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Update in understanding Common Variable Immunodeficiency Disorders (CVIDs) and the management of patients with these conditions

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Abstract

Common Variable Immunodeficiency Disorders are a mixed group of heterogeneous conditions linked by lack of immune globulin production and primary antibody failure. This variability results in difficulty in making coherent sense of either immunopathogenesis or the role of various genetic abnormalities reported in the literature. The recent attempt to collate the varied complications in these conditions and define particular clinical phenotypes, has improved our understanding of these diseases. Once refined and confirmed by studies in other series, these studies will facilitate improved accuracy of prognosis and better management of clinical complications; they may also provide a method of analysing outcomes as related to new immunopathologic and genetic findings.

Keywords

Common variable immune deficiency disorders; antibody failure; clinical phenotypes; genetic findings; management of patients

Introduction

Common Variable Immunodeficiency Disorders are a group of diseases in which failure to produce immune globulins and protective antibodies results in symptoms, usually but not always, of recurrent bacterial infections. The common feature is lack of antibodies to pathogens, though for many years it was only possible to demonstrate this by the surrogate measurement of levels of serum immunoglobulins, as assays for specific antibodies were previously unreliable or not available; now however assays for antibodies to panels of common vaccine or environmental antigens are used routinely.

Originally the name “variable” was used to describe a group of late-onset unclassified hypogammaglobulinemias in adults to distinguish these conditions from the more severe, inherited form of agammaglobulinaemia, X-linked agammaglobulinaemia (XLA) found in children (Fudenberg 1971). As more individual (often apparently single gene diseases) were discovered and named over time, the term “variable” was also used for those forms of primary antibody failure that presented in late childhood or in adults. These conditions came to be considered in the same way as the paediatric immune deficiencies, as likely to be

single gene diseases due to a variety of mutations (as yet unknown) in non-redundant genes needed for antibody production. However, just as awareness of the multiplicity of genes involved has aided understanding of other late onset immunologically-based diseases (such as diabetes, inflammatory bowel disease or multiple sclerosis), it is equally likely that CVIDs are polygenic disorders in the out-bred human species

So why update our understanding of this group of conditions now? In the past several years improvements in the management of patients with a CVID, including replacement immune globulin and improved microbial therapies, have enabled patients to survive longer (Chapel 2008). This has increased awareness of non-infective clinical complications of these conditions and has enabled the definition of clinical and immunologic phenotypes that can be correlated with outcomes. It is particularly timely to provide the clinical context in which to interpret the newly emerging genetic markers and thus confirmation of these phenotypes is likely to be of use in the study of immunopathogenesis and genetic influences. The different survival risks associated with the newly-defined clinical phenotypes may be helpful in guiding the use of riskier treatments that till now have been used sporadically to treat severe complications. The search for additional prognostic indicators continues. Finally we need improved definitions to ensure that only patients with recognisably similar immunological defects are grouped together, to avoid confusion in reporting complications and outcomes in patients with disparate types of CVIDs

Diagnosis

The need for an agreed definition was recognised internationally in the late 1990s; until this time there was confusion due to the variable definitions used in research papers, even though the need to exclude secondary causes of antibody failure was agreed universally. After much discussion, the original ESID and PAGID diagnostic criteria were published in 1999 (Conley 1999). Since then the criteria have been used variably; for example, the minimum age used to define CVIDs has changed, with general consensus but without obvious recognition, to a minimum age of 4 years of age due to the need to exclude children with other immune defects.

An additional starting point for a diagnosis of CVID is to confirm the use of “primary” antibody failure and to exclude other conditions known to cause failure of antibody production (Table 1), that may have added to confusion in previous series of “CVID” patients; however there will be only a few such patients in any large series. To avoid confusion with secondary antibody failure due to lymphoid malignancy, the definition insists on a period of 2 years following diagnosis of reduced serum immunoglobulin levels without development of a lymphoid malignancy before the diagnosis of a CVID is secure. Other known causes of primary antibody deficiency must also be eliminated (Geha 2007). Whilst this is simpler for common conditions with a known genetic defect, such as XLA, it is not always possible to test for mutations in all the genes currently known to be involved in antibody failure (such as *CD40L*, *CD40*, *BLINK*, μ chain, lambda 5, *AID*, *UNG*, *SAP* and *XIAP*, (Eastwood 2004)(Lopez-Granados – submitted), let alone the huge number of genes defects in which result in potentially leaky Severe Combined Immune Deficiencies (such as *ADA* *RAG1* or *RAG2* or *Artemis*) (Antony FC 2002) or those immune deficiencies combined with non-immunological conditions (Geha 2007). In practice boys with affected male relations or patients of either gender with a positive family history should be tested for the appropriate gene defect before a diagnosis of a CVID can be made; absence of B cells is no longer sufficient to exclude XLA.

The hallmark of CVIDs is reduced serum levels of serum immune globulins, IgG, IgA and or IgM. Assay results depend on the methods used, the ethnicity, gender mix and age of the

reference population. Since the distribution of serum immunoglobulin levels is non-parametric, the 97.5% centiles are used to define normal ranges for each age group. For CVIDs, the serum IgG levels must be below the minimum level found in the general population at that age, recognising that this will include 2.5% of normal subjects. Despite the wide range of IgG levels in CVID patients, the majority of patients (94.2%) had initial IgG levels <4.5 g/l at diagnosis in the European study, similar to those in the US where a cohort of 394 subjects followed at one medical centre, 85% had similar IgG baseline values (Figure 1). This suggests that a lower diagnostic level for serum IgG – potentially 4.5g/l – might provide more comparative cohorts of patients for studies. The small minority excluded from a diagnosis of a CVID by this definition could be classified as “possible CVID”.

The range of serum IgM levels is also very variable; these may be low, normal or even raised (Figure 1). Some of these patients may have an unrecognised hyper-IgM syndrome or switch defect. The increasing recognition of new hyper-IgM syndromes (Durandy 2007) and the awareness that these can and do occur in females as well as males, should alert immunologists to a known immunoglobulin class-switch defect, since 18% of patients in the US study (Cunningham-Rundles 1999) and 12% in the European study (Chapel 2008) were in this category. Initial serum IgM levels are also important in prognosis, since there is a significant correlation between increased IgM and the development of polyclonal lymphocytic infiltration or a lymphoid malignancy, both also associated with hyper-IgM syndromes (Chapel 2008).

The number of B cells in patients with CVIDs is also highly variable (Chapel 2008). Whilst 12% have no detectable B cells, 12% have reduced B cells, 54% have in the normal range for B cells (6-16% of circulating lymphocytes), 19% have slightly increased proportions (17-24%) of B cells and 5% have markedly increased numbers. This reflects the range of potential B cell defects that might be involved. For subjects over 49 years of age without B cells, the presence of a thymoma must be excluded by computerised tomography. Raised numbers of B cells may indicate the presence of B cell monoclonality.

