

Commonly Misdiagnosed Primary Immunodeficiencies

Finding the Right Diagnosis

for Patients and Caregivers





What are Primary Immunodeficiencies (PIDs)?

Primary immunodeficiencies, or PIDs, are a group of disorders that weaken the immune system, making it harder for the body to fight infections. People with PIDs may get sick more often or have infections that are harder to treat. These conditions are caused by defects in the immune system that you're born with, though they can show up at any age, from infancy to adulthood. While some PIDs are rare, recognizing them early is key to managing them effectively.

Why are PIDs Often Misdiagnosed?

Getting an accurate diagnosis of a PID can be difficult for several reasons, including:

- **Symptoms Mimic Other Conditions:** The most common sign of a PID is frequent infections, but many other conditions like allergies, asthma, or even chronic viral infections can cause similar problems. For example, frequent colds or sinus infections might be written off as a part of childhood or a seasonal problem, delaying proper diagnosis.
- **Nonspecific Symptoms:** PIDs don't always show up as just infections. Some people might feel tired all the time, have frequent fevers, or develop autoimmune issues, which are often confused with conditions like chronic fatigue syndrome or autoimmune diseases like lupus.
- **Severity Varies:** Not everyone with a PID has severe symptoms. Some people might only get frequent but mild infections, making it harder to suspect a serious immune problem.
- **Lack of Awareness:** PIDs aren't as common as conditions like asthma or allergies, so many doctors may not think of testing for them right away, especially if they're unfamiliar with the warning signs.

The Consequences of Misdiagnosis

Misdiagnosis or delayed diagnosis of PIDs can have serious consequences for patients:

- **Wrong Treatments:** Without the right diagnosis, patients might receive treatment for symptoms, like repeated antibiotics for infections, without addressing the root cause—an immune deficiency. This can sometimes make the situation worse or cause unnecessary side effects.
- **Worsening Health:** PIDs can lead to more serious infections, organ damage, or even cancer if left untreated, so early diagnosis and proper care are important.
- **Emotional Stress:** Not knowing why you're frequently sick or dealing with multiple misdiagnoses can cause a lot of anxiety, frustration, and emotional distress for both patients and caregivers.



My CVID wasn't diagnosed until I was in my 60s. A life-long history of sinus infections, bronchitis, pneumonias, and pleurisy, combined with decreasing antibiotic effectiveness, extended illnesses, and finding a good immunologist was my answer. A series of tests showed I wasn't making antibodies. I had an IgG, IgA test as a base, then a pneumonia vaccine and tetanus shot and my levels went down.

- PID Patient



Commonly Misdiagnosed PIDs and How to Improve Accurate Diagnosis

1. Common Variable Immunodeficiency (CVID)

Overview: CVID is one of the most common PIDs, but it is often overlooked. It involves low levels of immunoglobulins (antibodies) that help fight infections. CVID can present at any age, though it is often diagnosed in adulthood.

► Common Misdiagnoses:

- Chronic respiratory infections: Patients with CVID often suffer from recurrent pneumonia, bronchitis, or sinus infections, which may be misdiagnosed as asthma, chronic bronchitis, or COPD (chronic obstructive pulmonary disease).
- Autoimmune disorders: CVID can also cause autoimmune symptoms, leading to confusion with lupus, rheumatoid arthritis, or inflammatory bowel disease.

► How to Improve Diagnosis:

- Immunoglobulin testing: Checking levels of immunoglobulins (IgG, IgA, IgM) should be routine in patients with unexplained recurrent infections or autoimmune problems.
- Evaluate response to vaccines: Testing how the immune system responds to vaccines (eg., pneumococcal or tetanus vaccines) can give clues about immune function.
- Referral to immunologists: When CVID is suspected, early referral to an immunologist can help confirm the diagnosis through more specific testing, like checking B-cell function.

2. Selective IgA Deficiency

Overview: Selective IgA deficiency is the most common PID, where the body has low or absent IgA, an antibody that protects the mucous membranes in the respiratory and digestive tracts. Many people with IgA deficiency may have mild or no symptoms, but others can suffer from frequent infections and autoimmune diseases.

► Common Misdiagnoses:

- Frequent infections: Recurrent respiratory infections, ear infections, and sinusitis in patients with selective IgA deficiency are often misdiagnosed as allergies, asthma, or just frequent viral infections.
- Gastrointestinal problems: People with IgA deficiency may experience diarrhea and gastrointestinal distress, which can be confused with irritable bowel syndrome (IBS) or celiac disease.

► How to Improve Diagnosis:

- Routine immunoglobulin screening: Doctors should include IgA testing in the workup for patients with recurrent respiratory or gastrointestinal infections.
- Awareness of low-risk presentation: Even if patients don't have severe symptoms, clinicians should be aware that IgA deficiency can still lead to significant health problems, and monitor for secondary autoimmune diseases.



3. Severe Combined Immunodeficiency (SCID)

Overview: SCID is a severe form of PID that affects both B and T cells, making it extremely difficult for the immune system to fight infections. Babies with SCID are often diagnosed when they suffer from life-threatening infections early in life. However, in the absence of screening programs, SCID can be misdiagnosed or overlooked until serious illness develops.

► Common Misdiagnoses:

- Failure to thrive or chronic infections in infants: SCID may initially be mistaken for failure to thrive, recurrent viral infections, or even a gastrointestinal disorder.
- Allergies: Severe rashes or eczema-like symptoms in SCID patients may be confused with allergic conditions or eczema.

