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IMMUNODEFICIENCY REVIEW

Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID)

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DEFINITION AND CLINICAL DESCRIPTION

SIgAD

SIgAD, using 0·05 g/*l* of serum IgA as the upper limit for diagnosis in adults and a concomitant lack of secretory IgA, is the most common form of primary immunodeficiency (PID) in the western world and affects approximately 1/600 individuals [1]. However, there is a marked variability in the prevalence in different ethnic groups [2], with a lower frequency in Japanese (1/18 000) and Chinese (1/4000), suggesting a genetic basis for the disorder. The term 'selective IgAD' should be reserved for those individuals who do not have identifiable disorders which are known to be associated with low IgA levels (see below). However, in many cases a simultaneous change in the IgG subclass pattern is seen with a lack of specific anti-polysaccharide antibodies of the IgG2 subclass [3] or a total lack of serum IgG2 [4], IgG4 and IgE [5], reflecting a relative or absolute block in switching to genes downstream of the G1.

CVID

CVID affects about 1/25 000 Caucasians, the patients having a marked reduction in serum levels of both IgG (usually < 3 g/*l*) and IgA ($< 0{\cdot}05$ g/*l*); IgM is also reduced in about half the patients ($< 0{\cdot}3$ g/*l*) [1]. Symptoms of recurring infection can start at any time of life, but there are peaks of onset during 1–5 and 16–20 years of age [6], with equal distribution between the sexes. The condition is clinically more complex than X-linked agammaglobulinaemia (XLA), with patients being prone to chronic inflammatory and autoimmune complications [6,7].

INHERITANCE OF SIgAD AND CVID

Familial inheritance of either SIgAD or CVID occurs in about 20% of cases (Fig. 1). A different population prevalence in various ethnic groups, strong familial clustering of the disorder, a predominant inheritance pattern in multiple-case families compatible with autosomal dominant transmission, and a high relative risk for siblings suggest the involvement of thus far unidentified genetic factors in the pathogenesis of IgAD/CVID [8,9]. In multiple-case families with a dominant transmission of CVID/IgAD, CVID was usually present in the parents accompanied by IgAD in descendants [9]. This is consistent with the hypothesis that CVID may develop later in life as a more severe manifestation of a common, complex genetic defect, most likely involving immunoglobulin class switching. This is supported by a description of a gradual decline of IgG levels that progressed at similar ages in affected siblings [10]. Furthermore, CVID may develop from IgAD [11–13] and occasionally vice versa [14]. In both diseases anti-IgA antibodies have been detected. Since the disease phenotype is persistent and the phenocopy rate is low, chromosome susceptibility loci underlying this complex trait should be detectable by genetic linkage analysis. The recurrence risk of IgAD was found to depend on the gender of parents transmitting the defect: affected mothers are more likely to pass the defect on to their offspring than affected fathers. This was accompanied by a preferential transmission of associated alleles in the MHC, suggesting a role for this region in the parent-of-origin penetrance differences [9]. The role of the MHC is further supported by a higher prevalence of anti-IgA antibodies among females transmitting the disease to their offspring than in female non-transmitters.

MOLECULAR BASIS

Our recent study involving a large number of multiple-case families supported the presence of a predisposing locus in the class II or class III region [9]. A significant increase in sharing of MHC alleles in affected members of our family dataset was consistent with previous allelic associations observed in case control studies, which appear to be much stronger for IgAD than CVID. It is possible that the gene(s) involved predispose to the production of IgA antibodies.

A number of abnormalities in the cytokine network have been observed in SIgAD and CVID; however, attempts to find a defect in candidate cytokine genes have so far failed, including the available coding region of the cytokine genes in the MHC, such as lymphotoxin α and β (Vorechovsky et al., unpublished). Using the same family material, we were unable to confirm a susceptibility locus on chromosome 18, despite a number of anecdotal reports of patients with gross defects in the 18p region and SIgAD [15]. The finding of immunoglobulin deficiency in only one of two monozygotic twins suggests an environmental, possibly infectious agent as a triggering factor, but longer follow up of these twins is needed [16].