A potential misdiagnosis of a CVID is less likely, provided that those with a family history of a suspected immune deficiency, absent B cells, abnormal lymph-node architecture, raised serum IgM, raised B cell numbers or extensive lymphadenopathy are screened genetically (Eastwood 2004) for known single gene diseases

Failure of antibody production following known exposure or immunisation is the crucially important feature of CVIDs in the IUIS definition as well as in most national guidelines. The most commonly used, licensed vaccines include tetanus toxoid, diphtheria toxoid, hepatitis A subunit, hepatitis B surface antigen, rabies, tick-borne encephalitis, and pneumococcal polysaccharides (Pneumovax) and Haemophilus conjugate vaccines. Alternatively, failure of antibody production can be tested following documented infections such as chicken pox or shingles (VZV), measles or invasive *Strep. pneumoniae* infections. However there is a hierarchy to the strength of the antigens used in both vaccines and during exposure to environmental pathogens. For example tetanus toxoid, measles and VZV are strong immunogens whereas diphtheria toxoid is relatively weak; there are often low titre but detectable antibodies present to tetanus toxoid or measles antigens (Goldacker 2007). Transient antibodies were produced in patients infected with hepatitis C virus in 1994 (Healey CJ 1996) thus it seems logical to check not only titre but persistence (that is still present 6 months after immunisation or exposure). Patients with moderately reduced immune globulin levels and some retained antibody production may have declining immune functions later and should be re-evaluated at intervals as they may meet the full criteria for immunoglobulin replacement in time. We propose that the minimum criterium for

competence in antibody production is the demonstration of protective levels of specific IgG to two or more protein antigens after immunisation or exposure (Chapel 2007, Orange 2006). Patients with a CVID generally fail to produce a four-fold increase in specific IgG, or to have only transient antibodies, to protein antigens.

The production of antibodies after test immunisation to carbohydrate antigens, such as Pneumovax, is more problematic as there is huge variability in antibody responses amongst healthy individuals to existing panels of pneumococcal antigens (Hare ND 2008, Musher DM 2008), whilst a proportion of apparently healthy individuals do not appear to respond to some serotypes. The development of an assay to measure IgG antibody following Typhum Vi (salmonella carbohydrates) may help to define abnormal responses (Ferry et al 20 ADD REF). The lack of such antibodies does support a diagnosis of a CVID and other forms of antibody failure including chronic lymphocytic leukaemia (CLL) (Chapel HM 1987, Wadhwa PD 2006).

Suggested definitions of CVIDs have occasionally included a requirement for significant infections. However, while the majority of patients who have low levels of serum immunoglobulins have had recurrent acute /unusual/ persistent or severe infections, 10% of patients with remarkably low levels of immunoglobulins may be infection free. These may present with ITP, AHA, a sarcoid-like picture (Arnold, *et al* 2008), minor infections or even no infections. It is important to check specific antibody production in such patients, as immunoglobulin therapy is not usually required for those patients who are able to produce antibodies.

As discussed, CVIDs remain diagnoses of exclusion, as outlined on Table 1. We have used the following laboratory definition of common variable immunodeficiency disorders (CVIDs); we suggest that subjects included in clinical studies meet these criteria:

1. 4 years of age or older
2. Serum IgG levels < 4.5 g/l for adults or the 2.5th centile for age, usually with levels of serum IgA below the lower limit of normal for age but alternatively serum IgM below the lower limit of normal for age
3. Significant lack of antibody responses to protein antigens following immunisation or exposure antigens *in at least two assays*
4. Exclusion of all other known causes of failure of immunoglobulin production, as in the IUIS table (Geha 2007)

There are additional criteria that could be used, such as very low numbers of circulating switched or memory B cells, but these are not specific for CVIDs, as loss of these cells occurs in other forms of primary and secondary antibody deficiencies. The recommended investigations can be found in most national and international guidelines and are outlined in Table 2.

Prevalence

There have been no real changes in the reported prevalence of these conditions in recent years. The overall prevalence of primary antibody deficiencies in Sweden is 1:230 which includes selective IgA deficiency and all IgG subclass deficiencies not usually included in other surveys (Björkander J 1984, Grumach AS 1997, Kirkpatrick P 2007, Matamoros Flori N 1997, Rezaei N 2006, Stray-Pedersen A 2000). These figures vary due to different levels of ascertainment in differing countries (see Table 3). The most reliable minimum figure for CVIDs is a minimum of 1:30,000 (Stray-Pedersen A 2000).

Presentation

Several large series of patients have reported the tremendous variety of presenting symptoms in the past and the reader is referred to these (Cunningham-Rundles 1999, Hermaszewski 1993). There are no particular recent changes, other than awareness of the need to investigate those very few patients who develop systemic bacterial disease despite being immunised with appropriate bacterial vaccines (Heath 2000). Although most patients present with recurrent bacterial infections, some present with suggestive inflammatory or autoimmune complications (Arnold, *et al* 2008, Cunningham-Rundles 2002, Kalha and Sellin 2004, Knight and Cunningham-Rundles 2006).

Complications

Most of the complications have been known for some years and clinical immunologists are well aware of them (Figure 2). They include conditions due to acute or chronic infections, characteristic inflammatory or autoimmune processes and occasionally neoplastic disease. These complications may be present at the onset or may appear later. As patients are living longer, the prevalence of these complications is increasing. A striking finding in the recent analysis of 334 European patients (representing 9,461 patient-years) showed that there were significant differences in the prevalences of these complications between countries (Chapel 2008). Since the analyses included only those of Caucasian origin, differences due to racial background were excluded. With increased reporting of such patients from newly established registers in countries such as Malaysia, Japan and Iran, new patterns of complications of CVIDs may emerge.

While not easily dissected in every case, it is important to distinguish those complications due to previous infections from those associated with underlying immune dysregulation, a cardinal theme in the CVID syndromes. Thus complications can be divided into structural damage due to significant prior infections, particular and unusual infections, and the consequences of the underlying immune dysfunction.

Complications related to infections

The particular infection risk for patients with any form of antibody failure is from extracellular bacteria, especially those that affect the respiratory tract (Hermaszewski and Webster 1993), namely *Haemophilus influenzae* (non-encapsulated) and *Strep. pneumoniae*. Recurrent infections in the upper respiratory tract result in chronic sinusitis. Recurrent infection in the lower respiratory tract were also thought to result in bronchiectasis, since bronchiectasis is a common finding in CVIDs patients at presentation (Kainulainen 2001, Kainulainen, *et al* 1999b). However in the large European study, bronchiectasis was only related to previous serious infections (pneumonia/septicaemia)($p=0.03$) rather than recurrent moderate chest infections (Chapel 2008). Quite intriguing was the fact that these serious infections were not related to presenting levels of serum IgG < 1.5 g/l. Neither was bronchiectasis related to diagnostic delay (a surrogate for lack of immunoglobulin treatment), time since onset of symptoms (for length of disease) or smoking (Chapel 2008). Not surprisingly there was reduced survival in those with bronchiectasis ($p<0.001$), as reported previously (Ilowite J 2008). These data suggest that selected serious infections initiate a destructive pulmonary process and that serum levels of IgG antibodies are not the sole determinant of this outcome. Recent data shows that those patients who only suffer from bacterial infections have markedly improved survival compared with those that have other disease related complications (Figure 4), again reflecting the heterogeneity of these conditions (Chapel 2008).

