Clinical and Immunological Spectrum of Common Variable Immunodeficiency (CVID)

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ABSTRACT

We have analysed data from 150 patients initially classified as having CVID. About 10% had laboratory abnormalities suggesting known single gene disorders (eg: hyper-IgM syndrome), and in a few a genetic defect has been confirmed. We have attempted to sub-classify the remaining patients by analysis of their circulating lymphocytes. B lymphocyte markers have been used to estimate the numbers of circulating immature and class switched B cells; there is an association between the presence of high relative numbers of immature circulating B cells, splenomegaly and autoimmune disease. About 25% of CVID patients have a moderate CD4+ T lymphopenia, sometimes with a relative expansion of CD8+ T cells. About 30% of CVID patients have persistent relatively high levels of circulating CD8+ T cells binding immunogenic peptides from EBV or CMV. Many of these patients also have high relative numbers of circulating CD8+ perforin positive T cells, and there is evidence that these cells may be responsible for neutropenia or inflammatory bowel disease in some patients.

The clinical spectrum of CVID is diverse, with some patients suffering from few infections, and over 50% have evidence of structural lung damage. About 25% of UK patients have chronic inflammation in various organs, particularly the lungs, liver and spleen, often with granulomatous changes. Steroids are used to treat many of the patients with chronic inflammatory complications, although trials are in progress with anti-TNF agents. The incidence of these inflammatory complications is different between countries, being rare in Sweden. Attempts to correlate clinical phenotypes with the laboratory abnormalities described above have been disappointing, suggesting that unknown genetic factors unrelated to the cause of the immunodeficiency determine the complications; attempts to identify some of these factors will be discussed. Finally a provisional scheme to sub classify CVID patients according to lymphocyte abnormalities will be presented, the purpose being to focus the screening of candidate genes causing CVID to specific subsets of patients.

Keywords: Common Variable Immunodeficiency, Primary Immunodeficiency

INTRODUCTION

Common Variable Immunodeficiency (CVID) is a diagnosis of exclusion, classifying those patients with severe hypogammaglobulinaemia in whom no known genetic cause of immunodeficiency has been identified. In its severest form, patients with CVID have serum IgA levels below 0.1g/l, IgG levels below 3.0 g/l, and usually IgM levels below 0.2 g/l. The IUIS classification includes milder forms of CVID where patients may have low but not absent levels of serum IgA and IgG levels between 3-7g/l. CVID is the most common of the primary immunodeficiencies
Common Variable Immunodeficiency occurring in about 1:25 000 Caucasians although is very rare in African and Mongolian races. In a substantial subset of patients the disease is genetically associated with selective IgA deficiency (SlgA), a relatively common condition occurring in 1:700 Caucasians. About 20% of CVID patients have a first degree relative with an immunoglobulin deficiency, often SlgAD. A recent genetic linkage study on 101 families containing multiple members with CVID and/or SlgA suggested a major susceptibility locus in the MHC region on chromosome 6, with genes in the HLA Class II region being probable candidates. However, two individuals in one of these families have recently been shown to have a defect in the TACI gene on chromosome 17p (B. Grimbacher - pers. communication). In a different linkage study on individual families with IgAD a susceptibility locus was found in the HLA Class I region, so different loci are being found depending on whether the linkage data is from single or multiple families. A possible explanation for Class I and Class II alleles being involved in susceptibility to CVID will be discussed below.

