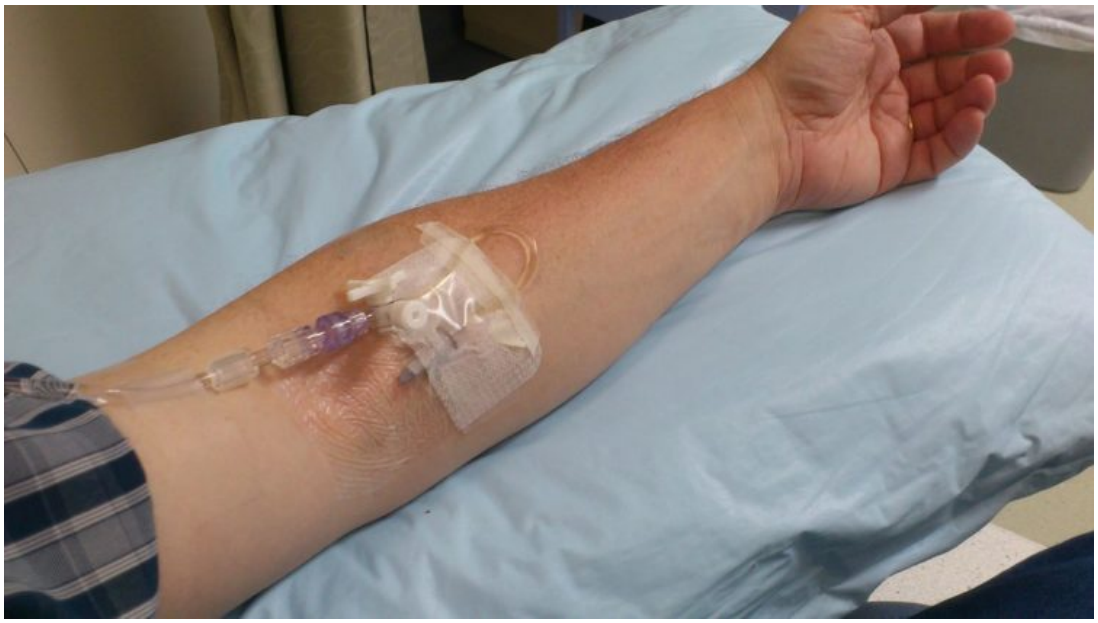
Humoral Immune Deficiency (Humoral Immunodeficiency) in Children — Clinical Presentation and Diagnostic Workup

See online here

CVID, also known as humoral immunodeficiency, is characterized by reduced serum levels of immunoglobulins G and A and, in some patients, also immunoglobulin M. Patients present with recurrent infections, an increased risk of autoimmune disorders and malignant disease. Quantification of serum levels of immunoglobulins, in addition to an assessment of the functional activity of lymphocytes, is indicated in the diagnostic workup of CVID. Specific culture and sensitivity tests should be performed in patients with infectious complications to guide antibiotic therapy. Treatment of CVID includes antimicrobial therapy, immunoglobulin replacement therapy and immunomodulation therapy in patients with autoimmune disease.



Definition

Common variable immunodeficiency (CVID), previously known as humoral immunodeficiency, includes a **group of different disorders** that are shared by **marked reductions in the serum levels of immunoglobulins A, G, and M**.

Immunoglobulin M is related to the acute immune response against infections, immunoglobulin G is related to long-term immunity and immunoglobulin A is implicated in secretory immunity; therefore, patients who have CVID are at risk of **recurrent infections**, **impaired immune responses,** such as autoimmune

diseases and granulomatous disease, and malignancy. The disease belongs to a heterogeneous group of immunologic disorders of unknown etiology.

Epidemiology of Pediatric CVID

CVID is a collective term that includes different disorders that all share the same features of reduced serum levels of immunoglobulins. The estimated incidence of CVID is approximately **1 per 30,000**. The prevalence of CVID varies by country. The disorder is reported to have the highest prevalence in France, Spain, and the Netherlands, but to be rare in Poland.

Mortality related to CVID is correlated with the severity of the recurrent infections and the development of certain diseases related to impaired immunity; therefore, patients who develop **bronchiectasis** and **severe lung damage**, those with **malignant disease** and patients with **autoimmune disorders** have a higher mortality rate compared to patients who do not develop any of these complications.