Patients with CVIDs are also known to be susceptible to infections with particular organisms. Recurrent urinary tract infections due to *Ureaplasma urealyticum* may result in a fibrotic bladder (Webster AD 1982). Joint infection with a *Mycoplasma* species (Bloom, *et al* 2008, Franz A. 1997, Lee, *et al* 1993) has resulted in severe destruction. Enteroviral infections causing meningo-encephalitis or dermatomyositis were largely restricted to antibody deficient patients (CVIDs and XLA) when lower doses (0.1 - 0.3 g/Kg/month) of therapeutic immunoglobulin were used (Halliday E 2003). The exact immunological deficiency that causes susceptibility to these particular organisms is unknown, though exploration of innate mechanisms is underway (Cunningham-Rundles, *et al* 2006). Susceptibility to gastrointestinal *Giardia* infections is also increased in antibody deficiencies and can cause both malabsorption and enteropathic histology (Onbaşı K 2005). Such selected infections occur more frequently in those with any form of severe antibody failure (e.g. CVIDs or XLA) in comparison with the general population; furthermore there has been a reduction in prevalence since higher doses of immunoglobulin have been used (Wood 2007), so it is likely that the immunopathogenesis involves a dysfunction of B cells.

Autoimmune/inflammatory/immunoproliferative complications

The non-infective, or disease related, complications of CVIDs have been known for some time (Cunningham-Rundles and Bodian 1999, Hermaszewski and Webster 1993) and yet for the most part are quite poorly understood. These intrinsic complications include autoimmune, inflammatory and immunoproliferative pathologies. The variation in cohorts from different countries suggests that these may be related to varying genetic backgrounds. There is some evidence that disease-related complications are more frequent in those with an earlier age of onset (Dalal 1998, Quartier P. 1998) and that these may be associated with a poorer prognosis. Whether or not such individuals represent a distinct antibody deficiency syndrome remains controversial.

Some of these complications can be divided into groups in terms of likely immunopathogenesis (Figure 3). In terms of prevalence, the commonest autoimmune conditions in CVID are the cytopenias, immune thrombocytopenia (ITP) in particular, also haemolytic anaemia or more rarely autoimmune neutropenia; all are much more frequent than in the general population. Cytopenias occur in 11-12% of patients (Chapel 2008, Wang and Cunningham-Rundles 2005), often before antibody deficiency is suspected; it is not uncommon for patients to have several episodes of acute thrombocytopenia or haemolytic anaemia, or both at different times and logistic regression showed no significant difference for autoimmunity when analysed for time since onset of symptoms. The ratio of females to males is 1.2 and there is no association with organ specific autoimmunity though there is a strong association with splenomegaly ($p < 0.001$) (Chapel 2008). Since a significant number of patients present with cytopenias, this has been used to define a particular clinical phenotype. The risk of early mortality in those patients with a CVID and an autoimmune disease was increased ($p = 0.03$; relative risk 2.5) (Table 5). There appear to be two separate immunologic features for subjects with these autoimmune manifestations, the presence of very low number of isotype switched memory B cells in peripheral blood, and the likelihood of having a mutation in the transmembrane activator and calcium-modulating cyclophilin ligand interactor, TACI. For example, of 14 individuals with TACI mutations (11 heterozygous and 3 compound heterozygotes, in a cohort of 199 CVID patients tested), 10 had significant splenomegaly. Comparing CVID subjects with and without mutations, these differences were significant (Zhang, *et al* 2007) and similar to those in a European cohort (Salzer, *et al* 2008). Whether or not these patients have a genetic predisposition, possibly shared with immunocompetent individuals, remains to be seen.

The solid organ-specific autoimmune diseases, such as pernicious anaemia, thyroid diseases and vitiligo have prevalences in patients with CVIDs that are more than 5%, more common

than in the general population. Other autoimmune/ inflammatory conditions include insulin dependent diabetes, psoriasis, systemic lupus, rheumatoid arthritis, juvenile rheumatoid arthritis and uveitis but the prevalence in comparison to other populations has not been clarified (Cunningham-Rundles 2008).

Another characteristic inflammatory phenotype in CVIDs is the presence of multisystem granuloma. The aetiology of these lesions remains a mystery; they may be a consequence of diminished cell mediated immunity resulting in persistent though undetected viral or other infection since they are significantly associated ($p = <0.001$) with, but not always present alongside, lymphoid interstitial pneumonitis or persistent unexplained lymphadenopathy. Such an infection could trigger an inflammatory response that fails to be down-regulated once the infection is resolved. Alternatively granuloma may represent an intrinsic autoimmune condition, since immune thrombocytopenia or haemolytic anaemia are commonly associated. Increased levels of TNF in serum (Aukrust, *et al* 1996) in patients with granuloma suggested chronic mononuclear cell activation, possibly with a predisposition to over production of TNF. We showed that the TNF 488A allele is strongly positively associated with granulomatous disease in CVIDs ((Mullighan, *et al* 1997); a later report suggested an association with particular IL-10 promoter haplotypes (Mullighan, *et al* 1997, Mullighan, *et al* 1999).

The aetiology of lymphoid interstitial pneumonitis (LIP) remains obscure. Attempts to demonstrate an infective cause by PCR, viral antigen staining or in situ hybridisation have failed. It is not clear whether or not LIP is the result of HHV-8 or an unknown viral or other agent (Wheat, *et al* 2005). Since treatment with low-dose oral corticosteroids does reverse the largely T cell (CD4+ or CD8+ cells) infiltration, chronic infection seems less likely. However, post-mortem studies have shown end-stage fibrosis in the lungs of those with LIP treated with steroids (Bhole – personal communication), maybe following cytokine-induced chronic inflammatory changes. This group has a high mortality rate ($p = <0.001$) (relative risk 3.0) (Table 5) (Chapel 2008).