Clinical Presentation

Most patients with Primary Antibody Deficiency (PAD) present with symptoms of upper respiratory infection, particularly recurrent sore throats and sinusitis, and middle ear sepsis. Recurrent bronchitis is common, and some patients may present with pneumonia, meningitis and/or septicemia. The organisms most commonly involved are Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis (Table 1). The age of onset of symptoms is variable, with about a third of patients presenting in childhood, and the majority presenting between 15 to 40 years of age; however CVID can present at any age, occasionally beyond 60 years. About 10% of patients present or develop a chronic mycoplasma infection, usually in joints but abscesses can occur in the lungs and other organs. Although infection is usually confined to one joint (e.g. knee or ankle) some patients develop an insidious polyarthritis which can be mistakenly diagnosed as rheumatoid arthritis. A novel mycoplasma strain was recently discovered in sputum from CVID patients, although it is not yet clear whether this organism (Mycoplasma amphoriphorme) is a true pathogen causing bronchitis. Since only a minority of CVID patients suffer from mycoplasma infections, it is likely that there are susceptibility co-factors. We have recently identified mannose binding lectin (MBL) as one factor, and shown that CVID patients with MBL genotypes associated with low production of MBL are prone to this complication (Hamvas et al - unpublished).

Table 1. Typical infectious complications of CVID.

<table>
<thead>
<tr>
<th>Respiratory tract:</th>
<th>Haemophilus influenzae (non-typeable)</th>
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<tbody>
<tr>
<td></td>
<td>Streptococi, Moraxella catarrhalis</td>
</tr>
<tr>
<td></td>
<td>mycoplasmas</td>
</tr>
<tr>
<td>Septicaemia*:</td>
<td>Strep. pneumoniae, meningococci,</td>
</tr>
<tr>
<td>(meningitis)</td>
<td>*H. influenzae type b</td>
</tr>
<tr>
<td>Arthritis*</td>
<td>Mycoplasmas, H. influenzae type b*</td>
</tr>
<tr>
<td>Meningitis/e</td>
<td>Enteroviruses</td>
</tr>
<tr>
<td>encephalitis</td>
<td>*very rare in patients on immunoglobulin replacement therapy</td>
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Patients with PAD are usually not susceptible to severe acute viral infections such as measles, mumps and varicella. However, enteroviruses are an exception, and a minority of CVID patients are prone to enteroviral meningoencephalitis which usually has a fatal outcome. Patients with X-linked agammaglobulinaemia are at more risk for this complication, probably because they have a more severe antibody deficiency at a younger age. Echoviruses, which are a common cause of diarrhoea and mild meningitis in the community are often involved, although coxsackie viruses can cause meningitis and sometimes myocarditis in these patients. Some patients with chronic enteroviral disease develop peripheral oedema and fibrosis of the limb muscles that has some features in common with dermatomyositis, although is caused by direct viral involvement of small vessels in these tissues.

Making the Diagnosis of CVID

Secondary causes of hypogammaglobulinaemia (e.g. drugs, myeloma) must initially be excluded (Table 2). The absence of circulating B lymphocytes should prompt screening for rare inherited defects in the development of B cells (Figure 1). X-linked agammaglobulinaemia (XLA) needs to be excluded in males with absent circulating B lymphocytes, although there are some XLA patients who retain B cells. Most XLA patients can be diagnosed by
showing reduced or absent expression of the Btk protein by Western blotting, but the routine sequencing of genes causing these B cell disorders is now feasible. X-linked lymphoproliferative syndrome (XLP), which can mimic CVID, should be excluded in males, but this is a very rare condition and affected males usually have had a severe EBV infection or presented at a young age with a B cell lymphoma. Other genetic defects in ICOS and BAFF-R (K. Warnatz - pers. communication) need to be excluded, but these are very rare defects accounting for less than 1% of CVID patients. Patients with a normal or raised serum IgM should be screened for genetic defects causing the hyper-IgM (HIM) syndromes (CD40-L, AID, UNG). Recent work suggests that up to 10% of CVID patients may have defects in TACI, a signalling molecule on B cells that regulates maturation in the germinal centre, with both homozygous and heterozygous mutations apparently causing immunodeficiency (B. Grimbacher - pers. communication). Strategies to screen for mutations in this gene at a reasonable cost using heteroduplex systems are currently being evaluated. It is likely that over the next decade most CVID patients will be diagnosed as having specific genetic defects, probably with additional inherited susceptibility genes determining the severity of the immunodeficiency and predisposing to complications.

