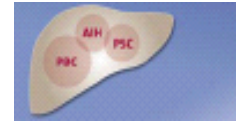# Dr Imad Aboukhamis
Ph-D France

Autoimmune Liver Diseases

أمراض الكبد المناعية الذاتية

Causes for liver diseases

Virus infection
Hepatitis A, B, C, D, E
CMV, EBV, etc.
Bacterial Infection
Brucella, Leptospiren
Parasite infection
Malaria, Amoebae

Autoimmune
Autoimmune hepatitis (AIH)
Primary Biliary Cirrhosis (PBC)
Primary Sclerosing Cholangitis (PSC)

Genetic
Morbus Wilson
Hämochromatose
α1-antitrypsin deficiency

Toxic
Alcohol
Drugs

Nonalcoholic fatty liver disease
Obesity
One or more abnormal cholesterol levels
Diabetes mellitus

Others
z.B. Budd-Chiari syndrome

Autoimmune Liver Diseases

1. Autoimmune hepatitis (AIH)التهاب الكبد المناعي الذاتي
2. Primary biliary cirrhosis (PBC)تليف الكبد الصفراوي الأولي
3. Autoimmune cholangitis (AIC)الامراض المناعية للأقنية الصفراوية

Autoimmune Liver Diseases

1. Autoimmune hepatitis (AIH) is a chronic inflammation of the liver caused by the immune system.

2. AIH is a serious disease and leads to liver cirrhosis without treatment

3. AIH is classified as either type I ,II or III

Liver
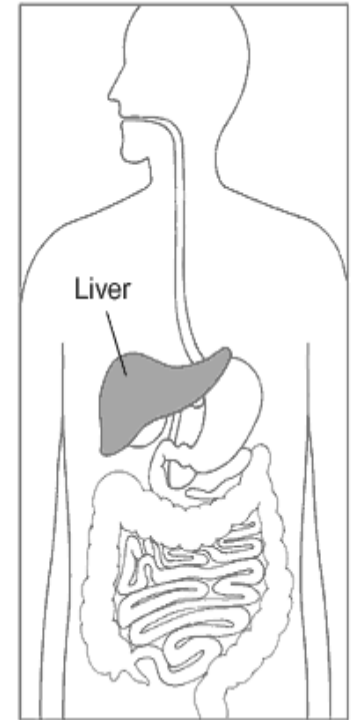
Autoimmune Hepatitis

| AIH	Type 1	Type 2
Age at onset (mean)	10 years	6.5 years
Onset at <20 yrs of age (%)	40	80
Preponderance (F/M)	7/1	9/1

F.Alvarez, Montreal
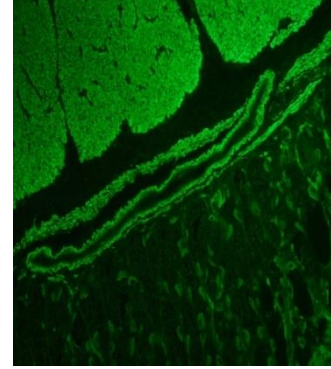
Diagnostic criteria for AIH

