Primary immunodeficiencies for General Practitioners – making a difference in diagnosing severe illness

**ABSTRACT**

PIDs are heterogeneous disorders caused by hereditary genetic defects of the immune system. The immune system normally helps the body fight off infections by germs/“micro-organisms” such as bacteria, viruses, fungi and protozoa. Because the immune systems do not work properly, people with PIDs are more prone than other people to infections. When PIDs are left undiagnosed or misdiagnosed, the immune system remains defective, often leading to illness, disability, permanent organ damage or even death. Too often infections are treated while missing the underlying cause. Current estimates of the prevalence are 1:1200 patients. Knowledge gaps, delayed diagnosis and treatment are leading into increased morbidity and mortality. Unlike many (rare) diseases, effective treatment options for PID patients are available, which can enable them to carry out a next to normal life. PID patients must therefore be diagnosed early and informed about the most adequate treatment for their particular condition. Unfortunately, none of the available therapies can reverse the damage of late diagnosis.

**Keywords:** Primary immunodeficiency, chronic disease, infections, autoimmunity

Most General Practitioners (GPs) will come across primary immunodeficiencies (PIDs) cases during their career but may not easily diagnose them. Therefore, it is important for GPs as frontline health-care provider to be aware these diseases.

Being aware means looking for patterns, test, and refer.

This will reduce the burden of undiagnosed illness. While reading this article, you will be ready to start to look for patients with PIDs and will give your ideas about how to manage these patients.

**Why Thinking Primary Immunodeficiencies?**

PIDs are heterogeneous disorders caused by hereditary genetic defects of the immune system. The immune system normally helps the body fight off infections by germs/“micro-organisms” such as bacteria, viruses, fungi, and protozoa. Since the immune systems do not work properly, people with PIDs are more prone than other people to infections. When PIDs are left undiagnosed or misdiagnosed, the immune system remains defective, often leading to illness, disability, permanent organ damage, or even death. Too often infections are treated while missing the underlying cause.

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**What are Primary Immunodeficiencies?**

PIDs are genetic disorders, some are monogenic while others are polygenetic. The defects cause typical severe, recurrent, and long-standing infections difficult to cure. PIDs are often running in families. There are being discovered more and more genes related to PIDs. Development of treatments and research within this field is developing very fast.

**Presentations of Primary Immunodeficiencies**

There are different genetic defects leading to PIDs, and there are epigenetic mechanisms that modulate gene expression without altering DNA sequences. This together causes a lot of different presentations of PIDs [Figure 1].

Infections – typical and opportunistic microorganisms are causing infections in these patients. Infections are found in the airways as sinusitis, middle-ear infections, pneumonia, and also gastrointestinal infections but also deep-seated infection and sepsis.

Inflammation – this can occur in all organs, most often in the intestines, lungs, and liver. This is because of regulatory defects, eventually triggered by infections. Inflammation can in some patients be a very large problem.
Autoimmunity – as you know it from inflammatory bowel disease, diabetes, thyroiditis, pulmonitis, and cytopenias. Patients with autoimmunity where the condition is difficult to treat with the usual treatment should be tested for PID.

Allergy – all kinds of allergy is seen in patients with PID.

Cancer – all kinds of cancers, especially lymphoma and other hematological cancers and cancers in the gastrointestinal tract. Patients with PID have a predisposition for cancers which is important to be aware of. The conditions are treated as in other patients and the patients are responding to treatment as other patients.

**Warning Signs of Primary Immunodeficiencies**

Looking for patterns, mainly the tendency of severe, longstanding, or atypical infections. The PID Community recommend that all patients affected by two or more of the “12 Warning Signs” should be tested for PID.

These signs are:
1. Family history with PIDs
2. Failure to thrive (children)
3. +6 ear infections within 1 year for children, 2 for adults
4. +2 sinusitis within 1 year
5. Pneumonia, at least 1/year, difficult to treat, long-standing antibiotics, and intravenous (IV) treatment
6. Persistent thrush in mouth or elsewhere on skin, after age 1
7. Need for IV antibiotics to clear infections and infections with atypical germs/microorganisms
8. Recurrent, deep skin, or organ abscesses
9. Deep-seated infections and sepsis
10. Recurrent and long-standing viral infections
11. Diarrhea and weight loss
12. Severe eczema

About one-third of PIDs patients does not show these above signs. And if all symptoms or infections come from one organ, you should maybe excluded anatomical abnormalities before PIDs.