Sub-Classification of CVID

During the past 30 years there have been many attempts to sub-classify patients according to various T lymphocyte abnormalities; more recently a sub-classification based on circulating B lymphocyte surface markers has been proposed.

T Cell Defects

Lymphocyte proliferation in vitro is consistently very low in about 10% of CVID patients, particularly with PHA stimulation, but sometimes also with-anti CD3 and anti-CD28 co-stimulation. These patients tend to have low circulating CD4 T cell counts (~200/ul) consequently having a reversed CD4/CD8 ratio, the majority of the CD8 T cells not expressing CD28.

Figure 1. B cell maturation/differentiation to a high affinity IgG secreting plasma cell.
(Mutations in molecules in shaded boxes are known causes of PAD)
-See reference 40 for early B cell defects-
Common Variable Immunodeficiency

Table 2. Diagnosis of CVID.

Excluding secondary hypogammaglobulinaemia

**Drugs:** hydantoin, carbamazepine, sulfasalazine, cyclophosphamide, penicillamine, gold (see ref. 41 for complete list)

**Lymphoid malignancy:** myeloma, chronic lymphatic leukaemia, lymphoma

**Hypercatabolism/protein loss:** nephrosis, lymphangiectasia, enteropathy, Dystrophia myotonica

Excluding known genetic defects:
1. XLP, ICOS, TACI, BAFF-R, CD19 defects
2. Low or absent B cells: XLA and other early defects (see Figure 1)
3. Normal or raised serum IgM: HIM syndromes
4. Lymphopenia: ‘leaky SCID’ e.g. ADA, RAG, Class 11 defects

Table 3. T lymphocyte abnormalities reported in subsets of patients with CVID.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
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<tr>
<td>Low CD4 T cell count</td>
<td>Failure of CD4+T cell priming to KLH</td>
</tr>
<tr>
<td>Decreased CD40 ligand expression after activation</td>
<td>Low IL-2 production <em>in vitro</em> after stimulation</td>
</tr>
<tr>
<td>Depressed proliferation with PHA/ConA; minority also with anti-CD3 + anti-CD28</td>
<td>Low numbers expressing attractin and L-selectin</td>
</tr>
<tr>
<td>Abnormal LDH iso-enzyme pattern</td>
<td>Abnormal kinetics of surface 5’nucleotidase and dipeptidyl peptidase 1V</td>
</tr>
<tr>
<td>Increased activation of protein kinase A type 1</td>
<td>Evidence of persistent T cell activation:</td>
</tr>
<tr>
<td>Increased numbers expressing:</td>
<td></td>
</tr>
<tr>
<td>HLA-DR</td>
<td>CD95 (Fas)</td>
</tr>
<tr>
<td>CD8+CD28</td>
<td>IL12/IL1Receptors</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>low numbers of CD45+RA+ cells</td>
</tr>
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</table>

The poor proliferation may therefore reflect altered sub-populations rather than a fundamental T cell defect (reviewed in 12). Altered circulating sub-populations of T cells may also explain the low IL-2 production reported in lymphocyte cultures. A variety of other abnormalities in surface and cytoplasmic proteins have been described in CVID (Table 3) but again it is not clear whether this reflects altered sub-populations due to chronic infection or fundamental defects.

**B Lymphocytes**

In the 1980s various workers identified subsets of CVID patients whose circulating B cells failed to differentiate and mature *in vitro* to produce the main immunoglobulin classes: IgG, IgA, IgM and IgE. In the ‘Bryant’ classification, three groups of patients were recognised when B cells were stimulated *in vitro* with SAC or anti-IgM in combination with IL-2: the largest group produced only IgM (Group B), a smaller number of patients producing no immunoglobulin (Group A), and a minority who produced IgG, IgA and IgM in normal amounts (Group C). In general these findings correlated with the levels of serum immunoglobulin in the patients, with Group C having a milder hypogammaglobulinaemia and less frequent symptoms, and Group A having more severe disease with inflammatory and autoimmune complications. Although the assays used varied in different laboratories, the B cells from many patients in Group B can be induced to make all immunoglobulin isotypes if additional cytokines such as IL-10 and IL-4 and anti-CD40 are added *in vitro*.