A poorly characterised gastrointestinal inflammatory complication, unexplained (or idiopathic) enteropathy, also occurs in CVIDs. While the pathology is similar to that of coeliac disease, unlike coeliac disease this enteropathy is not responsive to gluten withdrawal. (Arnold, *et al* 2008, Aslam A 2004, Daniels JA 2007, Knight and Cunningham-Rundles 2006, Mannon, *et al* 2006). The infiltrative lymphocytes are commonly T cells but this does not necessarily indicate an autoimmune aetiology. anti-Enterocyte antibodies found in a 13-year-old boy with common variable hypogammaglobulinemia and type I diabetes (ref Catassi 1988) could be responsible, suggesting an autoimmune pathogenesis. However these have also been reported in IPEX where they are thought to be of a secondary nature and not immunopathogenic (Ruemmele 2004)

There are associations between this gastrointestinal phenotype and persistent unexplained lymphadenopathy ($p = 0.01$) or hepatomegaly ($p = 0.03$), which might reflect a common aetiology. This complication has the highest rate of non-malignant mortality ($p = <0.001$) (relative risk 4.0) (Table 5) (Chapel 2008), possibly due to the resulting malabsorption. It is important to distinguish the secondary effects of particular complications. For example enteropathy was associated with iron deficiency ($p = <0.001$) (Chapel 2008) and failure to absorb fat soluble vitamin E is a complication of enteropathy even in patients without obvious symptoms of malabsorption (Aslam A 2004). In contrast low levels of vitamins A and D are found more generally in CVIDs patients, including in those without enteropathy or malabsorption.

Splenomegaly is common in patients with CVIDs (30%), though there are a variety of potential causes (hepatomegaly, infiltration, expansion due to cytopenias, excessive macrophage activity due to persistent infection). Hepatomegaly also has a variety of common causes, including infection with extrinsic agents (such as hepatitis C or alcohol), autoimmune liver disease (chronic active hepatitis or primary biliary cirrhosis) or infiltrative conditions (malignant metastases). Recently unexplained hepatomegaly in CVIDs has been shown to be due to nodular regenerative hyperplasia (Ward, *et al* 2008) (Malamut G 2008). There is no evidence of inflammation on liver histology and it is likely to be a non-specific tissue response to varied blood flow rather than being a specific pathological process (Wanless 1990), though there were associations with cytopenias and non-gluten sensitive enteropathy. It was reassuring that there was no correlation with length of time on immunoglobulin therapy, despite higher IgG trough levels (Ward, *et al* 2008), suggesting that transmission of an unknown pathogen is unlikely. There was only moderate fibrosis in our series though portal hypertension secondary to cirrhosis was common in the French patients (Malamut G 2008).

Continuing the theme of lymphoid hypertrophy, symptomatic lymphoid hyperplasia is another common feature in CVIDs, often in concert with splenomegaly. Investigations for the presence of lymphoma are inevitable. In most cases, benign lymphoid hyperplasia is found on biopsy. Clonal analysis can be misleading (Gompels MM 2003) as oligoclonal lymphocyte populations were demonstrated in biopsies irrespective of histology in a UK study of 29 such CVIDs patients, suggesting that isolated evidence of clonality in biopsy material is insufficient to determine malignancy.

Lymphoid malignancies

About 2-8% of subjects with CVID are diagnosed with a non-Hodgkin's lymphoma, particularly now that patients are living longer. In most cases these are B cell in type, are usually EBV negative and in many cases the B cells are well differentiated. (Gompels MM 2003) These are most likely to occur in the 6th or 7th decades of life but have been reported in younger patients too. These lymphomas almost always extra-nodal, and have a tendency to locate in mucosal regions. (Cunningham-Rundles, *et al* 2002). The development of lymphoma has been variously associated with the presence of lymphoid hyperplasia, granulomatous disease (Le Guern 2003) and the retention of serum IgM (Chapel 2008). As BCL-6 mutations have commonly been found in CVID lymphomas, a germinal centre origin has been suggested (Ariatti 2000). An earlier report noted a female preponderance; in a European cohort, in that 3 of the 4 lymphomas in 176 subjects were found in women ((Mellemkjaer 2002).

Due to the frequency of recurrent infections associated with low serum immunoglobulin levels in patients with proven chronic lymphocytic leukaemia or non-Hodgkin's lymphoma (NHL), it is important that such a malignancy is distinguished from lymphoma complicating a long standing CVID, particularly as all result in accompanying antibody production failure. The inclusion of a period of two years after a finding of primary antibody failure before a diagnosis of a CVID is confirmed aids the distinction between primary failure and a lymphoid malignancy complicating a CVID. The histology can be indistinguishable from a primary tumour, including absence of EBV antigens on immunohistology; this may be an important distinction from those lymphoid tumours associated with another condition confused with CVIDs, namely X-linked lymphoproliferative disease in which EBV driven tumours are seen. The pathogenesis of tumours associated with CVIDs remains unknown. Treatment however does not differ from spontaneous NHL.

While stomach cancer has been noted in patients with a CVID, it is usually associated with pre-existing pernicious anaemia and appears to be rare in large cohorts nowadays.

Complications due to therapies

Complications due to transmission of infectious agents, such as hepatitis B or hepatitis C, are now extremely rare (Bresee JS 1996, Chapel 2001), due to improvements in the elimination of viruses in the extraction processes of immunoglobulins from plasma. Although concerns remain about new or unknown infectious agents, there is no data to suggest that transmission is a current risk. However, it is still important to continue to monitor patients on replacement therapy.

The side effects of splenectomy, corticosteroid and immune suppressive therapies are well known and are particularly relevant in those who are already immune deficient.

Clinical Phenotypes, Outcomes and Prognosis

The recent analysis of a large cohort of 334 European patients (largely British and Swedish) showed that it is possible to use the clinical and immunologic characteristics described above, to sort out the various different syndromes that make up the group of CVIDs and define the distinct clinical phenotypes (Chapel 2008). This data relates mainly to adults since relatively few children presented with a CVID in this or indeed any other series.

The aim was to develop criteria for clinical phenotyping to help in the interpretation of disease causing and disease-modifying genes, a search was made for significant associations between the various characteristic complications. Only intrinsically related disease complications were used for clinical phenotyping and the criteria chosen were shown to be independent of each other. Common or secondary features, such as splenomegaly and bronchiectasis respectively, were not included. The criteria developed resulted in 83% of patients exhibiting features of one clinical phenotype only; 12.6% of patients showed criteria for 2 clinical phenotypes. Only 8.4% of the whole cohort had features of both lymphocytic infiltration and autoimmunity. The proportion of those suffering only breakthrough infections and or the structural consequences of previous infections was 35%.

Later onset of symptoms was associated with the “infections only” phenotype ($p = <0.001$) and also with autoimmunity ($p = 0.01$). Surprisingly the age at onset of symptoms was not predictive of polyclonal lymphocytic infiltration, enteropathy or malignancy. The phenotypic characteristics of individual subjects were stable over a period of years as there were no differences in the prevalences of these clinical phenotypes at 5, 10 or 15 years after diagnosis. This suggests that it may be possible to detect the likely ongoing phenotype within 5 years of diagnosis, though this needs to be confirmed. It is clear from the data that a considerable number of patients have not developed infiltrative, autoimmune or other inflammatory complications over 25 years, whereas other subjects are found to have these problems at the time of initial diagnosis.

