THE PATHCARE NEWS

DIAGNOSTIC TESTING FOR AUTOIMMUNE LIVER DISEASES

The autoimmune liver diseases include the triad of **Autoimmune Hepatitis (AIH), Primary Biliary Cholangitis (PBC)** and **Primary Sclerosing Cholangitis (PSC)**. These conditions represent perhaps only 5% of all liver diseases, although the true prevalence in South-Africa is uncertain. Autoimmune liver conditions should be considered as a diagnosis after viral, metabolic and drug induced liver injuries have been excluded.

Although most of the autoantibodies are not disease specific, their measurement is a prerequisite to diagnose AIH and PBC, since they are components of the diagnostic scoring system in these diseases. In PSC, on the other hand, autoantibodies are frequently present, but play a minor role in establishing the diagnosis. The autoimmune liver conditions are also frequently associated with extrahepatic autoimmune conditions.

AUTOIMMUNE HEPATITIS:

AIH is a **progressive chronic inflammatory liver disease** which occurs in children and adults of all ages and mainly affects females.

Characteristic features include the fluctuating spontaneous course, histologically determined interface hepatitis, as well as IgG hypergammaglobulinemia. In acute presentations the elevations in the aminotransaminases (ALT and AST) may exceed 10-20x the upper limit of the reference range, with the ratio of ALP : ALT (or AST) often being <1:5 to < 1: 10. In patients with chronic symptoms the elevations in the transaminases are less profound, and approaches an ALP: ALT (or AST) ratio of 1:2.

Autoantibodies are one of the distinguishing features of AIH. The discovery of autoantibodies directed against different cellular targets, including nuclear, cytosol, and microsomal antigens prompted a suggested subclassification of AIH based on the presence of specific autoantibody profiles:

- **Type 1 AIH:** Antinuclear Antibodies (ANA), and/or Smooth Muscle Antibodies (SMA) directed against F-actin. Non-conventional antibodies associated with type 1 AIH include: p-ANCA, anti-Soluble-Liver/Liver-Pancreas (SLA/LP) and dsDNA.
- **Type 2 AIH:** Anti-Liver-Kidney-Microsomal-1 (LKM-1). Non-conventional antibodies associated with type 2 AIH include: anti-Liver Cytosol-1 (LC1) anti-LKM-3, anti-SLA/LP, and dsDNA
- **Type 3 AIH:** This remains a controversial subtype of AIH and may represent a more aggressive subtype of type 1 AIH. Type 3 AIH is characterised by the presence of Anti-SLA/LP.

The diagnosis of AIH is mainly based on the presence of autoantibodies, elevated serum IgG, liver histology and the exclusion of other forms of chronic liver disease.

PRIMARY BILIARY CHOLANGITIS:

PBC is a **chronic cholestatic liver disease which affects mainly middle-aged women**. PBC starts with an inflammatory process of the small and middle-sized interlobular bile ducts leading initially to a proliferation, and then to a loss of bile ducts, to portal inflammation and in late stages to liver cirrhosis. PBC is characterised by **elevated serum alkaline phosphatase (ALP)**, the presence of **autoantibodies to mitochondria (AMA)** and/or PBC-specific **antinuclear antibodies** and granulomatous inflammation around the bile duct on **histological examination**.

The prevalence of **extrahepatic autoimmune conditions in PBC patients is frequent** and include: Sjögren's syndrome (40-65%), Autoimmune Thyroid Disease (10-15%), Limited Cutaneous Scleroderma (5-15%) and Rheumatoid Arthritis (RA – 5-10%). Other co-existing autoimmune conditions may include Systemic Lupus Erythematosus (SLE), Diabetes Mellitus type 1 (DM1), Mixed Connective Tissue Disease (MCTD), Poly/Dermatomyositis (PM/DM), Crohn's and Ulcerative Colitis (UC).

The serological hallmark of PBC is the presence of serum AMA (90-95% of patients). The presence of AMA in asymptomatic patients is usually indicative of eventual PBC development.

PRIMARY SCLEROSING CHOLANGITIS:

PSC is an **idiopathic chronic cholestatic liver disease** characterised by progressive inflammatory destruction of intra- and extrahepatic bile ducts affecting **males** more frequently than females. The median age of onset is usually in the 4th decade, but children and older adults may also be affected. Autoantibodies are frequently present but play a minor role in establishing the diagnosis.

In 70-90% of patients, PSC is associated with inflammatory bowel disease (IBD), primarily with Ulcerative Colitis (UC). Perinuclear-Antineutrophil Cytoplasmic Antibodies (p-ANCA) frequently associated with UC (to a lesser degree with Crohn's) can be found in up to 90% of PSC patients, followed by ANA (8-77%), and Anti-Smooth Muscle Antibodies (ASMA – 83%). Another antibody of importance in the differential diagnosis of PSC is IgG4, that may be present in Autoimmune Pancreatitis and IgG4-Asssociated Cholangitis (IAC).

Cholangiography is the gold standard for the diagnosis of PSC. Due to lack of specificity, autoantibodies can only support the diagnosis of PSC in selected patients, especially those lacking associated IBD.