Based on this initial work, a group in Freiburg, Germany has recently proposed a classification based on the appearance of maturation markers on circulating B lymphocytes; another group in Paris
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has proposed a similar system. The ‘Freiburg’ classification is based on the relative numbers of switched memory (CD27+ IgM-IgD-) B cells in the circulation, those having <0.4% of PBMCs being designated Group 1, with a further sub-division of this group into those with greater (1a) or less (1b) than 20% of the CD19+ B cells being immature (CD21-). Group 2 patients have normal numbers of switched memory B cells, and functionally correspond to Group C in the ‘Bryant’ classification, while the B cells in Group 1a or b patients were able to produce only IgM in vitro after SAC stimulation. A consensus has now been reached in Europe that CVID patients should be classified according to the number of class switched immature or mature circulating B lymphocytes. Work in various laboratories over the past 2 years has shown that this classification is robust, with patients generally showing the same B cell abnormalities when repeatedly tested. Most patients with splenomegaly and/or autoimmune complications are in Group 1a (Warnatz et al, submitted). The purpose of this subclassification is to assist in the search for molecular causes of CVID, focusing attention on genes involved in the maturation and differentiation of B cells. For example, the naïve (CD27-) B cells from many Group 1 patients have reduced up-regulation of surface CD70 and CD86 after stimulation, suggesting a primary defect in the relevant signalling cascade. Furthermore, very low numbers of circulating CD21+ (and CD38+) B cells is probably a useful clue for BAFF-R genetic defects (K. Warnatz - pers. communication).

**Dendritic Cells**

Two groups of workers have recently published data showing that myeloid derived dendritic cells (DCs) from some CVID patients fail to fully mature in vitro. Subsequent work in our laboratory shows a partial failure to fix Class 11 molecules on the surface of maturing DCs, probably due to the cells retaining some features of macrophages (T Scott-Taylor et al - unpublished). The cause of this in vitro abnormality is not known, but we are currently exploring the possibility that INF-γ produced from contaminating CD8+ T cells in the cultures is compromising DC maturation. However, a similar scenario may occur in vivo within the lymphoid apparatus of some CVID patients, perhaps explaining the previously reported failure of CD4+ T cell priming to non-viral antigens.

**Inflammatory Complications of CVID**

**Granulomatous Disease (GD)**

About 20% of CVID patients develop granulomatous and fibrotic changes in various organs, particularly the lungs, liver and spleen, and in a minority of patients also in the skin, kidneys, eyes and brain (reviewed in 12). Usually only one organ/system is affected by these changes, although rare patients have widespread granulomas. The spleen may be very large causing hypersplenism with low circulating neutrophils and platelets; in some cases splenectomy is indicated. Granulomatous infiltration of the liver is usually insidious, with the gradual development of cirrhosis over 10-30 years. The level of serum alkaline phosphatase is a useful marker of the severity of liver disease. Infiltration of the lung is usually more overt, manifested by increased shortness of breath and cough. Patients often have pre-existing bronchiectasis so it is important to regularly check for a reduction in carbon monoxide gas transfer which is a useful marker of alveolar disease (Figure 2).