The use of clinical phenotyping for prognosis, as well as to clarify the several conditions that make up CVIDs, was demonstrated by the different survival rates in individuals with different phenotypes (Figure 4), suggesting there is biological validity to clinical phenotyping. It also confirmed the clinical suspicion that the particular complications making up the polyclonal lymphocytic infiltrative phenotype are associated with reduced survival (Bates, *et al* 2004, Quinti, *et al* 2007) as each clinical phenotype was significantly associated with reduced survival. Not surprisingly those patients who developed a lymphoid malignancy had the worst prognosis (Table 5) and those with infections only had the longest survival, with life expectancy almost equalling that of the general UK population (Figure 4).

Immunophenotyping and clinical outcomes

The role of immunophenotyping has also demonstrated that CVIDs are a group of syndromes. The variability of the numbers and proportions of T, B, NK cells in the circulation of patients with CVIDs has been known for many years (Spickett 1990). The first attempt to classify patients depended on the ability of B cells to secrete different classes of immunoglobulins in vitro after appropriate stimulation (Bryant, *et al* 1990). This was successful in dividing patients with the most severe hypogammaglobulinaemia from those with more normal serum immunoglobulin levels. There were some correlations of more severe forms with an enlarged spleen but it was not possible at this time to correlate with clinical severity or with other complications.

More recently classifications based on the numbers of B memory cells have been proposed and these show some associations with splenomegaly or autoimmunity (Piqueras, *et al* 2003, Sanchez-Ramon, *et al* 2008, Warnatz, *et al* 2002, Wehr, *et al* 2008). Since low or absent B memory cell numbers is a feature of most antibody failure syndromes, the practical usefulness of these classifications remains to be determined. However they do provide useful pointers in studies of immunopathogenesis and have been shown to supplement the in vitro secretion classification of Bryant *et al.* (Ferry BL 2005, Livaditi O 2007).

The use of immunological markers to predict complications was attempted as part of the European study but only significant correlations between serum IgM levels at presentation and the development of polyclonal lymphocytic infiltration ($p=0.018$) or lymphoid malignancy ($p=0.02$) were found (Chapel 2008). In relation to cellular immunophenotyping, baseline CD8 proportions were lower in those that developed autoimmunity ($p=0.04$). Higher proportions of total CD4⁺ cells were associated with lower serum IgG levels at presentation but since these were not associated with more severe infections, this was not of prognostic significance though possibly interesting in terms of pathogenesis.

Genetics

Patients with CVIDs can be divided into those with a positive family history for some form of primary antibody failure (usually selective IgA deficiency) and those that do not; the latter group are known as spontaneous CVIDs and represent about 90% in Caucasian CVID populations (Cunningham-Rundles 1999). Linkage studies may not be revealing for these patients except for a few non-redundant genes. Comparison of this incidence of inheritance with that in Iran (20% in consanguineous families) (Aghamohammadi A 2008) may suggest autosomal recessive defects in this population. In rare families, perhaps accounting for 1% of CVIDs patients, a pattern of autosomal dominant inheritance involving chromosomes 4q, 16q or 6 appears to be associated with immunoglobulin deficiencies (Vorechovsky I 1995). However for most patients, a mixture of polymorphisms in conjunction with environmental factors are more likely to be involved since these diseases are not familial and are of late onset. In addition, genes that act in a disease modifying capacity, and so contribute to the varying clinical phenotypes, have been described (Tables 6 and 7).

Possible disease causing mutations

Using a candidate gene approach within families with several affected members, one form of CVID was shown to be caused by homozygous ICOS deficiency in 13 members of 9 families. A large deletion in *ICOS* was the same in all subjects and is likely to be a founder effect (Grimbacher 2003). This deficiency may be better classified as a hyper-IgM syndrome, being a defect in a T cell related protein involved in immunoglobulin class switching. Several patients with XLP, due to defects in the *SAP* gene, and gradual onset of antibody failure have been shown to have defects in ICOS and to have a CVID-like clinical

syndrome (Eastwood 2004). Mutations in the CD19 gene have also been shown to cause a CVID phenotype; three siblings in a family from Columbia (van Zelm MC 2006) and other subjects identified subsequently (Kanegane, *et al* 2007). These observations demonstrate that selected mutations in non-redundant genes can result in B cells that are incapable of antibody production.

In contrast, polymorphisms in genes that have more subtle effects on B cell function are also associated with CVIDs. These include *TACI* and *BAFFR*. The products of these genes are essential for B cell survival and differentiation. *TACI* homozygous null mutations or compound heterozygous states are associated in some patients with reduced or absent binding of B cell activating factors BAFF or APRIL though not necessarily with a CVID-like disease (Castigli, *et al* 2005, Garibyan, *et al* 2007, Salzer 2005). However there are multiple polymorphisms in *TACI*, of which some are also found in antibody sufficient individuals in the heterozygous state (Pan-Hammarstrom, *et al* 2007). These polymorphisms may contribute to susceptibility to antibody failure in our out-bred species. In addition, as discussed above, heterozygous mutations in *TACI* have been found to be significantly associated with an increased likelihood of developing autoimmunity and lymphoid hyperplasia in patients with a CVID. Whether or not there are mutations that are involved in plasma cell differentiation in those patients with some residual but low levels of antibodies remains to be seen (Mantchev, *et al* 2007). Since mutations in BAFF or BAFF-R cause B-cell lymphopenia and antibody deficiency in mice, defects of these were sought in patients with CVIDs. One patient and his apparently healthy elderly sibling were identified with identical homozygous deletions in *BAFFR* (Warnatz K 2005); the significance of this mutation is not yet clear.

Twelve percent of patients with a CVID are likely to have an immunoglobulin class switch defect. The DNA repair protein, Msh5, has been shown to be involved switch regulation and two single nucleotide polymorphisms in the *MSH5* gene have been associated with CVID and with selective IgA deficiency (Sekine H 2007). This may also represent a disease susceptibility polymorphism (see Table 6).

Possible disease modifying polymorphisms

Genes that may modify the clinical picture in a patient with a CVID include those for the cytokine TNF, the intracellular non-specific pattern recognition receptor NOD2, the enzyme inhibitor $\alpha 1$ antitrypsin, complement activator mannose binding lectin MBL, the regulator gene for IL-10, interleukins IL-12 and Interferon as well as Vitamin D receptors and CTLA4. These are the candidates that have been studied so far and the results are summarised in Table 7 (Fazlollahi MR 2006, Knight, *et al* 2007, Litzman J 2008, Martinez-Pomar N 2006, Mullighan, *et al* 1997, Mullighan, *et al* 1999, Mullighan, *et al* 2000, Sansom 2002).