Some possible predictive variables of reduced survival in CVID include an early age at diagnosis, lower baseline immunoglobulin G serum levels, and low peripheral B cells. Additionally, patients with malignancy or autoimmune disorders have a higher mortality rate compared to those with infectious complications. Nowadays, up to 60% of patients survive more than 40 years after the diagnosis.

CVID has been reported in **all ethnicities** and has an equal incidence rate in **both genders**. While most cases are diagnosed in their twenties, up to one-third of the patients are diagnosed during childhood.

<table>
<tr><th>0 – 6 months</th><th>2 – 6 years</th><th>> 6 years</th></tr>
<tr><td rowspan="2">X-linked agammaglobulinemia</td><td>IgA deficiency</td><td rowspan="2">Common variable immunodeficiency</td></tr>
<tr><td>Selective IgG deficiency</td></tr>
<tr><td rowspan="2">Hyper IgM syndrome</td><td>Hypogammaglobulinemia</td><td rowspan="2">Acquired disease (HIV, lupus, etc.)</td></tr>
<tr><td>Hyper IgE (Job syndrome)</td></tr>
</table>

Pathophysiology of Pediatric CVID

Patients with CVID have immunologic disorders that are characterized by **reduced serum levels of the different immunoglobulins**. Most patients have pronounced reduced serum levels of immunoglobulins A and G. Immunoglobulin M serum levels are also reduced in up to 50% of the cases.

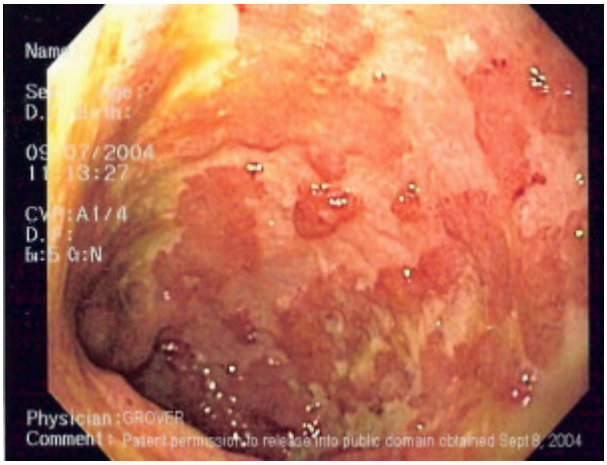


Image: “Endoscopic image of ulcerative colitis affecting the left side of colon. Note that the classic features of ulcerative colitis are not seen here, and that the image resembles Crohn’s colitis as it shows serpiginous ulcers. The purpose of this image is to show the difficulty in differentiating between the two disorders on endoscopy.” by Samir. License: CC BY-SA 3.0

Due to reduced immunoglobulin A levels, patients are at an **increased risk of recurrent bacterial infections**. Patients might develop pyogenic lung infections, pneumocystis jiroveci pneumonia and mycoplasma pneumoniae atypical pneumonia. Recurrent urinary tract infections due to mycoplasma pneumoniae, septic arthritis, and deep-tissue abscess are also common in CVID.

Due to the impaired immunity state in CVID, patients are at risk of developing different autoimmune disorders, such as immune thrombocytopenic purpura, hemolytic anemia, rheumatoid arthritis, and inflammatory bowel disease.

Most cases of CVID are **sporadic,** but **familial autosomal dominant CVID** has been described in at least 10% of the cases. Genetic testing in CVID is complicated because of the large number of possible etiologies of the disorder. Regardless, certain **genetic defects** have been clearly associated with CVID such as TACI, and ICOS mutations. CD19, CD81, CD20, and CD21 deficiencies have also been implicated with CVID. These genetic defects are usually linked to **impaired B-cell activity,** but ICOS mutations are linked to **T-cell function**.

Clinical Presentation of Pediatric CVID

Patients with CVID usually present with recurrent infections, autoimmune disorders, lymphoid hyperplasia, granulomatous disease, and malignancy.

Recurrent Infections

Patients who present with recurrent pyogenic lung and sinus infections due to ***Moraxella catarrhalis***, ***streptococcus pneumoniae*****,** and ***staphylococcus aureus*** should be evaluated for possible CVID. Unusual organisms, such as ***Pneumocystis jiroveci*** and **fungal pneumonia,** are also more common with CVID compared to healthy immune-competent children.

Patients might present with **persistent diarrhea** due to **giardia lamblia** as it is also common with CVID. Patients can also develop severe **herpes simplex infections,** and **herpes zoster eruptions** are common.

