IPOPI
INTERNATIONAL
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FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

A GUIDE FOR **HEPATOLOGISTS**

ABBREVIATIONS

CGD	Chronic granulomatous disease
CMV	Cytomegalovirus
CVID	Common variable immunodeficiency
EBV	Epstein Barr virus;
GvHD	Graft vs host disease
IBD	Inflammatory bowel disease;
IFN-y	Interferon-y
Ig	Immunoglobulin
IPOPI	International Patient Organisation for Primary Immunodeficiencies
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
MSMD	Mendelian susceptibility to mycobacterial disease
PID	Primary immunodeficiency
SADNI	Selective antibody deficiency with normal immunoglobulins
SCID	Severe combined immunodeficiency
XLP	X-linked lymphoproliferative syndrome

Primary immunodeficiencies: A guide for hepatologists (1st edition).

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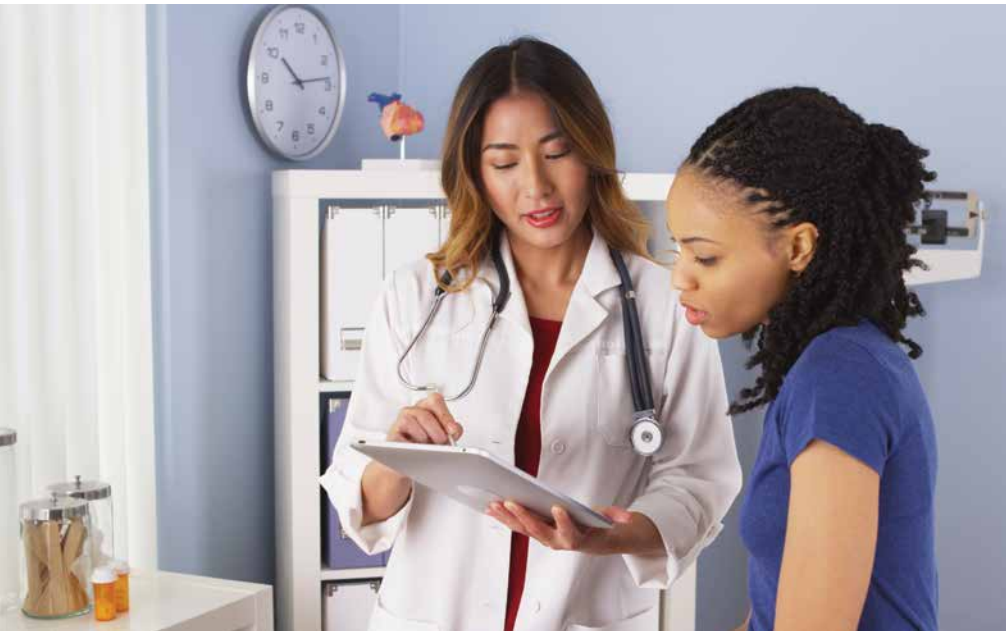
INTRODUCTION

This booklet introduces the complex presentation of adult patients with primary immunodeficiencies (PIDs) who may be referred to hepatology services with non-specific liver-related symptoms. Clinical indicators that may raise suspicion of PID are reviewed as are the needs for a multidisciplinary team to optimise care for such patients.

Primary immunodeficiencies (PIDs) are rare diseases that occur when components of the immune system are either not present or are not functioning normally, rendering the patient susceptible to potentially life-threatening infections.

The presentation of a PID is often complex with clinical indicators suggestive of multiple potential diagnoses especially after routine liver function tests. Such patients may be referred to a hepatologist with non-specific liver-related symptoms. Hepatologists have, therefore, the opportunity to identify patients with PIDs ensuring they receive a timely diagnosis and intervention to minimise the chronic effects and morbidity of PIDs and initiate prophylactic therapies as early as possible.

The following sections review the complex clinical presentations of patients with PIDs and the clinical indicators that may raise a suspicion of PIDs. Management strategies, including building a multidisciplinary team, are also explored.