A survey of 159 patients at the Royal Free Clinic, London, showed that 34 had evidence of GD. Many of these patients had relatively mild involvement of lungs and/or liver, but there were 10 patients with severe disease, one dying from lung and kidney involvement. Two of these patients presented with GD while the other eight developed this complication from between 3-15 years after starting immuno-globulin replacement therapy. There was no particular clinical phenotype associated with either severe or mild GD, with a range of complications such as autoimmune disease, splenomegaly and enteropathy occurring in some patients. In general, the prognosis is good with the disease slowly progressing in some patients, while apparently remaining stable in others. Steroid therapy was required for the 10 patients with severe disease, and except for the patient who died, most are maintained on 7-10mg of prednisolone daily, occasion-ally requiring increased doses for exacerbations. In the lung, exacerbations seem to follow bacterial or viral infection, a possible mechanism being the non-specific recruitment of activated T cells present in the blood of many CVID patients.
Figure 2. Mixed traction bronchiectasis and ‘granulomatous’ fibrosis in CVID patient.

patients (see below). Susceptibility factors may include genetic polymorphisms associated with high TNF-α production, but this needs to be confirmed. A few patients develop severe fulminating multi-organ GD which requires aggressive treatment with high dose steroids and other immunosuppressive drugs. There is no published data on the use of methotrexate or infliximab for GD in CVID, but these drugs should be considered in patients not controlled on low doses of steroids.

The incidence of GD in the Royal Free Clinic has been compared to that in Huddinge, Sweden, where only 8 out of 60 patients had evidence of this complication (L. Hammarstrom - pers. Communication). Furthermore, none of these patients had severe disease. The reason for this geographical difference in susceptibility is not known. Possibilities are differences in the prevalence of microbes that may trigger GD, or the type of immunoglobulin or antibiotic prophylaxis offered to patients; for example most Swedish patients are on subcutaneous immunoglobulin replacement, while in the UK this is usually given intravenously.

Enteropathy

CVID patients are prone to chronic inflammation of the bowel that is not related to known pathogens such as giardia, campylobacter or other organisms that commonly cause enteritis in the general population. About 20% of patients have chronic mild diarrhoea, the histology of colonic biopsies usually showing increased numbers of intra-epithelial lymphocytes. However, a minority of patients develop a severe enteropathy, sometimes effecting only the lower bowel with severe watery diarrhoea, dehydration and electrolyte loss. In other patients the inflammation is predominantly in the upper bowel, with fat and vitamin malabsorption. Previous surveys have shown that at least 20% of CVID have a chronic gastritis, sometimes with intrinsic factor deficiency and vitamin B12 malabsorption. This, and possibly a high incidence of *Helicobacter pylori* colonisation are the likely causes of the high incidence of gastric malignancy in CVID.

The treatment of bowel complications depends on the severity. No treatment is usually necessary for those with mild diarrhoea, but steroids are indicated in those with severe enteropathy and are effective at high dose (> 40mg prednisolone daily). There is no published data on the use of immunosuppressive agents such as cyclosporin, but one of our patients has improved on anti-TNF therapy (infliximab).
Autoimmune Complications

Many types of primary immunodeficiency are associated with autoimmune disease, including CVID where about 20% of patients suffer from autoimmune blood dyscrasias (thrombocytopenia, neutropenia, haemolytic anaemia) and/or vitiligo and more rarely autoimmune thyroid disease, diabetes and neuropathies. The mechanism for this susceptibility is not known, and is mostly seen in patients with very low numbers of circulating mature immunoglobulin class switched B cells (K Warnatz– pers.communication). Steroids are usually the first-line treatment for these complications, with anti-CD20 monoclonal antibodies (Rituximab) being used in those patients who do not rapidly respond. Other more toxic immunosuppressive drugs (eg: azathioprine or mycophenolate) are rarely required. Neutropenia is not always caused by auto- antibodies, and a bone marrow biopsy should be performed to exclude the possibility of large granular lymphocyte (LGL) infiltration; these cells probably originate from the expanded CD8+ CD28 - perforin+ cells in the circulation of some patients.