1. No alcohol abuse

2. or recent use of hepatotoxic drugs

3. No markers of current infection with hepatitis A, B and C viruses

4. Autoantibodies (ANA, SMA, LKM1, LC1, SLA)

5. Predominant serum aminotransferase abnormality

The presence of autoantibodies is prerequisite for the diagnosis of AIH

Autoantibodies in Chronic Hepatitis
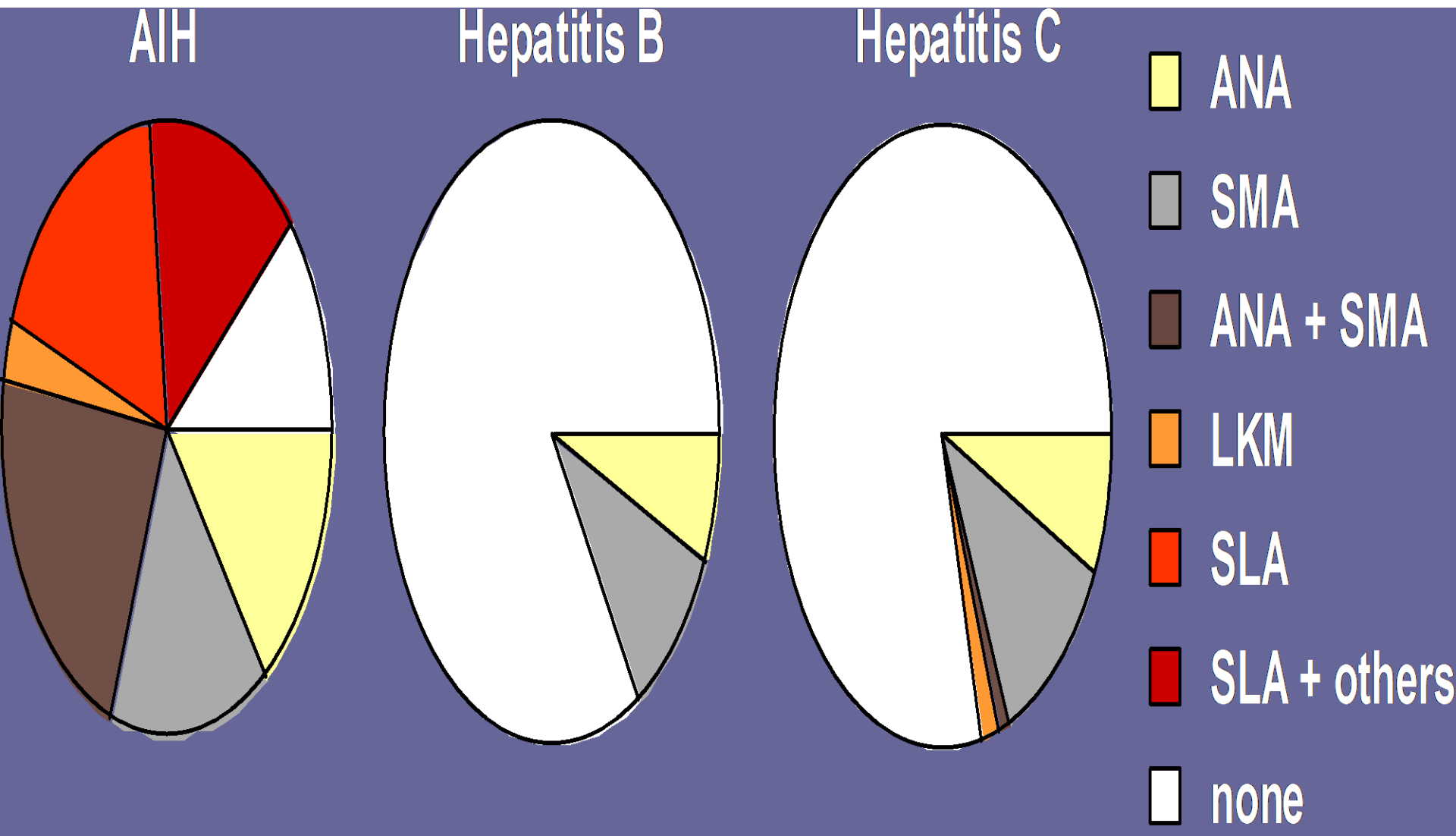
AIH Type I

- Most common form of AIH
- HLA-DR3 in younger patients
- HLA-DR4 in older patients
- Detection of ASMA (Anti Smooth Muscle Antibodies) and ANA (Antinuclear Antibodies)

AIH Type II

1. Predominance in female children
2. Anti-LKM-1 positive (CYP2D6)
3. Anti-LC-1 positive
   Formiminotransferase cyclodeaminase
4. More aggressive disease progression
5. More therapeutic relapsesالانتكاسات

AIH (Type III)

-

1. IIF is not helpfulمفيد
2. ELISA and/or immunoblot for detection of Anti-SLA essential   Anti-Liver/Pancreas Antigen, tRNP$^{(Ser)Sec}$
3. In a few cases of AIH Anti-SLA may be the only autoantibody present
4. Previously classified such cases as non-A-non-B hepatitis

Autoimmune Hepatitis

Diagnostic Criteria of Autoimmune Hepatitis

Requisites	Definite	Probable
No genetic liver disease	Normal α_1 antitrypsin phenotype	Partial α_1 antitrypsin deficiency
	Normal serum ceruloplasmin, Iron and ferritin levels	Nonspecific serum copper, ceruloplasmin, Iron, and/or ferritin abnormalities
No active viral infection	No markers of current infection with hepatitis A, B, and C viruses	No markers of current infection with hepatitis A, B, and C viruses
No toxic or alcohol injury	Daily alcohol < 25 g/d and no recent use of hepatotoxic drugs	Daily alcohol < 50 g/d and no recent use of hepatotoxic drugs
Laboratory features	Predominant serum aminotransferase abnormality Globulin, γ-globulin or immunoglobulin G level $\geq$ 1.5 times normal	Predominant serum aminotransferase abnormality Hypergammaglobulinemia of any degree
Autoantibodies	ANA, SMA, or anti-LKM1 $\geq$ 1 :80 in adults and $\geq$ 1 :120 in children ; no AMA	ANA, SMA, or anti-LKM1 $\geq$ 1 :40 in adults or other autoantibodies*
Histologic findings	Interface hepatitis No biliary lesions, granulomas, or prominent changes suggestive of another disease	Interface hepatitis No biliary lesions, granulomas, or prominent changes suggestive of another disease