PIDs: NOT JUST A PAEDIATRIC DIAGNOSIS

To date, over 430 different PIDs have been identified genetically, biochemically and phenotypically, ranging from the very rare (e.g. severe combined immunodeficiency [SCID]) to the relatively common (e.g. selective immunoglobulin A deficiency).

Whilst PIDs are generally recognised as rare disorders, some are more common than others and, taken as a whole, they represent an important group of people whose lives are profoundly impacted by their condition. PIDs can be diagnosed throughout the lifespan of a person with the most severe forms of PIDs usually being diagnosed in childhood. That said, others are frequently recognised during adulthood because of their late onset and as a result of being misdiagnosed or undiagnosed.

PIDs can have widely differing presentations, from relatively mild to life-threatening. Some develop over time and worsen as late manifestations or complications appear. People with PIDs are more susceptible to infections, allergies, autoimmunity, malignancies and complications resulting from infections and inflammation. Indeed, many patients with PIDs go undiagnosed for several years, during which time they are often treated several times with antimicrobial agents with no permanent cure or long-term positive outcome.

HEPATIC INDICATORS FOR PIDs

The main hepatic and gastrointestinal symptoms that could alert a hepatologist to a potential PID presentation are highlighted in the table.

HEPATIC AND GASTROINTESTINAL MANIFESTATIONS OF PIDS[1]

Manifestation	Potential PID
Hepatitis (CMV), colitis, candidiasis, chronic diarrhoea, maternofetal GvHD [symptoms can be present from birth]	Severe combined immunodeficiency (SCID)
Hepatic veno-occlusive disease, hepatosplenomegaly	Veno-occlusive disease with SCID
Hepatosplenomegaly, diarrhoea, eosinophilic enteropathy	Omenn syndrome

Hepatitis (autoimmune, toxic, CMV), diarrhoea, colitis, candidiasis	Adenosine deaminase deficiency SCID
Progressive liver disease, sclerosing cholangitis, colitis and hepatitis (CMV), candidiasis, protracted diarrhoea (*Cryptosporidium*)	MHC-II deficiency (Bare lymphocyte syndrome)
Progressive liver disease (*Cryptosporidium*), diarrhoea (*Cryptosporidium*), sclerosing cholangitis, malabsorption, oral ulcers	Hyper-IgM syndrome
Diarrhoea (*Giardia lamblia*), nodular lymphoid hyperplasia, villous blunting, IBD-like colitis, pernicious anaemia, nodular regenerative hyperplasia, hepatosplenomegaly	Common variable immunodeficiency (CVID)
Liver abscesses, periodontitis, eosinophilic enteropathy	Hyper-IgE syndrome
Post-EBV fulminant hepatic failure, hepatosplenomegaly, lymphoma	X-linked lymphoproliferative syndrome (XLP)
Hepatitis, liver abscesses, oral ulcers, oesophageal dysmotility, gastric outlet obstruction, small bowel obstruction, colitis, perianal fistula and abscesses	Chronic granulomatous disease (CGD)
Mycobacterial liver and spleen abscesses, salmonella gastroenteritis	IFN-y and IL-12 circuit defect (MSMD)

CMV, cytomegalovirus; EBV, Epstein Barr virus; GvHD, graft versus host disease; MHC, major histocompatibility complex; IBD, inflammatory bowel disease; MSMD, Mendelian susceptibility to mycobacterial disease.

At least 10% of patients with common variable immunodeficiency (CVID) exhibit some degree of liver involvement.[2] Elevated liver enzymes are common in patients with CVID together with fibrotic changes.[3]

Transient elevation of liver enzymes is a common incidental finding in chronic granulomatous disease (CGD) and this is often associated with liver abscesses (occurs in 25–45% of patients with CGD). These patients may be particularly sensitive to drug-related hepatotoxicity.[2]

Liver involvement is also a common feature of hyper-IgM syndrome and these patients may be particularly susceptible to biliary tract carcinoma.[2]

ACHIEVING A DIAGNOSIS OF PID

Initial investigations, which may have been performed in the primary care setting, should include complete blood count including leukocytes and differentiation, IgA, IgM, IgG and IgE. A computed tomography (CT) scan should be requested in cases of recurrent pulmonary infections to assess lung damage. Evidence of autoimmunity symptoms should be investigated.