In SIgAD the defect is manifested at the stem cell level, since a bone marrow transplant from an IgA-deficient donor transfers the defect to the recipient [17], whereas bone marrow from a normal

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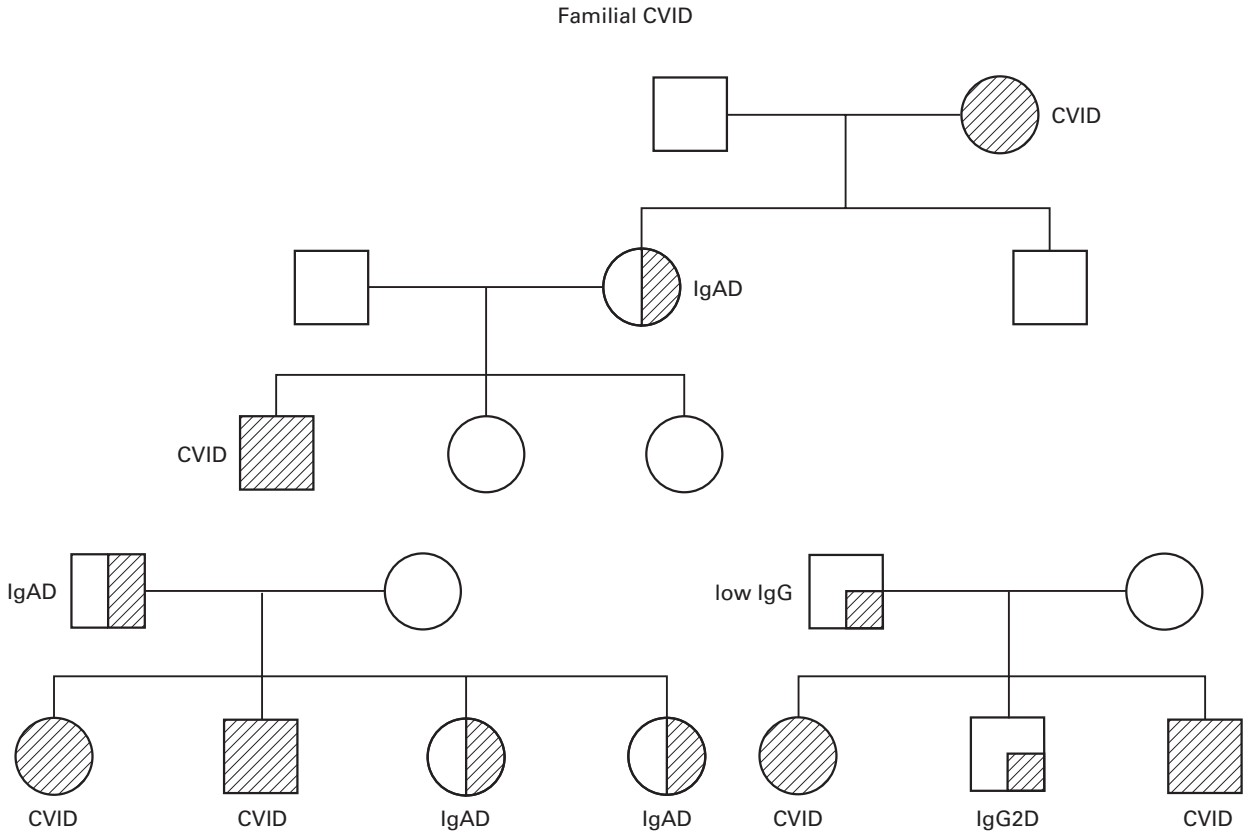

Fig. 1. Three pedigrees are shown demonstrating the inheritance patterns for IgAD and CVID. Note that in some families there are relatives with minor IgG abnormalities.

