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Review Article

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Common Variable Immunodeficiency / Cvid

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Abstract

"Variable" refers to the heterogeneousclinicalmanifestations of thisdisorder, which can include: recurrentinfections, chroniclungdisease, autoimmune disorders, also involve varioussegments of the gastrointestinaltract and a heightenedsusceptibility to lymphoma. Itis a primaryimmunodeficiencythataffects 1 in 50,000 peopleworldwide. Itischaracterized by reducedimmunoglobulinserumlevels and absent or impairedantibody production. The pathogenic of CVID isnotknown; however, therehavebeennumerousassociatedlaboratoryfindingsincludingnumerousmutations in the genesresult in dysfunctional B cells. The mostfrequentmutationsoccur in the TNFRSF13B gene. Genesthathavebeenimplicated in monogenic CVID include ICOS, TNFRSF13B (TACI), TNFRSF13C (BAFF-R), TNFSF12 (TWEAK), CD19, CD81, CR2 (CD21), MS4A1 (CD20), TNFRSF7 (CD27), IL21, IL21R, LRBA, CTLA4, PRKCD, PLCG2, NFKB1, NFKB2, PIK3CD, PIK3R1, VAV1, RAC2, BLK, IKZF1 (IKAROS) and IRF2BP2 [1]. In addition, thereisevidence of complexinheritanceratherthan a monogenic CVID.

Keywords: CVID, diagnosis, variable, pathogentics

Introduction

CVID can be assigned to a patient over age four who demonstrates all of the following characteristics:

Significantly reduced total serum concentrations of immunoglobulin G (IgG). **Low immunoglobulin A (IgA) and/or immunoglobulin M (IgM)**. Serum immunoglobulin G (IgG) should be below the lower limit of normal and generally under 400 mg/dL. Immunoglobulin A (IgA) and/or low immunoglobulin M (IgM) should be below the **lower limit of normal**.

If there is a concomitant illness that could cause **secondarily low immunoglobulin levels (eg, nephrotic syndrome or protein-losing enteropathy**), then the measurement should be repeated approximately three months after resolution of the illness. **In contrast**, neither acute infection, such as pneumonia, nor short-term administration of systemic glucocorticoids, should significantly reduce or increase immunoglobulin levels. However, chronic systemic glucocorticoids may reduce serum IgG levels.
Poor or absent response to immunization.

Vaccine response

The patient's response to both **protein- and polysaccharide-based vaccines** should be assessed in all cases, **unless antibody levels are very low** (eg, IgG<200 mg/dL) or undetectable, in which case vaccine response can be assumed to be deficient.

The absence of any other defined immunodeficiency state (ie, CVID is a diagnosis of exclusion).

Additional testing: However, neither of these is required for diagnosis

Flow cytometry

Most patients with CVID have normal numbers of circulating T and B lymphocytes. However, **most** can be shown to have somewhat reduced levels of circulating memory B cells (CD27+ B cells) and especially low levels of isotype switched memory B cells (CD27+ IgD- IgM-). Some have impaired T cell function. Abnormal cytokine levels have also been described.

Molecular analysis

Genome-wide association identifies diverse causes of CVID. It might be considered if there are other affected family members, making detection of a discrete defect more likely. It is also sometimes useful for excluding other immunodeficiencies that arise from known genetic defects.

The primary phenotypic defect is a failure in B cell differentiation, resulting in impaired secretion of IgA, IgG and IgM. Diagnosis is difficult because of the infrequent incidence, high clinical variability of CVID and lack of specific laboratory tests, and is generally established years after the onset of the disease. Phenotypic approach; to categorizing CVID has been proposed, based upon the type of complications the patient develops. This arise from an analysis of the European Common Variable Immunodeficiency Disorders registry (composed of patients from nine centers in Europe and the United Kingdom), in which 334 patients with CVID were followed for an average of 26 years [2]. Five phenotypic categories were proposed:

- Patients with no complications.
- Patients with autoimmune disease.
- Patients with lymphocytic organ infiltration (ie, lymphocytic enteropathy, granulomas, unexplained hepatomegaly, persistent lymphadenopathy, splenomegaly, and/or lymphoid interstitial pneumonitis).
- Patients with predominant enteropathy.
- Patients with lymphoid malignancy.