The low levels of vitamins A and D are associated with reduced receptors for retinoic acid (Aukrust P 2000, Kilic SS 2005). Since not all CVIDs patients have these findings, it is may be possible to distinguish a disease modifying polymorphism. There are also patients with unexpected Vitamin D deficiency in the absence of enteropathy. The mechanism of this deficiency is unknown, though vitamin D receptor expression was found to be lower in the peripheral blood mononuclear cells and hair follicles of CVIDs patients when compared to a control group (Ardeniz O 2008); searches continue for disease modifying polymorphisms in the genes for these receptors.

Management

There is new data on survival of patients. Mortality was high in patients in an earlier series (Cunningham-Rundles 1999) and patients with selected complications still have shortened life (Chapel 2008) (Figure 4) but in general patients are surviving longer (Figure 4), maybe due to higher doses of therapeutic protective antibodies and more liberal use of antibiotics (Wood 2007).

However other factors also play a role. With the growth of patient organisations to assist with patient & physician education, patients understand that recurrent or untreated infections can result in either the development of bronchiectasis or worsening of pre-existing disease. This results in prompt treatment of breakthrough infections and easier access to wider range of antibiotics from their medical advisers; many patients hold their own reserves at home with careful instructions for use. One outstanding issue is the role of prophylactic antibiotics in those with pre-existing bronchiectasis.

Patients are followed regularly by clinicians with experience of primary immune deficiencies for the variety of common and rare complications. Careful monitoring of CVID patients to detect autoimmune conditions (including cytopenias), enteropathy or lymphoproliferation is undertaken, since those with such clinical phenotypes have reduced survival. NRH usually develops slowly in patients with chronic systemic illness and regular monitoring of liver function, originally undertaken to detect transmission of HCV, should be continued and endoscopy instigated if portal hypertension is suspected. CVIDs patients with a liver alkaline phosphatase level more than 1.5 times the upper limit of normal for more than 6 months should have a liver biopsy (including reticulin staining) to look for NRH and granulomata (Ward, *et al* 2008). Immunologists should have a low threshold for obtaining biopsy material from other sites to confirm other treatable complications.

As with other immune deficient or suppressed patients, it is important that advice about travel and everyday risks is available. Provided there is good compliance with immunoglobulin replacement therapy and prompt treatment of any intercurrent infection, patients are not at any known risk relating to travel, life-style, employment or pregnancy.

Treatment with replacement immunoglobulin

Basic treatment for CVIDs is the replacement immunoglobulin in adequate doses. This has been standard therapy for over 30 years, commencing with intramuscular products but abandoned once safe intravenous (IVIg) or rapid subcutaneous (SCIg) administration was possible. The aim of therapy is a significant reduction of bacterial infections and prevention of all serious, life-threatening infections. This has been largely achieved by the IgG trough level reaching normal levels, with data to show that use of larger doses of immunoglobulin (usually 0.4-0.6 g/Kg/month in divided doses) does obviate breakthrough infections (Eijkhout HW 2001, Riofman C. 2003, Roifman C. 1987). A few individual patients require higher doses but these are exceptions. It is important to realise that individual patients require very variable doses to prevent infections and that simply relying on IgG trough levels is not sufficient.

There have been few recent advances in the methods for replacement immunoglobulin therapy. Both IVIg and SCIg have been proven to be efficacious in infection prevention, to be safe in terms of infusion related adverse events (Brennan V. 2003) and to result in improved quality of life for affected patients (Gardulf A 1995a, Gardulf A 1995b). Whilst self-infusion by the IV route at home in the UK, US and now France, has been accepted for many years, the use of SCIg (Gardulf A 1995b) has increased the availability of home treatment programmes in the rest of Europe and world-wide.

Management of complications

Not all complications require therapy and the instigation of additional treatments aside from standard measures, depends on a risk assessment in each patient. However some complications do necessitate therapy, such as cortico-steroid therapy (with or without steroid sparing measures) for significant autoimmunity, substantial granulomatous or lymphoid infiltrations in essential organs (Bates, *et al* 2004, Meyer, *et al* 2005, Misbah, *et al* 1992, Park 2005, Thatayatikom, *et al* 2005), including acute ITP, AIHA or reduced lung function (Bates, *et al* 2004, Mechanic, *et al* 1997, Morimoto and Routes 2005). The course of such treatment is a matter of clinical judgement; higher doses tapering in a few weeks or low doses for several months will depend on other factors such as the condition being treated, complications such as secondary candidiasis, herpes simplex infection or the presence of pre-existing osteopenia.

In general moderate doses of corticosteroids have been safe in CVIDs patients and should be used as in immunocompetent individuals, though there are a few reports of intestinal cytomegalovirus infection after long-term high dose steroids in CVIDs (Daniels JA 2007, Kainulainen, *et al* 1999a, Medlicott SA 2006, Raeiszadeh M 2006). The use of antiviral agents, such as Ganciclovir, appears to be as safe (as in patients with HIV) and effective but again the data is anecdotal (Medlicott SA 2006). Greater use of biopsy material with immunostaining for CMV antigens and in situ hybridisation as well as blood tests such as PCR to determine CMV status, should be used to monitor those in whom prolonged corticosteroids are used. Unfortunately neither Pleconaril or Ribavirin were not found to be useful against enteroviruses in those few that developed enteroviral meningo-encephalitis (Rotbart HA 2001).

A controversial area is that of new therapies for granuloma in CVIDs. As for sarcoidosis, there is international agreement (Arnold, *et al* 2008) that if therapy is to be used, corticosteroids are the first line of therapy. The use of steroid sparing agents, such as azathioprine, 6 mercaptopurine, cyclosporine A, mycophenolate mofetil, or methotrexate have been used successfully in anecdotal reports but the low prevalence of this complication makes controlled or open trials difficult. The same is true for the use of hydroxychloroquine for the treatment of granuloma and lymphoid interstitial pneumonitis. Reports of the use of TNF antagonists are sparse (Bates, *et al* 2004, Chua I 2007, Hatab and Ballas 2005, Lin, *et al* 2006, Smith and Skelton 2001, Thatayatikom, *et al* 2005) and the outcomes not established. An international treatment register for the rare use of anti-TNF monoclonal antibodies (or other therapies in due course) is needed urgently, along with agreed methods for monitoring, in order to capture successful and unsuccessful courses of treatment.

Therapies for the lymphoid infiltration resulting in gluten-insensitive enteropathy have been largely unsuccessful, though the non-absorbable corticosteroid, budesonide, or low dose 6 mercaptopurine have been found to be useful. The malabsorption resulting from the enteropathy can be extremely debilitating and potentially fatal. Since most patients are not screened for nutrient deficiencies, including vitamins A, D and E, deficiencies are often missed. All patients with unexplained malabsorption should be screened initially for low levels of fat-soluble vitamins and have a bone scan even if they are free of osteomalacia or gastrointestinal related symptoms (Ardeniz O 2008).