individual transplanted into an SIgAD patient will correct the defect [18]. The genes for $\alpha 1$ and $\alpha 2$ can readily be demonstrated in the genome of IgAD patients [19] and these 'silent' genes can be re-expressed in the children of SIgAD parents [20], suggesting that the defect is due to a defect in switching or expression of the immunoglobulin genes. This is supported by the production of IgA *in vitro* by lymphocytes from both SIgAD [21] and CVID [22] patients when cultivated together with anti-CD40 antibodies and IL-10. The physiology of this *in vitro* system is questionable, but it clearly demonstrates that secretion of IgG1, IgG3, IgG4 [23] and IgA [21,24], with a biased expression of IgA1, can occur if appropriate stimuli are added. Although it is technically difficult to detect the normally small numbers of circulating IgA-bearing B cells, they have been found in SIgAD [25]. Furthermore, T cells from SIgAD patients will support IgA production *in vitro* by B cells from normal subjects. In a few selected cases the defect is restricted to one of the two IgA subclasses and this is most often, although not invariably [26], due to deletions of the corresponding heavy chain constant region gene [27].

The mechanism of CVID is equally elusive, one problem being that the syndrome probably includes a number of different disorders [28]. At least 30% of patients are lymphopenic, the $CD4^+$ subset being mainly depressed, and this probably accounts for the low levels of IL-2 produced *in vitro* from stimulated peripheral blood mononuclear cells (PBMC) [29]. The expression of CD40 ligand on activated T cells is usually normal, but is very low in a small group of patients, implying a defect in isotype switching [30]. The B cells from another small subgroup have defective signalling through the CD40 pathway [31]; these patients have raised serum IgM and may be misdiagnosed as XHIM. Levy *et al*. [32] recently demonstrated somatic hypomutation in B cells from two patients; subsequent work indicates that this occurs in about 20% of patients, but cannot yet be linked to any clinical pattern (Y. Levy, personal communication). Since hypermutation occurs predominantly within the germinal centres (Gcs) of the central lymphoid apparatus, the defect may reflect the fact that splenic Gcs are often poorly developed or disrupted by granulomatous infiltrates in these patients [33]. Another possibility is that inherited subtle defects in DNA repair, which could impair hypermutation, may contribute to an already compromised B cell maturation system. This is supported by the finding of increased chromosomal sensitivity to radiation damage in lymphocytes from some CVID patients [34], and clinical surveys showing an increased susceptibility to some cancers [35]. IgAD, and sometimes a more broader immunoglobulin deficiency, is associated with ataxia telangiectasia and the Nijmegen breakage syndrome, both conditions caused by inherited defects in DNA repair [36].

The majority of patients have a defect in $CD4^+$ T cell priming to antigen, as measured by the numbers of circulating responsive cells following immunization [37]. This could be due to a defect in antigen-presenting cells (APC), and not T cells, since various defects in APC have been reported [38]. There may be a small subgroup of patients with defects in CD3 complex triggering, but this needs to be confirmed [39].

The majority of patients show a pattern of raised production of interferon-gamma by circulating T cells, particularly by the $CD8^+$

subset, increased numbers of DR-expressing $CD4^+$ T cells with up-regulated Fas expression, and an increased rate of apoptosis [40,41]. There is increased chronic 'activation' of circulating monocytes producing reactive oxygen [42], and IL-12 after *in vitro* lipopolysaccharide (LPS) stimulation (Cambronero *et al*., unpublished). This suggests a 'pathological' shift towards a Th1 type of immune response. Tumour necrosis factor (TNF) production from both T cells and monocytes is raised in a subgroup of patients with granulomas [43], probably due to the coincidental inheritance of TNF-α (high) genetic polymorphisms [44]. These abnormalities appear specific to CVID and are not seen in patients with XLA, who have the same therapy and suffer from the same infections.