The clinical heterogeneity of CVID suggests that multiple immunoregulatory defects can result in the final common pathway of hypogammaglobulinemia. The hallmark immune defect in CVID is defective B cell differentiation into plasma cells, with impaired secretion of immunoglobulin. However, CVID is associated with a high incidence of inflammatory, autoimmune, and malignant conditions. This suggests that CVID represents a more global form of immune dysfunction.

B cell Abnormalities

Many have reduced percentages of isotype-switched memory B cells and lack plasma cells; capable of producing antigen-specific immunoglobulin G (IgG) and immunoglobulin M (IgM), immunoglobulin isotypes that are critical for recall (or secondary) antibody responses.

A number of abnormalities that appear to have occurred in the bone marrow. These include:

- Aberrant gene rearrangement.
- Decreased V gene replacements, which normally occur to counteract autoimmunity.
- Decreased diversity of the naïve B cell repertoire.
- Impaired somatic hypermutation.
- Abnormal expansion of unmutated B cell clones.

Memory B cells

Studies have attempted to identify and classify CVID patients based on numbers of isotype-switched memory B cells:

One study proposed that <0.4 % switched CD27+IgM-IgD- memory B cells based on total blood lymphocytes (compared with healthy donors at 1.6±0.6 percent) could be used to classify patients with CVID [3]. These patients had a higher prevalence of splenomegaly and autoimmune cytopenias. Another study classified CVID patients into three groups based on different subpopulations of memory B cells and found that certain disorders that are seen in patients with CVID (eg, splenomegaly, lymphoid proliferation, and granulomatous disease) were more prevalent in patients with the lowest numbers of memory B cells [4]. Subsequently, a study of 105 patients with CVID found that a level of <0.55 % switched memory B cells, based on total blood lymphocytes, was an independent risk factor for autoimmune disease, granuloma formation, and splenomegaly. In addition, female patients were found to have significantly higher levels of memory B cells. Lower levels of circulating IgM memory B cells and poor antipneumococcal polysaccharide IgM responses were associated with recurrent bacterial pneumonia and the development of bronchiectasis in patients with CVID [1]. In contrast, CVID patients with no chronic pulmonary disease had relatively normal measurements of these two parameters. However, another study followed 33 CVID patients, from 3 to 19 years after diagnosis, and found that the percentage of switched memory B cells changed in some patients over time. Therefore, classification of patients based on switched memory B cells may not be ideal.

Toll-like receptor signaling

B cell maturation is defective in patients with CVID, and the function of toll-like receptor (TLR) 7 and 9 on both B cells and dendritic cells is impaired. Normally, B cell responses may be initiated by binding of viral RNA to TLR7 or bacterial DNA to TLR9, both of which lead to B cell activation, cytokine secretion, proliferation, and survival. The loss of these stimuli may contribute to the B cell defects observed. The relevance of impaired TLR9 dysfunction in CVID was demonstrated in a study showing that stimulation with microbial extracts from Streptococcus pneumoniae and Haemophilusinfluenzae resulted in impaired activation and proliferation of B cells.