Autoimmune Conditions

Possible presentations of autoimmune disorders due to CVID include anemia and recurrent infections due to cytopenia, recurrent bruising and petechia due to idiopathic thrombocytopenic purpura and thyroid disorders.

Vitiligo, type 1 diabetes mellitus, psoriasis, systemic lupus erythematosus, arthritis, and ulcerative colitis or Crohn's disease are also more common in patients with CVID.

Granulomatous diseases

Granulomas in the lungs, lymph nodes, skin, and the gastrointestinal tract resemble sarcoidosis on histologic examination.

Malignancies

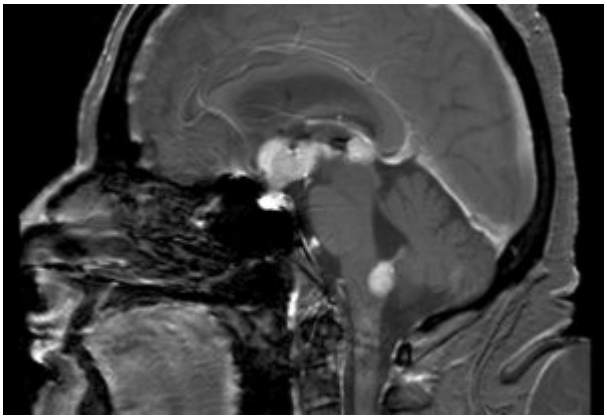


Image: "Brain MRI showing primary central nervous system B-cell non-Hodgkin lymphoma of the sella turcica and hypothalamus, continuing to the tectum." by Steven Fruitsmaak – Own work. License: CC BY-SA 3.0

The most common malignancy associated with CVID is **non-Hodgkin's lymphoma**. Gastric malignancy, breast cancer, colon cancer, prostate cancer, and ovarian cancer are also commonly associated with CVID.

The most important features in clinical examination of a child with CVID are the presence of **lymphadenopathy** and **splenomegaly**. Patients could also have localized signs that are specific to the infectious complication they are presenting with, i.e. crackles and reduced breath sounds in pneumonia.

Job syndrome	X-linked agammaglobulinemia, hypogammaglobulinemia	Common variable immune deficiency
Extremely high levels of IgE	No immunoglobulins in the blood	B-cell deficiency
"Coarse facies"	Male gender (x-linked recessive)	High risk of autoimmune disorders (AHA, ITP)
Recurrent sinopulmonary infections	Failure to thrive (x-linked agammaglobulinemia)	Higher risk for malignancy (lymphoma, gastric carcinoma)

Eczema	Later childhood or early adult presentation (hypogammaglobulinemia)	Later onset (average age of presentation: 26 years, but earlier possible)
Recurrent cellulitis	Recurrent otitis media, sinusitis, pneumonia	
→ Treatment is **supportive**	→ Treat with regular IVIG infusions (every 3 weeks)	→ Treat with IVIG

Diagnostic Workup for Pediatric CVID

Patients who present with recurrent pyogenic lung and sinus infections, autoimmune disorders and lymphoid hyperplasia should be evaluated for possible CVID.

The first diagnostic test would be to determine the **levels of the different immunoglobulins**, i.e. IgG, IgM, and IgA.

All patients with CVID have **decreased IgG and IgA levels but not absent IgG and IgA**. IgM levels are usually reduced, but some patients might have normal or even elevated IgM levels. **Radial immunodiffusion** is the preferred method for the quantification of serum immunoglobulins. Serum levels of immunoglobulins are age-dependent; therefore, age-adjusted normal values should be used whenever you try to interpret the results.

Once reduced levels of immunoglobulins are confirmed, the next question would be whether this deficiency is due to decreased synthesis or to the loss of the immunoglobulins. Patients with CVID have **decreased synthesis of immunoglobulins**. Determination of serum levels of the different immunoglobulins following active immunization is a possible technique to differentiate between immunoglobulins deficiency due to a loss versus impaired synthesis.

Enumeration of circulating B cells and T cells:

Serum peripheral B cell count should also be determined as low peripheral B cell count has been associated with reduced survival in CVID. Patients with CVID can also have **impaired lymphocyte response to certain antigens**. Lymphocytes can be isolated from the patient’s blood and presented with different mitogens, antigens, and specific antibodies against T-cell surface molecules. The common antibodies used in immunofluorescence staining for this quantification include CD3 and CD4 for T cells and CD20 and CD21 for B cells. other non-specific antibodies include CD16, CD56 and CD57.