The use of splenectomy for those patients with ITP or AHA remains controversial in the absence of data. There is an international audit underway in Europe, though local audits in Oxford and Mount Sinai found that patients were not at increased risk of serious or life-threatening infection with encapsulated organisms if the patients remained on replacement immunoglobulin therapy. Data on the use of Rituximab (anti CD20 monoclonal antibody)

therapy in CVIDs patients is limited to anecdotal experience (Cunningham-Rundles 2008); the proven low risk and apparent efficacy for ITP and AIHA in immunocompetent patients is reassuring.

Treatment of malignancies in patients with a CVID is no different from that in an otherwise immunocompetent patient, though it is particularly important to monitor adequacy of replacement immunoglobulin therapy by the serum trough IgG level and to increase the dose of immunoglobulin if needed.

Current controversies

Definition

There are many aspects to this group of primary antibody failure syndromes that are not understood at present but the first responsibility of those who diagnose and manage these patients is to agree on a revised international set of diagnostic criteria. For example, once the age of onset is agreed, i.e. that late onset (>4 years) is a more practical cut-off, registers can use standardised data for diagnostic validation (Chapel 2008). The inclusion of patients with evidence of recurrent or severe infections should distinguish patients with CVIDs from those healthy individuals with low serum immunoglobulin levels but normal antibody production. Whether or not the serum level of IgA should be low, and if so how low, is also unresolved. This is variable depending on the population studied: 49% of European patients had undetectable serum IgA (<0.07g/l) (Chapel 2008) compared with 70% in the US study (Cunningham-Rundles 1999). This might be explained by the difference in gender distribution (58% and 41% males in the studies respectively), since normal levels of serum IgA are higher in women with a CVID (Cunningham-Rundles 1999). The 1999 diagnostic criteria stated that IgG and one of the other 2 major immunoglobulin levels needed to be below the normal range; those with normal IgA but low IgM are still included, though they may form a separate subgroup with a distinct immunopathogenesis.

Diagnostic delay and age of onset

Although there is greater medical and public awareness of immune defects, the length of diagnostic delay for subjects with a CVID has not changed significantly over 20 years (Quinti, *et al* 2007, Seymour 2005). Since it has been difficult to be certain of the date of onset of characteristic symptoms, greater attention to the patient's past history is essential, particularly if data relating to potential triggers is to be determined. The ages of patients at diagnosis varies markedly as in other late-onset diseases such as insulin dependant diabetes (now known to be polygenic in nature). Whether or not there are particular age peaks for presentation will depend on the use of precise definitions and larger groups of patients than those reported so far. Cunningham-Rundles suggested two age peaks of diagnosis (Cunningham-Rundles 1999) but statistical analysis on the largest group (Chapel 2008) showed no significant variation with age and confirmed the range of age of diagnosis to be 4 – 80+ years. Once national registers are truly representative of both adult and paediatric populations, this will become clear.

Causes of complications

Unfortunately nothing definite is known of the causes of enteropathy or lymphoid interstitial pneumonitis. Nor are the aetiologies of the widespread granuloma or the nodular regenerative hyperplasia in the liver known. Granuloma may be due to intrinsic lymphocyte or macrophage activation in patients with an increased genetic susceptibility due to polymorphisms in genes such as *TNF* or *NOD-2*. NRH may have a vascular pathogenesis but this is speculative.

Immunopathogenesis

Finally the role of genetics in terms of causative mutations, susceptibility polymorphisms or both, remains controversial and poorly understood at present. It is also problematic to attempt to correlate the numerous studies of selected cell types reported in the literature. This is due to the small numbers of patients, often with poorly characterised disease, studied in any one report. Searching for a single aetiology or even pathogenesis is unlikely to yield significant results in view of the diverse nature of CVIDs. However failure to demonstrate vertical or horizontal transmission of CVIDs makes a transmissible infective agent an unlikely cause.

Defects in pathways involving dendritic cells, T cells and B cells have been reported in patients with CVIDs but usually without reference to the clinical phenotype of these patients. Clinical evidence that failure of antibody production is due to T cells, at least in some patients, comes from reversion to full antibody production with HIV infection (Branda, *et al* 1996, Webster AD 1989, Wright JJ 1987), suggesting that B cell function is reversible in some situations. On the other hand irreversible intrinsic B cell differentiation defects probably account for those cases with very low numbers of B cells. Since there are different pathways for the production of antibodies to viruses, bacterial cell walls and polysaccharide capsules, involving different cell types, many B cell pathways could be dysfunctional in the majority of patients with normal B cell numbers. Furthermore, presentation of auto-antigens is quite different from that of extrinsic antigens, so that those patients with autoimmune defects as well as primary antibody failure may have more than one defect.

Abnormalities in T cell numbers and function, reviewed in (Giovannetti, *et al* 2007), have been associated with granuloma and only rarely with unusual viral infections (Narula S 2007). Furthermore enteroviral infections occur in XLA patients in whom T cells are thought to be normal. It is important to distinguish primary T cell abnormalities from those secondary to disease or therapy. Abnormalities of T cells in 19 CVIDs patients with raised inflammatory markers showed enhanced CXCR3 serum levels as well as CXCR3 receptor expression when compared with 44 CVIDs patients with normal acute phase proteins (Fevang B 2008). This suggests that ongoing inflammation does affect immunophenotyping, making identification of the various immunopathogeneses even more complicated.

Future work

- Progress in understanding the causes of antibody failure will be limited until the separation of this heterogeneous group of diseases into distinct phenotypes is confirmed and clinical and immunological markers are found.
- There is a need to improve and standardise further the criteria for each phenotype, so that these phenotypes can be tested in other populations, particularly in view of the country variations in the rates of complications.
- Since the European analysis was published, the majority of patients with CVIDs and unexplained hepatomegaly have been shown by two independent groups to have nodular regenerative hyperplasia. Since these patients have few other complications, it seems sensible to move them to a new subgroup if NRH is biopsy proven, particularly as the aetiology is likely to be different.
- Disease related polymorphisms should be sought using the new techniques such as DNA microarrays and RNA expression arrays but only on well-defined, large populations

- The search for disease modifying mutations continues, especially for complications such as bronchiectasis, granuloma, polyclonal T or B cell proliferation, the development of lymphoid malignancy or autoimmunity
- Animal models, by knock out or knock in methods, are unlikely to provide useful information as CVIDs are not single gene diseases; furthermore mice may have rather different B cell physiology

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Figure 1.

Figure 1(a): European Cohort: Serum Immunoglobulin isotypes at diagnosis.