Other Cellular Abnormalities

Decreased T lymphocyte proliferation to mitogens and antigens (demonstrated in up to 40% of patients in some groups). Low CD4/CD8 T cell ratio due to a decrease in CD4+ cells or an increase in the absolute number of CD8+ cells in some. Those with the most reduced numbers (<200 x 106 cells/L) may have opportunistic infections and a higher prevalence of splenomegaly, granulomatous disease, gastrointestinal disease, and lymphoma. Reduced numbers of T regulatory cells in a subset of patients. Reduced numbers of T cell receptor excision circles (TRECs), suggesting thymicdysregulation. One study found that low TREC levels, kappa-deleting recombination excision circle (KREC) levels, or both, correlated with severity of illness and overall survival [2]. Deficiency of antigen-primed T cells, Reduced T cell production or expression of interleukin-2 (IL-2) and other cytokines, Defective T cell receptor signal transduction, Reduced capacity of dendritic cells to secrete interleukin-12 (IL-12), Increased serum levels of soluble CD26 and CD30 in patients with CVID compared with controls. While serum levels of CD26 were not associated with any clinical phenotypes, serum levels of CD30 were associated with splenomegaly and malignancy [5].

Genes that have been implicated in monogenic CVID include:

ICOS, TNFRSF13B (TACI), TNFRSF13C (BAFF-R), TNFSF12 (TWEAK), CD19, CD81, CR2 (CD21), MS4A1 (CD20), TNFRSF7 (CD27), IL21, IL21R, LRBA, CTLA4, PRKCD, PLCG2, NFKB1, NFKB2, PIK3CD, PIK3R1, VAV1, RAC2, BLK, IKZF1 (IKAROS) and IRF2BP2. With the increasing number of disease genes identified in CVID. Moreover, there is accumulating evidence that at least a subgroup of patients with CVID has a complex rather than a monogenic inheritance.

CVID, a complex disorder?

It is increasingly believed that besides rare monogenic forms, CVID is a polygenic or multifactorial disorder. This is based on the following:

1. Identification of pathogenic mutations in only 2–10% of patients with CVID despite tremendous efforts.
2. largephenotypical variability between patients with the same primary genotype.
3. Presence of variants in asymptomatic relatives and/or in the general population above a certain threshold frequency.
4. Sporadic occurrence in about 90% of cases.
5. Delayed disease onset in many patients.

Approximately 90% of patients with CVID have no history of affected family members, while 10% of patients have at least one family member with either CVID, selective immunoglobulin A deficiency (sIgAD), immunoglobulin G (IgG) subclass deficiency, specific antibody deficiency, and relative hypogammaglobulinemia. About 5-25% of patients have a positive family history, of which most demonstrate an autosomal dominant inheritance. As considerable

phenotypical and genetic heterogeneity. It has become clear that the clinical diagnosis of CVID is an umbrella covering several genetic subtypes.

In addition, mutations in transmembrane activator and calcium-modulator and cyclophilin ligand (CAML) interactor (TACI) have been found in 8 to 10% of CVID patients. TACI is expressed on B cells and activated CD4+ T cells, and it mediates isotype-switching through its ligand, a proliferation-inducing ligand (APRIL). However, mutations in the TACI gene appear to induce susceptibility to CVID rather than directly causing the disorder, as the same mutations can be found in healthy controls and unaffected family members of patients with CVID. The gene for TACI, tumor necrosis factor receptor superfamily 13B (TNFRSF13B), is on chromosome 17p. In a subset of CVID patients with early-onset, inflammatory, or autoimmune complications, one study revealed 17 probable disease-causing mutations in 15 of 50 patients (30 %) [6]. Patients selected for this analysis presented before the age of 10 years, with disorders such as autoimmune cytopenias and organ-specific autoimmune disorders, interstitial lung disease, lymphoid hyperplasia, inflammatory bowel disease, nodular regenerative hyperplasia of the liver, and granulomatous infiltrations.

Genome-wide association studies

A genome-wide association (GWA) and gene copy number variation (CNV) study in patients with CVID previously found a strong association with the MHC region and with a disintegrin and metalloproteinase (ADAM) gene, among others.

Conclusion

This review aimed to discuss current knowledge regarding the molecular genetic of CVID in addition to; the relationship with the clinical and immunological phenotype in adult. However, further exploration of innate lymphoid cell biology in CVID may uncover key mechanisms underlying the development of inflammatory complications in these patients.

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