Malignancy

Surveys of CVID patients in the 1970s in the UK, and more recently in other countries, have consistently shown a raised incidence of carcinoma of the stomach and lymphoma in CVID patients. However, very few cases of gastric cancer have been reported in the UK during the last 20 years, although the reason for this improvement is not known. One possibility is the more frequent use of prophylactic antibiotics in these patients which may reduce colonisation of the stomach by Helicobacter pylori, while another may be the increased doses of immunoglobulin replacement therapy with normal levels of serum IgG being achieved in most patients; this contrasts with the sub-normal levels that were acceptable when gastric malignancy was more prevalent. On the other hand, lymphoma has become a common cause of death in CVID. Many of these lymphomas are B cell derived although usually not Burkitt’s type. Sometimes clonal expansions of cells of T or B cell lineage infiltrate organs such as the lung or a lymph node without clinical evidence of invasive or generalised disease; such patients are difficult to manage because of the uncertainty over whether they have a truly malignant disorder. There is no clear evidence that CVID patients are prone to other types of tumours.

Immunoglobulin Replacement Therapy and Treatment of Infections

Symptomatic patients should be given prophylactic immunoglobulin therapy, the aim being to keep the trough (pre-infusion) level of serum IgG within the normal range (ie: >7g/l). There is some evidence that maintaining these levels prevents enteroviral and mycoplasma infections. Although most patients were treated with intravenous immunoglobulin therapy (IVIG) every 2-4 weeks until the late 1990s, regular subcutaneous infusions (SCIG) are now gaining popularity, mainly because patients can administer immunoglobulin by this route more easily by themselves, and also because SCIG maintains a more even level of IgG in the serum. A total dose of 400mg/kg/month is usually sufficient to maintain a normal serum IgG level, but some patients who hypercatabolise IgG may need higher doses. Many patients in Europe administer their own immunoglobulin therapy at home, usually with the help of a spouse or partner.

Respiratory Infection

Despite immunoglobulin therapy, many patients still suffer from repeated infections, particularly in the respiratory tract with organisms such as non-typeable Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis being isolated from sputum, sinuses or the ears. There is no consensus on the best prophylactic antibiotic regimen for patients with repeated infections, although we favour the use of quinolones (e.g. ciprofloxacin) which prevents H. influenzae bronchitis. Regular monitoring of patients is necessary to prevent the gradual development of bronchiectasis that occurs in at least 30% of CVID patients on adequate immunoglobulin replacement. There is evidence of poor penetration of IVIG into the lungs of these patients (D. Webster - unpublished), which might be overcome by giving much higher doses of immunoglobulin, although long-term trials are needed to show whether this expensive strategy is cost effective.

Enteroviral meningo-encephalitis is now rare in patients on adequate immunoglobulin replacement, but CVID patients may present with this
complication. Unfortunately, pleconaril, a drug shown to be effective against enteroviruses, is no longer available so we currently have no specific anti-viral agent for this group of viruses. Once infection is confirmed, high dose IVIG (2-4g/kg over 2 weeks) is a sensible option, as this should provide some antibodies to the relevant enterovirus and help clearance. Live oral polio vaccination is contra-indicated in these patients because of the potential problems with long term excretion in the stools of a revertant virulent virus. Immunodeficient patients excreting such viruses have been of concern to the World Health Organisation (WHO) as they are planning the withdrawal of routine polio immunisation worldwide.

**Mycoplasma** infection is the commonest cause of arthritis and deep abscesses in CVID; those patients with low levels of mannose binding lectin (MBL) are particularly susceptible (Hamvas et al - unpublished). These patients need to be treated for at least 8 weeks with appropriate antibiotics. There are very few laboratories in the world able to culture mycoplasmas and perform antibiotic sensitivity studies, and it is useful to ask for help from a specialist centre before embarking on a long period of treatment. Combinations of clindamycin and doxycycline are often effective, although a new experimental drug, Econor, has been impressive.