Complete blood count:

A **complete blood count** is also indicated in CVID as it can reveal anemia which is usually hemolytic, thrombocytopenia and lymphopenia. Lymphopenia is more common in severe CVID.

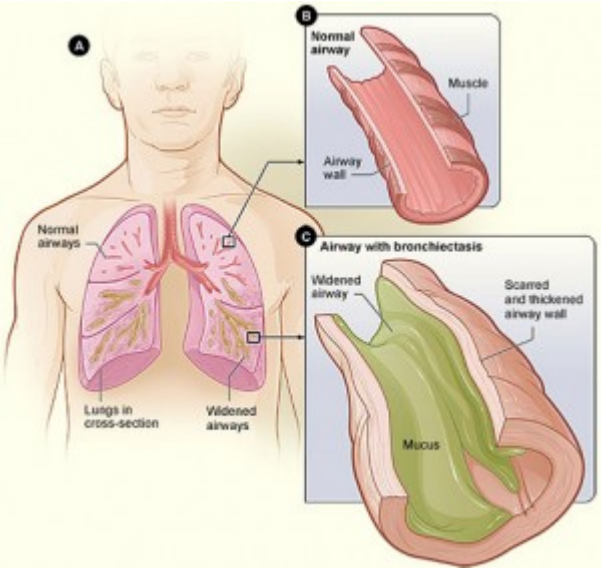


Image: “Figure A shows a cross-section of the lungs with normal airways and widened airways. Figure B shows a cross-section of a normal airway. Figure C shows a cross-section of an airway with bronchiectasis” by National Heart Lung and Blood Institute. License: Public Domain

Assessment of comorbid conditions for proper management:

Patients who have CVID are at an increased risk of developing recurrent lung infections and possibly bronchiectasis. **High-resolution computed tomography scanning of the lungs** is indicated to exclude the presence of damaged lung architecture which is associated with reduced survival.

The **identification of the causative infective organism** in a patient presenting with infectious complications of CVID should be attempted. **Culture and sensitivity testing** are recommended as they can help in the identification of the causative organism and guide antibiotic therapy.

Patients with lung nodules should undergo a **bronchoscopy** to examine the nodule and a biopsy should be obtained. **Histologic examination of the biopsy** allows for the differentiation between lymphoid hyperplasia, non-Hodgkin’s lymphoma, and granulomatous lesions. The differentiation between the different types of nodules has an impact on the survival rate.

Treatment of Pediatric CVID

The most common presentation of CVID is that of infectious complications. **Antibiotic and/or antifungal therapy** is indicated in the treatment of infectious diseases in CVID. The choice of anti-microbial drugs should be based on the location of the infection, the most likely causative organism, and the results of culture and sensitivity testing.

Immunoglobulin replacement therapy is the mainstay treatment of CVID. Regular intravenous immunoglobulin replacement therapy is indicated and usually successful in patients with recurrent pyogenic lung and sinus infections due to CVID. Immunoglobulin replacement therapy does not influence the incidence of autoimmune or malignant disorders.

Patients who have an existing infection should be treated with appropriate antimicrobial therapy before starting immunoglobulin replacement therapy as the risk of **non-anaphylactic reactions** is more common in this subgroup. Possible non-anaphylactic reactions to immunoglobulin replacement therapy include headaches, chills, fever, chest tightness, myalgia, fatigue, and nausea.

Patients with autoimmune disorders due to CVID might need **short-term corticosteroid therapy**. Patients who have lymphoid interstitial pneumonitis, an autoimmune disorder, might benefit from **cyclosporine A**. Patients presenting with thrombocytopenia or neutropenia should be treated with **anti-CD20**. Granulomatous disease in CVID responds to **anti-TNF therapy** (infliximab).

Finally, patients who develop deep skin abscesses or lung abscesses should undergo an **incision and drainage procedure**. Surgical treatment of bronchiectasis involves the **resection of the affected lung lobes** and might also be needed.

Selective IgA deficiency

Presentation	Treatment
1. Recurrent sinopulmonary infections	Treat infections, consider IVIG
2. GI disorders (celiac disease, IBD)	Treat disease, consider IVIG
3. Autoimmune disease (lupus, JIA)	Treat disease, consider IVIG
4. Anaphylaxis to transfusion of blood or IVIG	Desensitize to blood products

References

Pediatric Common Variable Immunodeficiency via medscape.com

Notes