- PathCare offers a wide range of autoimmune antibody tests related to liver conditions: -

Group	Antibody	Comment	Disease
IIF	Company	Antinuclear Antibody as detected on Immunofluorescence (ANF): Different ANA IIF patterns may give an indication to associated autoimmune conditions. Common patterns seen in autoimmune liver conditions may include: Nuclear Rim/Punctate Nuclear Envelope, Multiple Nuclear Dots, Centromere, Nuclear Homogenous. ANA IFA is frequently the 1st line test for autoimmune liver conditions.	-
Indications and limitations:	AMA-M2	Anti-Mitochondrial M2 Antibody (AMA-M2) are pathognomonic of PBC, detected in 90-95% of patients with PBC. AMA may occasionally be found preceding clinical PBC for years. AMA may transiently be detected in patients with acute liver damage of any etiology.	*PBC, AIH (rare), HCV (rare)*
	M2-3E	The presence of Anti-Mitochondrial M2-3E-binding protein of pyruvate dehydrogenase complex (AMA-subtype M2-3E) is strongly predictive of PBC, present in 90-95% of PBC patients.	*PBC*
	Sp100	Anti-Sp100 may be present in 30-50% of AMA-negative PBC patients and have been described to be inversely correlated to the development of fibrosis. Sp100 Antibodies is not specific for PBC and can infrequently be detected in Rheumatological Diseases and Acute Hepatitis of any origin.	*PBC*
	PML	Promyelocytic (PML) protein frequently co-exist with Sp100, and may be present in AMA-negative PBC patients.	*PBC*
	Gp210	Gp-210 antibodies are present in around 20% PBC patients, and in approximately 30-50% of AMA-negative patients. Gp-210 are considered specific for PBC, and are associated with a higher incidence of progression to advanced liver failure, as well as hepatocellular carcinoma.	*PBC*
	LKM-1	Liver-Kidney-Microsomal Antibodies (LKM-1) are the signature antibodies for type 2 AIH, but may occasionally be seen in type 1 AIH, Drug Induced Hepatitis, and Chronic Hepatitis C infection.	*AIH type 2* *HCV*
	LC-1	Liver-Cytosol type 1 Antibodies (LC-1) are present in approximately 30% of type 2 AIH, and occur isolated or in combination with anti-LKM-1. Also detected in patients with Chronic Hepatitis C infection.	*AIH type 2* *HCV*
	SLA/LP	Soluble Liver Antigen/Liver-Pancreas Antibodies (Anti-SLA/LP) are present in only 10-20% of AIH patients but have the highest specificity for AIH than all other AIH-related antibodies. Anti-SLA/LP was originally associated with type 3 AIH but may belong to a subgroup of AIH type 1. It may also be present in patients with type 2 AIH, PBC and Chronic Hepatitis C infection.	*AIH type 1/3, PBC-AIH overlap, HCV (rare)*
	SS-A	Anti-SSA are non-specific antibodies and are associated with Sjögren's, SLE, Dermatomyositis, Systemic Sclerosis (SSc) and with undifferentiated connective tissue disease, which may co-exist with PBC.	*AID* *Co-exist PBC*
	Ro-52	Anti-Ro-52 is associated with a broad range of autoimmune conditions but specifically idiopathic inflammatory myopathies, which may co-exist with PBC.	*SLE, DM/PM, SSc, Sjo ± PBC*
	Scl-70	Scl-70 (Topoisomerase I) is most commonly associated with progressive Systemic Sclerosis (SSc) – 25% of SSc patients may have co-existing PBC.	*SSc ± PBC*
	CENP A	Centromere A (CENP A) antibodies are strongly associated with limited cutaneous Systemic Sclerosis – that may exist with concurrent PBC.	*SSc ± PBC*
	CENP B	Centromere B (CENP B) antibodies are strongly associated with limited cutaneous Systemic Sclerosis – that may coexist with concurrent PBC. CENP B is associated with progression to Portal Hypertension.	*SSc ± PBC*
	PDGH	D-3-phosphoglycerate dehydrogenase Antibodies (PDGH) may be positive in up to 80% of AIH, 15.8% of PBC and in 12.8% of Chronic Hepatitis B patients but may also be positive in other autoimmune conditions.	*AIH, PBC, HBV, other*
Single	ASMA	Smooth Muscle Antibodies (ASMA) are not disease specific and can be seen in various liver diseases such as fatty liver disease. Anti-SMA are present in approximately 50% of patients with AIH type 1 and can be the only detectable autoantibody in these cases.	*AIH type 1, non-specific*
ANCA IFA	p-ANCA	The presence of p-ANCA can support the diagnosis of AIH, especially in the absence of other autoantibodies. p-ANCA can also be detected in Chronic Viral Hepatitis, Inflammatory Bowel Disease (IBD), Primary Sclerosing Cholangitis (PSC) or Microscopic Polyangiitis, and Eosinophilic Granulomatosis with Polyangiitis. Atypical p-ANCA (p-ANNA) seem to be more specific for Autoimmune Liver Diseases and IBD.	*IBD,* *PSC, AIH type 1*
Single	IgG4	IgG4-Associated Cholangitis (IAC) can display a cholangiographic pattern similar to PSC.	*IAC*

PathCare offers the Autoimmune Liver Disease Antibodies as part of a Profile (Blot) test. This profile will include the familiar AMA and LKM-1 antibodies, as well as 11 other relevant autoantibodies to improve diagnostic sensitivity of Autoimmune Liver Disease and related conditions.

References:

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