**Database: OMIM**
**Entry: 240500**
**LinkDB:** 240500
MIM Entry: 240500
Title:
#240500 COMMON VARIABLE IMMUNODEFICIENCY; CVID
;;COMMON VARIABLE HYPOGAMMAGLOBULINEMIA;;
HYPOGAMMAGLOBULINEMIA, ACQUIRED;;
IMMUNOGLOBULIN DEFICIENCY, LATE-ONSET
Text:
A number sign (#) is used with this entry because common variable immunodeficiency can be caused by mutation in the TNFRSF13B gene (604907), which encodes the transmembrane activator and CAML interactor (TACI).

CLINICAL FEATURES

Wollheim (1961) described 2 females with 'acquired' hypogammaglobulinemia who came from different parts of Sweden but were remotely related. He suggested that a recessive genetic factor may be involved in 'acquired' hypogammaglobulinemia. Kamin et al. (1968) found that phytohemagglutinin-induced incorporation of labeled precursors into DNA and RNA by lymphocytes is significantly diminished in cells of adults with so-called 'acquired' agammaglobulinemia. The difference was independent of the characteristics of the culture-medium, indicating a cellular abnormality. Cooper et al. (1971) found normal numbers of B lymphocytes bearing membrane-bound immunoglobulins; germinal centers were normally formed in antigen-stimulated lymph nodes. They postulated that although the B lymphocytes in such patients have surface recognition antigens, they lack the mechanism for plasma cell differentiation.

With a prevalence of about 1 in 800 Caucasians, selective IgA deficiency (IgAD; 137100) is the most frequently recognized primary immunodeficiency. The clinical consequences are highly variable. Many of the affected persons have no obvious health problems, while others may have recurrent infections, gastrointestinal disorders, autoimmune diseases, allergies, or malignancies. A central feature in pathogenesis is an arrest of B-cell differentiation. Affected individuals have a normal number of IgA-bearing B-cell precursors but a profound deficit in IgA-producing plasma cells. Although common variable immunodeficiency (CVID), defined by panhypogammaglobulinemia, has long been considered a 'wastebasket' category that includes a number of immune disorders, most individuals with CVID show a distinctive phenotype characterized by normal numbers of immunoglobulin-bearing B-cell precursors and a broad deficiency of immunoglobulin isotypes. Schaffer et al. (1989) proposed that CVID of this particular subset and selective IgA deficiency may represent polar ends of a spectrum reflecting a common underlying genetic defect. The proposal was supported by findings that persons with these immunodeficiencies have in common a high frequency of C4A (120810) gene deletions and C2 (217000) rare gene alleles.

Common variable immunodeficiency is a heterogeneous group of disorders characterized by hypogammaglobulinemia, antibody deficiency, and recurrent bacterial infections. Most CVID patients have normal numbers of circulating T cells and surface immunoglobulin-positive B cells;

however, CVID B cells fail to differentiate into immunoglobulin-secreting plasma cells in vivo. Consequently, CVID patients have reduced levels of serum immunoglobulin and respond abnormally to immunization with protein and polysaccharide antigens. Various defects, including an intrinsic B-cell defect, excessive T-suppressor activity, and defective T/B-cell interaction, have been postulated as responsible for the failure of CVID B-cell differentiation. Farrington et al. (1994) found that 23 of 31 patients (74%) exhibited a T-cell defect, whereas the remaining 8 patients did not. Patients with T-cell dysfunction could be further subdivided into those with a broader defect (n = 11) resulting in depressed expression of gp39 (CD40LG; 300386) and variable lymphokine deficiency; others had a more selective defect of either CD40 ligand expression (n = 2) or deficiency of 1 particular lymphokine (n = 10). Thus, CVID may arise from a number of different molecular aberrations. Inefficient signaling via CD40 may be responsible, in part, for failure of B-cell differentiation in these patients.

In a study of 8 patients (6 with CVID and 2 with hypogammaglobulinemia and recurrent infections), Levy et al. (1998) found that 2 CVID patients showed a dramatic reduction in IgV-gene somatic hypermutation, with 40 to 75% of IgG transcripts totally devoid of mutations in the circulating memory B-cell compartment. Functional assays of the T-cell compartment pointed to an intrinsic B-cell defect in the process of antibody affinity maturation in these 2 cases.

Hammarstrom and Smith (1999) provided a comprehensive review. They estimated that CVID affects approximately 1 in 10,000 to 100,000 individuals. The patients display a marked reduction in serum levels of both IgG and IgA. In half of the patients, IgM is also reduced. The incidence of infections thought to have occurred at the onset of the disease shows 2 peaks around 1 to 5 and 16 to 20 years of age (Hermaszewski and Webster, 1993) and is equally distributed between the 2 sexes. The disorder is thought to appear in previously immunologically normal individuals, although the induction phase has been documented in a few cases (Smith et al., 1985). Usually the patients present with clinical symptoms due to hypogammaglobulinemia, reflected in frequent respiratory and gastrointestinal tract infections. In addition to the B cell defect, variable degrees of T cell dysfunction have frequently been noted in CVID patients.

Cunningham-Rundles and Bodian (1999) described the clinical and immunologic status of 248 consecutively referred CVID patients of age range 3 to 79 years who had been followed for a period of 1 to 25 years. Median age at the time of onset of symptoms was 23 years for males and 28 years for females; the mean age at which the diagnosis if CVID was made was 29 years for males and 33 years for females. Forty percent of patients had impaired T-cell proliferation to 1 or more mitogens; lymphocyte transformation to mitogens was directly related to the level of the serum IgG. Females at all ages had higher levels of serum IgM than males. Survival 20 years after the diagnosis of CVID was 64% for males and 67% for females, compared to the expected 92% population survival for males and 94% for females. Parameters associated with mortality in the 20-year period were lower levels of serum IgG, poorer T-cell responses to phytohemagglutinin, and particularly, a lower percentage of peripheral B cells.

