7,22–24]. Patients with more severe disease tend to have the greatest reductions in CD4⁺ T cells and in B cells [7,22].

The routine value of *in vitro* B cell function tests to classify CVID patients has not been fully established and at present is probably not essential to the diagnostic process. Other tests that may give helpful information include serum β_2 -microglobulin and neopterin, which are raised in CVID [25–27], organ-specific autoantibodies, which may be present even if total IgG is low. Urine should be checked to rule out gross nephrosis. Other testing is directed by clinical features. It is important to remember that serological testing for infectious disease is unreliable in antibody-deficient patients. Diagnosis is therefore dependent on either direct culture or nucleic acid identification. This is important, as hypogammaglobulinaemia secondary to infection forms part of the differential diagnosis. If lymph nodes are enlarged then biopsy is mandatory; it is important to ensure that the reporting pathologist is familiar with the lymphoid architecture patterns seen in CVID.

Aetiology including genetics

Despite over 40 years of research, we are still no closer to understanding the primary cause of CVID. A wide range of immunological abnormalities has been identified [17,28] but much of the early research is likely to be confusing

because of the inclusion of patients suffering from XLA or hyper-IgM syndrome. There seems little doubt, however, that there are defects in antigen-presenting cells (dendritic cells, macrophages) [29], T cells and B cells. The abnormalities of T cells include poor activation and proliferation [30,31], defective antigen-driven responses due to a reduction in antigen-specific T cell precursors and abnormal antigen handling [32,33], abnormal expression of adhesion molecules [34], abnormal cytokine production [35] and abnormal CD8⁺ T cells [36]. B cell function [37] and apoptosis [38,39] has also been shown to be abnormal.

Of cases of CVID, 20% will have evidence of other affected members; this will include asymptomatic individuals who have minor humoral problems such as IgA and IgG subclass abnormalities, as well as members with more significant humoral deficiencies. There is evidence that the susceptibility gene is linked with the class III MHC region, although the precise gene involved remains to be identified [40–42]. Deficiency of mannose-binding lectin has been associated with early onset of disease and a propensity to develop autoimmune disease, indicating that other genetic factors contribute to the overall clinical picture [43].

There is no currently convincing evidence that CVID is caused by an infection, and although there was a vogue in the mid-1980s for attributing it to retroviral infection, there is no convincing evidence that this group of pathogens is involved [44]. One of the difficulties with investigating such patients for an infectious aetiology is knowing whether any identified pathogen is causative or merely secondary. The infective trigger, if there is one, may simply be a hit and run event in someone who is genetically susceptible, and as the patients usually present some years into their illness, the chances of identifying a causative pathogen are almost nil.

CVID and its associated disorders are not, however, static diseases and the severity of immunological defects may be progressive or in rarer cases may even regress [45,46]. Whether there are environmental factors amenable to manipulation that control this is not known. The association of hypogammaglobulinaemia with certain classes of drugs, such as anti-convulsants, and certain infections, suggests that there may well be. Although in many such cases of drug and virally induced hypogammaglobulinaemia there is spontaneous recovery, in some the disordered immune function persists long-term after the withdrawal of the insult. Unfortunately virtually no cases of anti-convulsant-induced humoral immune deficiency have baseline, predrug, humoral function tests carried out [8].

More accurate clinical, genetic and immunological case definition may allow a more precise evaluation of the aetiological factors and the immunological abnormalities.

Clinical management

The mainstay of treatment is replacement immunoglobulin therapy. Attempts to modulate humoral immune function, for example with drugs (cimetidine, retinoids) or with cytokines (PEG-IL-2) have had some limited success [47–50]. There is no place in management for intramuscular immunoglobulin, which was the original treatment, or for plasma, as adequate antibody levels will not be achievable and infection will not be prevented. Intravenous immunoglobulin (3–12% solutions) or subcutaneous immunoglobulin (16% solution) is the preferred treatment, aiming to achieve a trough IgG level within the normal range [51–53]. This usually requires a dose of between 0.2 and 0.6 g/kg per month, given in divided doses. For intravenous therapy, treatment should be given every 2–3 weeks, and intervals should not be longer. For subcutaneous therapy, volume of administered IgG means that infusions are required every 1–2 weeks. Both dose and frequency may need to be adjusted to achieve an adequate trough level and complete resolution of symptoms.

Fatigue and malaise in the week before the infusion is invariably a sign of inadequate treatment and will disappear with an increase in therapy. An unanswered question is whether a higher trough level has any advantage over one just within the normal range. The only published evidence on efficacy relates to a trough level of 5 g/L [54]. Many immunologists looking after CVID patients believe that levels of 7–8 g/L are important in patients with established structural damage, but evidence to support this view is lacking. Both i.v. and s.c. routes appear to be therapeutically equivalent in terms of achieving stable trough IgG levels and preventing infections [53]. Subcutaneous therapy allows easier treatment in patients with poor venous access. For i.v. therapy, as access will be required long-term, use of plastic cannula should be avoided, as they cause vein sclerosis: butterfly needles should be used instead. Implantable venous access devices should be avoided if possible, because of the infection risk, although a small number of patients have used these for long periods without problems.