Patients are divided into four boxes depending on their presenting IgA level. Each box is subdivided by the IgM level into three columns, with those with the lowest IgM levels (≤ 0.1 g/l) in the first column; those with the highest IgM (> 0.5 g/l) in the third column and those with IgM levels between (0.11-0.5 g/l) in the second column. Each column is divided into three, depending on the IgG level; those in the lower part with IgG ≤ 1.0 g/l; those with IgG $> 3.0 \leq 6.5$ g/l at the top and those with IgG 1.1-3 g/l in the middle. The number of patients in each group is in each box and plotted on the y-axis. (from Chapel et al 2008 with permission from Blood)

Figure 1(b): United States Cohort: Serum Immunoglobulin isotypes at diagnosis.

Similar to Figure 1a, 349 subjects from one medical centre (Mount Sinai, NYC) are divided into the same categories based on presenting serum immunoglobulin levels.

Figure 2. Types of complications in patients with CVIDs and proportions of patients affected
 Patients may have had more than one complication (Data from Chapel et al 2008)
 [Abbreviations: L/N lymphadenopathy; LIP lymphoid interstitial pneumonitis; NHR nodular regenerative hyperplasia].

Figure 3. Individual complications associated with CVIDs across Europe

Patients may have had more than one complication. (from Chapel et al 2008 with permission from Blood)

Figure 4. Survival of patients with CVIDs, by years since diagnosis and by clinical phenotype
 (a) Yellow line represents those patients without complications. (b) Turquoise line represents those patients with at least one disease related complication. Kaplan-Meier plot of survival. (Data from Chapel et al 2008)

Table 1

Differential diagnosis of patients with recurrent bacterial infections by age group

-
- Under 4 years – leaky Severe Combined Immune Deficiencies, transient hypogammaglobulinemia of infancy, XLP syndrome, XLA, hyper-IgM syndromes, myelodysplastic syndromes, Wiskott-Aldrich Syndrome, rare combined immune deficiencies, cystic fibrosis, HIV
 - 5-55 years – loss of immunoglobulin due to renal / gut disease; side effects of medications particularly anticonvulsants and anti-rheumatics (refer to IUIS list)
 - >56 years – thymoma, lymphoid malignancies, side effects of medications particularly anticonvulsants and anti-rheumatics, loss of immunoglobulin due to renal / gut disease;
-

Table 2

Investigations in patients with suspected CVIDs

-
- Serum immunoglobulin levels and electrophoresis
 - Full blood count – particularly absolute lymphocyte count, platelet count and size,
 - Renal and liver function tests including albumin for loss
 - Serum IgG antibodies to exposure and immunization antigens
 - Lymphocyte – T, B and NK cells; B memory (isotype switched and naïve) Urinary protein electrophoresis
 - Any investigations for specific diseases – e.g. fungal or mycobacterial antigens (if granuloma), TSH (if excessive fatigue), faecal fat (if malabsorption), sweat test (to exclude cystic fibrosis),
 - Base line respiratory tests including CT (since bronchiectasis, fibrotic or interstitial disease are common complications)
-

Table 3

Prevalence of antibody deficiencies around the world (based on data for last two decades and population figures for 2000)

		Numbers of patients*	Population in 2000 [$\times 10^6$]	Prevalence
Sweden	Fasth 1982	100	5	1:50,000
San Paulo, Brazil	Grumach 1997	101	157	1:79,000
Spain	Matamoros Flori 1997	300 (213)	35	1:117,000
Norway	Stray-Pedersen 2000	303 (150)	4.45	1:15,000
Iran	Rezaei 2006	242 (195)	22	1:91,000
Australia & New Zealand	Kirkpatrick 2007	930	23	1:25,000

* (Numbers for CVIDs, where given, is in brackets).

Table 4
Correlations between complications (Numbers and p values for associations) (data from Chapel et al 2008)

	Granuloma	Enteropathy -unexplained	Hepatomegaly - unexplained	Lymphadenopathy - persistent	Iron deficiency	Splenomegaly
Lymphoid interstitial pneumonitis (n=10)	5 p=0.0005	1 p=1.0	2 p=0.21	8 p=4.5 × 10 ⁻⁶	6 p=0.04	7 p=0.009
Granuloma (n=28)	-	6 p=0.09	6 p=0.09	13 p=2.3 × 10 ⁻⁵	13 p=0.047	17 p=0.0004
Enteropathy – unexplained (n=29)		-	6 p=0.03	9 p=0.01	17 p=0.0004	14 p=0.03
Hepatomegaly – unexplained (n=29)			-	11 p=0.001	16 p=0.002	22 p=1.1 × 10 ⁻⁷
Lymphadenopathy – persistent (n=49)				-	23 p=0.003	35 p=7.5 × 10 ⁻¹¹
Iron deficiency (n=96)					-	36 p=0.06
Splenomegaly (n=100)						-

Table 5

Prognostic data for different clinical phenotypes in patients with CVIDs (data from Chapel et al 2008)

Phenotype	Significance for increased mortality rate compared with infections only group (p values)	Relative risk
Enteropathy	<0.001	4.0
Polyclonal lymphocytic infiltration	<0.001	3.0
Lymphoid malignancy	0.002	5.5
Autoimmunity	0.03	2.5

Table 6

Types of disease causing genes involved in CVIDs

<i>Single genes</i>
Mutations in which lead to disease on an AD or an AR basis
<ul style="list-style-type: none">• ICOS– one large deletion in a single extended family (founder effect)• CD19 – four families; homozygous and heterozygous mutations in a non-redundant gene
<i>Polymorphisms</i>
Associated with disease susceptibility
<ul style="list-style-type: none">• TAC1 -multiple polymorphisms but also found normal relatives and some controls• BAFFR – limited to 2 families• Msh5

Table 7

Disease modifying genes - polymorphisms studied for associations with different clinical complications

Gene	Clinical phenotype	Association	Reference
TNF	Granuloma	TNF 488A allele, ($p = 0.0009$)	(Mullighan, <i>et al</i> 1997, Mullighan, <i>et al</i> 1999)
IL-10	Granuloma	IL-10 <i>a-t-</i> ($p = 0.002$)	(Mullighan, <i>et al</i> 1999)
NOD2	Granuloma	?	Hackwood submitted
Alpha 1 antitrypsin	Bronchiectasis	No	(Fazlollahi MR 2006, Sansom ME 2002)
MBL	Bronchiectasis Lung fibrosis	Yes ($p = 0.009$) Yes ($p = 0.037$)	(Litzman J 2008, Mullighan, <i>et al</i> 2000)
CTLA4	Autoimmunity	No	Knight <i>et al</i> 2007
IL-12, IFN	Acute phase responses	No	(Martinez-Pomar N 2006)
Vitamin D receptors	VDR <i>ApaI</i> AA	Yes ($p = 0.002$),	(Mullighan, <i>et al</i> 1999)