## PATHOGENESIS

In a provocative although not thoroughly convincing report of the family of a patient with hypogammaglobulinemia of the common variable hypogammaglobulinemia type associated with deficiency of alpha-1-antitrypsin, Phung et al. (1983) suggested genetic linkage of the PI locus (107400) and a locus exercising a regulatory role in immunoglobulin synthesis. Two members of the kindred were thought to be recombinants; they had hypogammaglobulinemia with normal PI MM phenotype. Because of the relatively close situation (on the distal end of 14q) on the PI locus and the loci for immunoglobulin heavy chains, the observation was of considerable interest. Phung et al. (1982) had concluded that a serum suppressive factor, which prevented pokeweed mitogen-induced differentiation of B lymphocytes both in the proband and in normal subjects, was present in the proband. Heterogeneity in this disorder was emphasized by Geha et al. (1974). Kirkpatrick and Schimke (1967) focused on low IgM as a 'marker' in familial hypogammaglobulinemia. Litwin and Fudenberg (1972) reported quantitative deficiency in the expression of the Gm gene in families with primary antibody deficiency.

Holm et al. (2003) found that T cells from CVID patients activated by anti-CD3 (see 186740) and anti-CD28 (186760) secreted less IL10 (124092) than healthy controls, regardless of proportions of T-cell subsets. Furthermore, sensitivity to cAMP-dependent inhibition of protein kinase A type I (see 188830)-mediated T-cell activation was greater in CVID patients. Holm et al. (2003) proposed that impaired IL10 secretion by CVID patient T cells may be a link between T-cell deficiency and impaired B-cell function in CVID.

Using flow cytometry to assess the immunologic profiles of 32 patients with CVID, Cunningham-Rundles et al. (2006) found that, in addition to reduced levels of CD27 (TNFRSF7; 186711)-positive memory B cells, CVID patients had unrelated, pronounced TLR9 (605474) defects. CpG oligonucleotides did not activate CVID B cells, even when costimulated by B-cell receptor, and they did not stimulate surface or intracytoplasmic expression of TLR9 or production of IL6 (147620) or IL10. In addition, CVID plasmacytoid dendritic cells, which expressed normal amounts of intracytoplasmic TLR9, produced only low amounts of IFNA (147660). No TLR9 mutations or polymorphisms were detected. Cunningham-Rundles et al. (2006) concluded that CVID patients have broad TLR9 activation defects that result in impaired CpG-initiated innate immunity.

## MOLECULAR GENETICS

In an analysis of the MHC haplotypes of 12 IgA-deficient persons and 19 CVID persons from 21 families and of 79 of their immediate relatives, Volanakis et al. (1992) found that a small number of MHC haplotypes were shared by the majority of immunodeficient persons. Five of the families contained more than 1 immunodeficient individual and all of these 5 families included both IgA-deficient and CVID members. At least 1 of 2 MHC haplotypes was present in 24 of the 31 (77%) immunodeficient persons. No differences in the distribution of these haplotypes were observed between IgA-deficient and CVID persons. The analysis suggested that a susceptibility gene (or genes) for both immunodeficiencies is located within the class III region of MHC, possibly between the C4B and

C2 genes.

By studying cohorts of immunodeficient individuals from Europe (162 individuals with CVID) and the US (19 individuals with CVID and 16 with IgAD), Salzer et al. (2005) and Castigli et al. (2005) found that mutations in the TNFRSF13B gene (604907), encoding transmembrane activator and CAML interactor (TACI), were associated with both familial and sporadic forms of the disease. Martin and Dixit (2005) noted that 3 of the 6 mutations were found in both cohorts and were seen in both familial and sporadic cases, suggesting that a small number of common mutations could account for most TACI-associated immunodeficiency cases. See IGAD2 609529 for a discussion of IgAD related to mutation in the TNFRSF13B gene.

See Also:

Charache et al. (1965); Hermans et al. (1976); Wollheim (1968)

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Clinical Synopsis:

INHERITANCE:
- Autosomal recessive;
- Autosomal dominant;
- Isolated cases

HEAD AND NECK:
- [Head];
- Acute sinusitis;
- [Ears];
- Acute otitis media;
- [Eyes];
- Conjunctivitis

RESPIRATORY:
- [Airways];
- Bronchiectasis;
- [Lung];
- Pneumonia

ABDOMEN:
- [Spleen];
- Splenomegaly;
- [Gastrointestinal];
- Diarrhea

NEUROLOGIC:
- [Central nervous system];
- Meningitis

IMMUNOLOGY:
- Recurrent bacterial infections;
- Lymphadenopathy;
- Low plasma cells number in bone marrow;
- Normal numbers of T cells;
- Variable degree of T cell dysfunction;
- Normal numbers of surface immunoglobulin positive B cells;
- Lymph nodes show reactive follicular hyperplasia and non-caseating granulomas

NEOPLASIA:
- Lymphomas

LABORATORY ABNORMALITIES:

Markedly reduced IgA levels;
Markedly reduced IgG levels;
Reduced IgM levels;
Anti-IgA antibodies commonly present

MISCELLANEOUS:
Disease onset shows two peaks: 1 to 5 and 16 to 20 years of age;
Iatrogenic form is drug induced, eg: sulfasalazine, hydantoin, carbamazepine
and levamisole

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terry: 9/23/1999
carol: 12/4/1998
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