The recovery of antibody production following HIV infection in CVID patients is important [45]. There have been three published case reports, with a fourth patient currently in our (D.W.'s) clinic with familial CVID, having survived 5 years without immunoglobulin therapy; highly active anti-retroviral therapy (HAART) has now reduced the HIV load to unrecordable levels. Only IgG and IgM antibody production recovered in three of the patients, the IgA remaining unrecordable. These cases demonstrate that CVID is potentially reversible by immunoregulatory factors, and supports the view that SIgAD predisposes to CVID.

ANIMAL MODELS

Although there are a number of reports on IgA-deficient dogs [46–48] and chickens [49], the molecular basis of these deficiencies has not been elucidated. There is no rodent model available yet which resembles the human disease, although knock-out mice with a deleted J chain [50] or Iα region [51] have been described. Only secretory IgA is impaired in the former and serum levels of IgA are up to 30-fold higher than in normal wild-type mice. There seems to be J chain-independent IgA transport in the intestinal, mammary and respiratory epithelial cells of these mice [52], adding to the complexity of the 'secretory' IgA machinery. The mice with an Iα region deletion, contrary to what was expected based on mice with deleted I regions or I region promoters for γ1, γ2b and ϵ, produced normal levels of IgA. This suggests that the I region as such is redundant and can be replaced by other gene sequences [53] and that splicing of germ-line transcripts rather than transcription itself controls DNA rearrangement leading to class switching. Mice with a targeted deletion of the α gene and its associated switch region [54–56] not only lack IgA but also have low serum levels of IgG3 and IgE, but raised levels of IgM and IgG2b, to some extent mimicking the situation in IgAD patients.

Targeted disruption of the IL-5 receptor α gene in mice leads to a reduction in the number of IgA-producing cells at mucosal effector sites such as intestinal lamina propria and nasal mucosa, but normal numbers at inductive sites. Furthermore, serum levels of IgA were normal [57]. Targeted deletions of either the lymphotoxin α [58,59] or lymphotoxin β [59] gene cause reduced serum and secreted IgA with disrupted development of secondary lymphoid organs and a diminished capacity for affinity maturation of the antibodies produced. This has some parallels with a subgroup of CVID patients [32]. Transcription factor knockouts, such as the NF-κB, p65 [60] or p50 Rel-A [61] deficient mice, have defective class switching and could be a model for a subgroup of IgAD/CVID patients [62,63]. Other 'knockouts' for various critical immunoregulatory proteins in mice have major general effects on the immune system, but the phenotypes are not consistent with CVID.

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC TESTS

The diagnosis is one of exclusion [64]. The family history and the age of onset of symptoms is important, because patients presenting after 15 years are unlikely to have one of the known single gene PIDs such as XLA or X-linked hyper IgM syndrome (X-HIM). There is a typical pattern of immunoglobulin class deficiency, with very low IgA and IgE and variable but usually low IgM. A chest radiograph is necessary to exclude thymoma in patients presenting over 45 years; these patients may only have moderate hypoimmunoglobulinaemia despite having no circulating B cells. This appears to be a distinct entity, with a much worse prognosis than CVID [65]. There is usually no confusion with secondary hypoimmunoglobulinaemia, in which IgA levels are usually only moderately low. Nevertheless, routine screening for nephrotic syndrome, chronic lymphatic leukaemia and myeloma should not be forgotten. Protein losing enteropathy with low immunoglobulins can be confusing, but is usually obvious when the serum IgG fails to rise on immunoglobulin therapy.

IgAD has been associated with a variety of anti-rheumatic and anti-epileptic drugs [66] (Table 1). In about half the cases the deficiency is apparently reversible after cessation of therapy, although full recovery may take months or even years. IgAD was induced by multiple anti-rheumatic drugs in a patient with rheumatoid arthritis [67], suggesting that selected individuals may be genetically predisposed to develop this complication. On the other hand, different drugs with a common molecular mechanism of action (ACE inhibitors) may actually vary in their capacity to induce IgAD in a given patient [68].