Additional tests that should be undertaken once a patient has been referred for specialist evaluation include:

- Abdominal (endoscopic) ultrasound
- Abdominal CT scan or magnetic resonance imaging (MRI)
- Liver fibroscan
- Auto-antibodies
- Liver biopsy (via the jugular vein or fine needle aspiration) and liver function testing.
- Vaccination response in case of recurrent infections: in a patient with normal immunoglobulin levels an impaired vaccination response may point to a selective antibody deficiency with normal immunoglobulins (SADNI).
- Microbial diagnosis: RNA, DNA or direct antigen testing may be required to confirm a diagnosis, especially if a patient has hypogammaglobulinaemia or has been initiated on immunoglobulin therapy.

It is often necessary to involve additional specialities to achieve a diagnosis, usually a clinical immunologist but possibly also a specialist in infectious diseases or haematologist. A key step is to rule out haematological malignancy as an alternative diagnosis.

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[1] Al-Muhsen SZ. Gastrointestinal and hepatic manifestations of primary immune deficiency diseases. Saudi J Gastroenterol 2010;16:66-74.

[2] Song J, et al. Common variable immunodeficiency and liver involvement. Clin Rev Allergy Immunol 2018;55:340-51

[3] Crotty R, et al. Spectrum of hepatic manifestations of common variable immunodeficiency. Am J Surg Pathol 2020;44:617-25.

[4] Murakawa Y, et al. Liver transplantation for severe hepatitis in patients with common variable immunodeficiency. Pediatr Transplant 2012;16:E210-6.

CARING FOR PATIENTS WITH A PID

Early diagnosis and long-term antimicrobial prophylaxis and/or immunoglobulin replacement therapy treatment remain the primary interventions for patients with PID and are critical to optimising outcomes.

No specific treatments are yet available for the liver manifestations of PID although in certain cases steroids and immunosuppressants can be used. Ursodeoxycholic acid may be used in cases of biliary damage,[3] while liver transplantation may be an option for some patients with complicated cirrhosis or severe hepatitis.[4] All PID patients should receive on-going monitoring for the emergence of liver involvement.[3]

BUILDING A MULTIDISCIPLINARY TEAM FOR PATIENTS WITH PIDs

Patients with PIDs may present comorbid conditions (such as type 2 diabetes mellitus, autoimmune cytopenias, colitis and bronchiectasis), which may require the involvement of additional specialist physicians. Intravenous immunoglobulin treatment may cause complications due to volume overload for patients with congestive heart disease and may require input from a cardiology specialist. Similarly, patients with haemolytic anaemia may require input from haematology specialists.

Patients with PIDs are more vulnerable to the development of malignancies, especially gastrointestinal cancers and lymphoma. Hence, oncology specialists may need to be included as part of a multidisciplinary team. Referral to centres specialising in the management of PIDs may be appropriate where available.

PIDs: A GUIDE FOR HEPATOLOGISTS

- While more severe PIDs are usually diagnosed during childhood, PIDs can present throughout a person's lifetime. Improved medical care during life has led to more elderly persons with PIDs that have also developed age-related diseases such as type 2 diabetes and heart disease.
- Patients with complex, non-specific conditions may be referred for specialist evaluation by hepatologists for whom a variety of clinical indicators can raise the suspicion for PIDs.
- Clinical indicators include a family history of PIDs, repeated severe, refractory or unusual infections, bronchiectasis, therapy-resistant asthma (or other allergies) and autoimmune/inflammatory comorbidities.
- Patients with PIDs may require care from a range of specialties depending on their individual symptoms and the organ systems affected.
- Some patients may require liver transplantation.

FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **www.ipopi.org**.

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