Immunoglobulin preparations are all derived from donated plasma and patients should be counselled prior to starting therapy of the infective risks. While there appears to be no risk of HIV transmission, due to the rapid elimination of the virus during the manufacturing process, more robust viruses such as HCV have caused significant problems in the past [55]. HCV infection runs a more severe course in patients with CVID [56]. Obtaining baseline HCV polymerase chain reaction (PCR) to confirm a lack of infection pretreatment is essential to allow subsequent attribution of any infection to treatment. Current commercially available products all have at least

two specified antiviral steps in the manufacturing process, and there have been significant improvements in screening donors and the plasma pools, including the introduction of nucleic acid techniques to identify viruses in the window period prior to seroconversion [57]. The risks of transmission of spongiform encephalopathies by IVIG are unquantified, but the UK regulatory authorities have phased out the use of UK plasma in IVIG manufacture as a precautionary measure.

There is a range of different products available. These are not therapeutically or immunologically equivalent and must not be used interchangeably, as severe adverse reactions have been noted on switching products. Content of IgA and IgG subclasses may vary substantially; formulations include both liquid and lyophilized; there are differences in stabilizing agents and antiviral processes, which may lead to problems with adverse reactions. CVID patients who are completely deficient in IgA may produce anti-IgA antibodies if infused with products containing significant amounts of IgA, and therefore they should receive a very low IgA product [58,59]. Adverse reactions often relate to inadequate treatment, as persistent infection leads to immune complex formation during infusions, or to inappropriately fast infusions. Occasional patients react persistently to one product, but reactions will usually disappear if the product is changed.

Home therapy is possible for both i.v. and s.c. therapy and is known to be safe and effective [60–62]. National Guidelines on how this should be conducted exist in the UK and have been revised recently, and approved by the Association of Clinical Pathologists. A network of training centres, defined on critical patient load to maintain expertise, exists and patients should be referred to one of these for training and follow up [63].

The question of continuous prophylactic antibiotics is frequently raised. Very few patients require continuous antibiotics when appropriately treated with immunoglobulin. Despite the T cell lymphopenia and T cell functional abnormalities, opportunist infections are rare and cotrimoxazole prophylaxis is not required. Occurrence of *Pneumocystis carinii* pneumonia in an antibody-deficient patient should raise the question of hyper-IgM syndrome. Antibody-deficient patients require higher doses and longer courses of antibiotics to clear infections, although optimum therapeutic strategies have not been defined. Antibody deficiency predisposes to infections with normally non-pathogenic Mycoplasmas and Ureaplasmas, often giving rise to a septic arthritis which is sterile on normal culture; special media are required to identify these organisms and failure to do so can lead to a severe destructive arthropathy [64]. These organisms are usually but not always sensitive to tetracyclines and macrolide

antibiotics. Pleuromutilin antibiotics, currently used in veterinary medicine, are being investigated as potentially useful agents in humans.

Granulomatous disease occurs in up to 20% of patients, and is usually accompanied by splenomegaly and/or lymphadenopathy. Interstitial lung disease may occur [7,17]. Differentiation from lymphoma is important. Histology shows non-caseating granulomata, indistinguishable from sarcoidosis [65]. Patients may be relatively asymptomatic, in which case no treatment is required, but may develop progressive dyspnoea from lung involvement, and may be hypercatabolic for infused IgG and for circulating cellular components (platelets, erythrocytes) due to hypersplenism. Corticosteroids may be effective in some patients, but add their own risk of infection; splenectomy may be necessary both for diagnosis and for treatment [66], but again this increases the risk of infection substantially. Splenectomized CVID patients may have an increased risk of death from infection.

There is an increased incidence of lymphoma and gastric carcinoma in patients with CVID [11,67,68]. However, as noted above there may be difficulties in diagnosing lymphoma in the context of CVID, particularly before molecular techniques became available; a retrospective reanalysis is underway in the UK (Gompels *et al.*, in preparation). Historic studies may therefore overestimate the occurrence of lymphoma by including non-clonal proliferative lesions. There is a suspicion that the occurrence of true lymphoma may be decreasing since the introduction of higher dose IVIG regimes, compared with the period of IMiG treatment. Better treatment of infection may reduce the chronic stimulus to ineffectual lymphocyte proliferation that may precede clonal escape; there is no hard evidence to support this conjecture at present. Gastric carcinoma appears to be associated with the increased gastric atrophy found in CVID. We have found no conclusive evidence of increased colonization with *Helicobacter pylori* in a small cohort of CVID patients (Davidson & Spickett, unpublished data), although a more recent study has suggested that *H. pylori* may play a role in gastric cancer in CVID [69]. A lack of a role for the secretory immune system in *Helicobacter* infection has been demonstrated in IgA-deficient patients [70].

There has been considerable recent interest in ocular problems in CVID. There have been reports of retinal vasculitis, requiring treatment with steroids and cyclosporin [71]. Sterile corneal perforations have also been reported [72]. Observations in the Newcastle cohort have shown that many patients have reduced tear production comparable with Sjögren's patients (Spickett & Pandit, unpublished observations).

Survey results and current status in UK

A consensus on the diagnosis and management of antibody deficiency has been previously agreed and published [63]. We have recently completed a 3-year audit project for antibody-deficient patients in the UK, to assess the management in the light of the agreed consensus and to look at the patient implications of failure to achieve the standards [73]. (Copies of the full report are available to interested parties for a small fee from the author.) As part of the study, and before the agreed consensus was made public, Consultant Immunologists were contacted to assess their approach to the management of antibody deficiency [74]. This study demonstrated that even among Immunologists there were significant deviations in clinical practice from those recommended in published work on antibody deficiency; of particular concern was the approach to therapy, with inappropriate routes of administration and inadequate doses and frequency being recommended. The summary of the main findings has already been published in this journal [73]. To improve the quality of care, an organization devoted to primary immunodeficiencies is being established in the UK, and this will have a prime responsibility to develop and monitor standards of care for these patients.

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