CVID and IgG2-IgA deficiency can also be induced by some of the above drugs [66], and recently zonisamide, a new anticonvulsant [69], was added to the list. The presence of drug-associated pan-hypo-immunoglobulinaemia, IgAD with IgG2

Table 1. Pattern of drug-induced immunoglobulin deficiencies

Drug	CVID	IgG2-IgAD	IgAD
Sulfasalazine	X	X	X
Gold			X
Chloroquine			X
Penicillamine			X
Captopril			X
Fenclofenac			X
Hydantoin	X	X	X
Zonisamide		X	
Carbamazepine	X		X
Valproate			X
Thyroxin*			X
Levamisole*	X		
Ibuprofen*			X
Salicylic acid*			X
Cyclosporin A*			X

*Requires independent confirmation.
See [2,67,68,93,94].

subclass deficiency and selective IgAD suggests that it shares features with the primary forms of SIgAD/CVID and that the pathophysiological process may involve common key steps. There is no common molecular denominator for the drugs used, although a majority appear to act at the level of lysosomes or are lysosomotropic, suggesting that the pathway leading to IgAD involves this organelle and APC. Some of the drugs implicated contain a highly reactive sulphydryl group and it is possible that the immunological dysregulation induced by these agents, including the formation of immune complexes and induction of autoimmune phenomena [70], plays a role in the development of the immunodeficiency in genetically susceptible patients. Sulfasalazine, one of the antirheumatic drugs implicated in immunoglobulin deficiency, prevents NF-κB-dependent transcription through inhibition of IκBα degradation [71]. This suggests that this form of IgAD/CVID may be associated with a defect in transcription either of constant region genes or of the switching process.

Various single gene disorders causing hypo-immunoglobulinaemia should be excluded, including 'leaky' severe combined immunodeficiency, which can rarely present after childhood [72]. A detailed family history is required. Male patients with low numbers of circulating B cells should be screened for XLA [73], and other autosomal recessive causes of agammaglobulinaemia considered in females [74]. Male patients with X-HIM or X-linked lymphoproliferative syndrome (XLPS) may be confused with CVID, particularly since the former may have normal serum IgM levels [75].

CLINICAL MANAGEMENT

SIgAD

Most individuals with SIgAD are not prone to infection, and are diagnosed during routine tests for other conditions or following family screening of a proband with SIgAD/CVID. There is no consensus on whether they should be routinely screened for anti-IgA antibodies, partly because there is no agreement on what level of antibodies constitutes a risk of anaphylaxis to blood products. A minority are prone to infection, and these should be screened for additional IgG subclass or functional IgG defects (i.e. response to test immunization); however, IgG subclass levels correlate poorly with susceptibility to infection [76]. Most patients can be managed with prophylactic or periodic antibiotics, but a few may benefit from immunoglobulin therapy, regardless of whether an associated IgG functional defect can be demonstrated [77]. Such patients will require immunoglobulin products containing low or minimal IgA if they have high levels of IgA antibodies.

CVID

Respiratory tract. Nearly all patients have recurrent symptoms of bronchitis, and to a lesser extent sinusitis, usually due to non-encapsulated *Haemophilus influenzae*, although streptococci, *Moraxella catarrhalis* and mycoplasmas are also important pathogens [78–80]. Until the late 1970s, most patients developed and eventually died from bronchiectasis. Many CVID patients continue to suffer from recurrent bronchitis despite IVIG therapy, and need prophylactic antibiotics to prevent bronchiectasis. Some clinicians favour rotating regimes, but in our experience compliance is poor and breakthrough infection is common. Prophylactic quinolone antibiotics, which have a very low minimum inhibitory concentration (MIC) for *H. influenzae*, are a better alternative, with amoxycillin for 'breakthrough' resistant streptococcal infection (Webster *et al*., unpublished).

Other infections. About 5% of CVID patients develop mycoplasma infections in the urinary tract and joints, occasionally with systemic spread and deep abscesses [81]. Although most patients respond to doxycyline, they should be referred urgently to a specialist centre where the organism can be characterized and appropriate antibiotics given. There is a promising new pleuromutilin antibiotic under trial for those with resistant organisms (Heilman and Webster, unpublished).