**Testing for Possible Primary Immunodeficiencies - Why is Diagnosing Important?**

The purpose of knowing about the patient-specific genetic defect is to give the disease a name and to understand the pathology. From there, it is possible to choose targeted treatment and to being better to asses prognosis and to provide genetic counseling.

Most of these diseases are inherited, which means that genetic counseling is very important.

Basic testing for PID is fast and cheap.

It includes a few tests but very important is the medical history.

Blood test – IgG and IgG-subclasses, IgM, IgA, IgE, leukocytes, differential count, thrombocytes, hemoglobin, albumine, HIV, and creatinine.

Diary – with information about illness, fever, infection, and staying home from day care/work is also very important. The diary enables you to see the pattern.

If you have a suspicion about PID test and medical history should be done, and the patients should be referred to a specialist for further immunological testing.

Normal blood test results cannot exclude PID. Have the medical history and the disposition in mind.

**Further tests**

Further examinations include:

Immunological testing the function or malfunction of the immune system.

Genetic testing, either whole genome sequencing, exom sequencing, or just testing for a panel of genes related to the medical history of the patient.

**Primary immunodeficiencies-classification**

Classification is discussed and changed since more and more diagnosis are found, and more and more genetic defects are discovered.

The diagnosis is based on the defect, either T-cell defect or B-cell defect or both, complement defect, phagocytic defect, and so on.

**Treatments**

Immunoglobulins – The majority of PID patients are treated with IgG substitution-therapy. This enables the immune system
to function better. IgG-treatment is developed from plasma from healthy donors, purified, and cleaned from virus-infections. The treatment is given either as IV-infusion or SC infusion. It can be received at home, in a clinic, or at a hospital. The side effects are few for most patients. It is typical given 1-3 times as SC-infusion and as IV-infusion every 3–4 weeks depending on the individual need and the bodyweight.

Antimicrobiotics are used both as treating infections and prophylactic for shorter or longer periods. For example, antibiotics can be used prophylactic during the winter or when PID patients are in larger groups of people. Treatment with antimicrobiotics has often to be mere days than in healthy persons, and broad-spectrum antibiotics are often used. Antimicrobiotics are used in treatment against both bacteria, viruses, and fungi.

Hematopoetic stem cell transplantation is a highly specialized treatment used for the most severe PIDs. It can in PID patients be effective with as little as 10% engraftment because this can be enough for the basic function of the immune system. There are challenges about organ damage before transplant and conditioning before the transplant, for example, short-term and long-term side effects and the condition of the patient before transplant, because the PID patients may have organ damage and chronic infections with fungi, virus, or bacteria before diagnosed and these infections have to be. There are of course also challenges about finding a matching donor (best is haploidentical siblings) which is very important for the outcome. Posttransplant ejection and GvH-reactions are also conditions are also known as challenges. In more and more countries newborn screening for the most severe immunodeficiencies is now done as a routine. These make it possible to find children that need transplantation immediately after birth, and there will be time finding a matching donor as well as isolating the child preventing infections and organ damage.

Gene therapy is a treatment under development, and there are successful results already. Side-effects as vector disease and induced cancer are about to be overcome, but the treatment is still mostly experimental. With gene therapy, it is possible to correct one defect gene; therefore, it is used for monogenetic diseases.

Raising awareness

If you think this is interesting and important, please consider being part of the GPs-for-PIDs-network. We are working across borders in an international network. We inspire each other and help developing knowledge about PIDs among our colleagues. We have also a strong network of specialists, who can provide us with guidance and new knowledge as well as assisting when we are doing presentations as here or writing articles. Find us on Facebook: GPs for PIDs and apply for membership or write to the author: Denninglotte@gmail.com

Resumé

- Be aware of Warning signs, diary, and tests
- Refer and call a friend
- Treatment available.

Guide for GPs: http://www.ipopi.org/uploads/WEB_IPOPI_GuideFOrGPs.pdf

Further information are available on: www.esid.org and www.IPOPI.org

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