**Gastrointestinal Infection**

Giardia and campylobacter enteritis occur more frequently in CVID patients as compared to healthy individuals, and tend to be more resistant to treatment. However less than 5% of patients in the UK suffer from these infections, although in warmer and less hygienic environments CVID patients often have repeated episodes of diarrhoea caused by a variety of enteric pathogens, including salmonella and shigella.

**Other Rare Infections**

Finally, CVID patients can rarely develop opportunistic viral infections such as JC polyoma virus encephalitis or cytomegalovirus enteritis, possibly due to exhaustion/senescence of viral specific CD8 cytotoxic cells (see below). These patients may have a distinct genetic condition which gradually compromises T cell function, leading to severe combined immunodeficiency (SCID) in later life.

Patients with thymoma associated with hypogammaglobulinaemia (classified separately from CVID) are particularly at risk of fatal opportunistic viral infection.

**Response to Persistent Viral Infections**

Apart from enteroviruses that require antibody for clearance, CVID patients are not susceptible to acute severe infection with common viruses such as measles, mumps and varicella. Despite some patients having low numbers of circulating CD4 T cells and other evidence of partially compromised cellular immunity, these viruses seem to be cleared by a cellular mechanism which probably depends on the generation of efficient cytotoxic lymphocytes (CTLs) and NK cells.

The situation in regards to latent/persistent viruses, such as EBV and CMV, has not previously been investigated. Using EBV and CMV viral peptides linked to HLA Class I tetramers, we have shown that about 30% of CVID patients have expanded numbers of circulating viral peptide specific CD8+ T cells. Furthermore, we and others have found high numbers of perforin positive CD8 T cells in CVID patients, although the specificity of the majority of these cells is not known. Preliminary work shows that the pattern of CD8 T cell response to these viruses is normal, in that for EBV most of the cells have a ‘memory’ phenotype (CD27+), while for CMV there is a mixture of memory and activated cells (Reiszadeh et al.- unpublished). In one CVID patient with severe diarrhoea we found evidence of CMV replication in the colonic mucosa associated with an infiltration of CD8+ T cells, suggesting that the expansion of CD8 T cell activity in the blood is a response to persistent viral replication in the bowel. A similar mechanism may explain inflammatory complications in other organs such as the lungs and liver, perhaps with different viruses triggering the process. This preliminary work suggests either a dysregulation of CTL responses to persistent viral infection and/or a partial defect in killing viral infected cells. The expansion of CTL responses to EBV is similar to that seen in patients with X-linked lymphoproliferative syndrome (XLP), where there is also an expansion in the relative numbers of perforin positive T cells (Plunkett et al-unpublished). XLP is caused by
mutations in the gene coding for SAP which appears to have a role in both controlling the size of the CTL response and in killing of EBV infected B cells. Hypogammaglobulinaemia occurs in many XLP patients, one possibility being that the dysregulated T cell response promotes the production of excessive amounts of TH-1 cytokines, such as IFN-γ, which inhibit antibody production (Figure 3). Screening for mutations in candidate genes involved in the regulation and function of CTLs may now be useful in selected CVID patients. The presence of a genetic susceptibility locus for CVID within the MHC region found in family studies may be explained by specific Class I or II alleles influencing the size of the anti-viral CTL response.

CONCLUSION

The discovery of more genetic causes of CVID is expected over the next few years although, as demonstrated by the clinical heterogeneity of patients with ICOS and TACI defects, an understanding of the clinical phenotype will depend on a greater knowledge of polymorphisms in genes regulating lymphocyte maturation/differentiation, inflammation and responses to infections. More detailed sub-classification of CVID patients based on surface markers and function of T and B cells is required to focus attention on candidate genes. A substantial subset of patients appear to have a dysregulated CTL response to persistent herpes viruses that may be caused by an inherited genetic abnormality. However the severity of the immunodeficiency and the complications are likely to be determined by other modifying genes and environmental factors that may differ between countries.

REFERENCES

Common Variable Immunodeficiency