Enteroviral infection of the central nervous system is a rare complication, but can present either acutely or insidiously with signs of encephalitis, seizures, headache, sensory motor disturbances and even personality changes [82]. Cerebrospinal fluid (CSF) should be obtained, but may not grow the virus, particularly if the patient is on IVIG therapy. Polymerase chain reaction (PCR) for enterovirus should be requested routinely [83], and if positive patients should be offered a trial of pleconaril, a new anti-enteroviral drug which appears to have been effective in an open trial (Rotbart and Webster, unpublished).

Granulomas are a special feature of CVID, and do not occur in other primary lymphocyte disorders. In the lungs they can mimic sarcoidosis [84]. Granulomatous infiltration of the spleen occurs in about 20% of patients, and often extends to the liver causing presinusoidal venous congestion with oesophageal varices, sometimes progressing to cirrhosis and liver failure requiring liver transplantation [85]. Steroids can usually control the lung disease but new strategies are needed for liver involvement.

Inflammatory bowel disease is common, with about 30% of patients having some degree of chronic diarrhoea. Although the colon is preferentially involved, the histology showing lymphocytic mucosal infiltration [86], about 10% of patients have a severe gastroenteropathy involving the small and large bowel, with malabsorption, and occasionally fibrotic ileal strictures. The mucosal inflammation often involves the stomach, and a small number of patients develop achlorhydria and pernicious anaemia [87]. This probably explains the apparently raised incidence of carcinoma of the stomach in CVID patients [35], although this is now a very rare complication in the UK and Sweden. Although regular immunoglobulin therapy reduces the susceptibility to giardia and campylobacter enteritis, it does not prevent the unexplained mucosal inflammation; treatment for the latter is currently unsatisfactory and in severe cases involves trying antibiotics, elemental diets and steroids [86].

Autoimmune disease occurs in about 10% of patients, usually immune thrombocytopenia (ITP), haemolytic anaemia or neutropenia. Much rarer complications are red cell aplasia, thyroid disease and neuropathy. Steroids may be useful but in refractory cases high dose IVIG, splenectomy or more aggressive immunosuppressive therapy may be needed [88]. There is a raised incidence of lymphoma [89], which is now more common as patients survive longer. Unexplained fever, weight loss, recent lymphadenopathy and abdominal or chest pain should prompt a search for clonally derived lymphocytes in the blood, followed by lymph node biopsy, and if necessary a diagnostic splenectomy.

Immunoglobulin therapy. Nearly all CVID patients require immunoglobulin replacement therapy, given either 2–4 weekly at a total dose of 400 mg/kg body weight monthly, or as a subcutaneous injection (using an infusion pump) every 1–2 weeks [90,91]. Unfortunately, CVID patients with hepatitis C have a very poor prognosis [92], and most who were infected by contaminated immunoglobulin in the 1980s have died; nowadays

only products known to be subjected to formal viral inactivation should be used.

USEFUL CONTACTS

Various European registries, and subregistries, under the auspices of the European Society for Immunodeficiency (ESID), are listed below, together with the contact person for assistance. Also listed are international nursing and patient support groups, which can advise on specific country based groups.

ESID registries

Main CVID/IgAD registry L Hammarstrom, M Abedi
Lennart.Hammarstrom@csb.ki.se
Website: http://www.cbt.ki.se/esidregistry/intro.html
Subregistry for (i) Mycoplasma infection
C. Heilmann (carsten_heilmann@online.pol.dk) and
D. Webster (dwebster@rfhsm.ac.uk)
(ii) Enteroviral infection
D. Webster (see above)

International

International Nursing Group for Immunodeficiences (INGID)
Ann Gardulf, Sweden, Fax: + 468 58586850
International Patients Organization for Primary Immunodeficiency (IPOPI): pimmune@dial.pipex.com

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