► How to Improve Diagnosis:

- Newborn screening: Early diagnosis of SCID can be life-saving, and many countries now include SCID in newborn screening programs. Expanding these programs is critical.
- Immediate referral to specialists: If an infant shows signs of severe infection or failure to thrive, quick referral to an immunologist is essential for early diagnosis and treatment, often through bone marrow transplantation.

4. X-Linked Agammaglobulinemia (XLA)

Overview: XLA is a condition where the body cannot produce B cells, which are necessary for making antibodies. This leads to frequent bacterial infections starting in infancy or early childhood, especially in boys, since it is X-linked.

► Common Misdiagnoses:

- Recurrent bacterial infections: XLA is often mistaken for recurrent viral infections, allergies, or even asthma due to the frequent respiratory infections like pneumonia or sinusitis.
- Delayed speech or developmental delays: Some children with XLA may have delays in development because of frequent illness, leading to misdiagnosis as developmental disorders.

► How to Improve Diagnosis:

- Early blood testing: Measuring levels of B cells and immunoglobulins should be standard in children with frequent, severe bacterial infections.
- Family history: Since XLA is inherited, a family history of male relatives with recurrent infections or early death should raise suspicion and prompt early testing.

5. Chronic Granulomatous Disease (CGD)

Overview: CGD is a condition where certain immune cells (phagocytes) are unable to kill bacteria and fungi, leading to severe infections and granuloma formation (clusters of immune cells).

► Common Misdiagnoses:

- Chronic infections: People with CGD may suffer from persistent or severe infections in the lungs, skin, or bones. This is sometimes mistaken for

tuberculosis (TB), fungal infections, or even inflammatory bowel disease.

- Skin abscesses: The recurrent skin infections and abscesses seen in CGD patients may be confused with staphylococcal infections or other common bacterial skin issues.

► How to Improve Diagnosis:

- Phagocyte function testing: A simple blood test, called a neutrophil oxidative burst test, can help diagnose CGD by evaluating how well immune cells are functioning.
- Genetic testing: Genetic testing can confirm the diagnosis and guide treatment, and family members may also benefit from testing if there is a history of recurrent infections.

6. Hyper IgM Syndrome

Overview: Hyper IgM syndrome is a rare PID where patients have high levels of IgM but very low levels of other immunoglobulins (IgG, IgA, and IgE). This leads to frequent bacterial infections.

► Common Misdiagnoses:

- Frequent infections in childhood: The recurring respiratory infections and diarrhea caused by Hyper IgM syndrome can be confused with other conditions like chronic sinusitis, ear infections, or gastrointestinal infections.

► How to Improve Diagnosis:

- Immunoglobulin level testing: Doctors should assess not only total immunoglobulin levels but also the balance of different types (IgG, IgA, and IgM) in patients with frequent infections.
- Early genetic testing: Identifying genetic mutations linked to Hyper IgM syndrome can confirm the diagnosis and prevent long delays in treatment.

How to Get an Accurate Diagnosis

If you or a loved one suspect that frequent or severe infections might be due to a primary immunodeficiency, there are steps you can take to help get the right diagnosis:

01

Know the Warning Signs: Some key signs that might point to a PID include:

- Recurrent, persistent, or severe infections, especially in the sinuses, lungs, or skin.
- Infections that need long courses of antibiotics or don't clear up completely.
- A family history of immune system problems or early deaths due to infections.
- Autoimmune issues like anemia, arthritis, or skin disorders without a clear cause.

02

Track Symptoms: Keeping a detailed record of your or your loved one's symptoms, including the frequency, type, and severity of infections, can help doctors get a clearer picture. Note any hospitalizations, the types of treatments you've tried, and how well they worked.

03

Ask About Testing: If frequent infections or other signs are present, you can ask your doctor to run some basic tests. These may include blood tests to check your white blood cell count, levels of infection-fighting proteins called immunoglobulins, and your body's response to vaccines. These can be helpful starting points to identify possible immune problems.

04

Consult an Immunologist: If your primary doctor is unsure about the cause of frequent infections or immune problems, consider seeing an immunologist (a doctor who specializes in the immune system). They can perform more advanced tests to evaluate how well your immune system is functioning and may suggest genetic testing to find out if there's a specific inherited issue causing the problem.

05

Consider Genetic Testing: In some cases, especially if there's a strong family history of immune problems, genetic testing can help pinpoint the exact cause of a PID. Knowing the genetic cause can guide treatment and help family members who might also be affected.

How Screening Can Help

In some places, newborn screening for severe forms of PID, like severe combined immunodeficiency (SCID), is becoming more common. Early diagnosis through screening means treatment can begin right away, often saving lives.



The Importance of Education and Advocacy

Many healthcare providers may not be fully familiar with PIDs, which is why it's so important for patients and caregivers to advocate for themselves. Learning about PIDs, connecting with patient support groups, and sharing information with your healthcare team can help ensure you get the best care.

What Can You Do as a Patient or Caregiver?

- ▶ **Ask Questions:** Don't hesitate to ask your doctor about PIDs if you suspect it could be a possibility.
- ▶ **Seek Second Opinions:** If you're not getting answers that explain the symptoms, consider seeking another opinion, especially from a specialist.
- ▶ **Find Support:** Join PID patient groups or communities where you can connect with others facing similar challenges and access helpful resources.

Conclusion

Misdiagnosis of primary immunodeficiencies is common because these conditions often look like other, more familiar illnesses. Being aware of the warning signs, keeping track of symptoms, and working with specialists are key steps toward getting an accurate diagnosis. Early diagnosis and appropriate treatment can make a huge difference in the quality of life for people with PIDs, allowing them to lead healthier, fuller lives.