Abbreviation : AMA, antimitochondrial antibodies

* Includes perinuclear anti-neutrophil antibodies, SLA, Actin, LC1 and gp210 (asialoglycoprotein receptor)

Based on recommendations of the Internationsl Autoimmune Hepatitis Group (J Hepatol 1999 ; 31 :929-938)
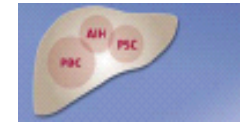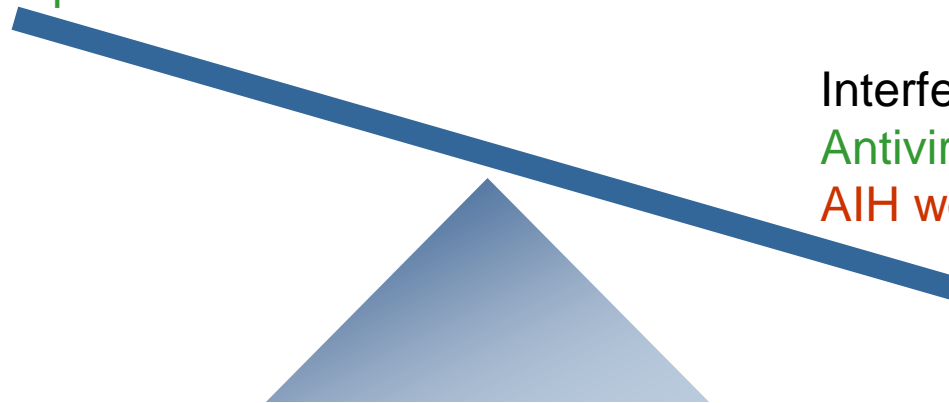
Autoimmune Liver Diseases

•In 1999 the International Hepatitis Group published a scoring system for the diagnosis of autoimmune hepatitis (AIH). AIH could be differentiated from chronic hepatitis C with a sensitivity of 97 - 100 % and a specificity of 66 - 92 %.

Czaja et al., Hepatology 2002, 36:479-497
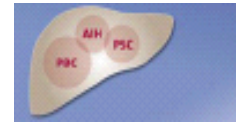
Immunsuppression
Virus replication increased
AIH improved

Interferon alpha
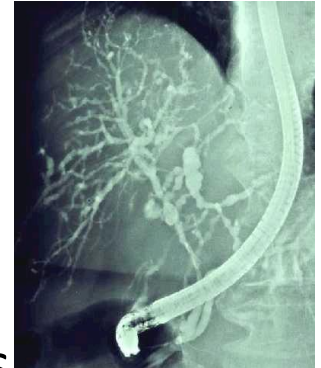Antiviral
AIH worsening
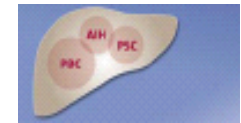
Autoimmune Liver Diseases

- **<u>Primary Biliary Cirrhosis</u>**

- الابتدائية صفراوية
  - Progressive destruction of the small bile ducts
  - Prevalence 25 : 100.000
  - Female preponderance (F:M 9:1)
  - Association to other autoimmune diseases
  - Ursodeoxycholic acid therapy
  - Immunosuppressive therapy questionableمشكوك فيه

Autoimmune Liver Diseases

Laboratory Diagnosis

- elevated liver parameters phosphatase, AST, ALT)

- AMA-M2 positive in 95 % (Pyruvat-Dehydrogenase Complex)

- Anti-Sp100 present in 35 - 50 % of AMA negative patients

- Additional markers of minor importance gp210, Anti-Lamin B Receptor (LBR)

AMA
anti-mitochondrial Abs of PBC

(alkaline

AMA
anti-mitochondrial Abs

ANA
anti-nuclear Abs

Sp100
anti-nuclear Abs

Figure 1: The determination of anti-nuclear autoantibodies as a basis for the diagnosis of AMA-negative patients.
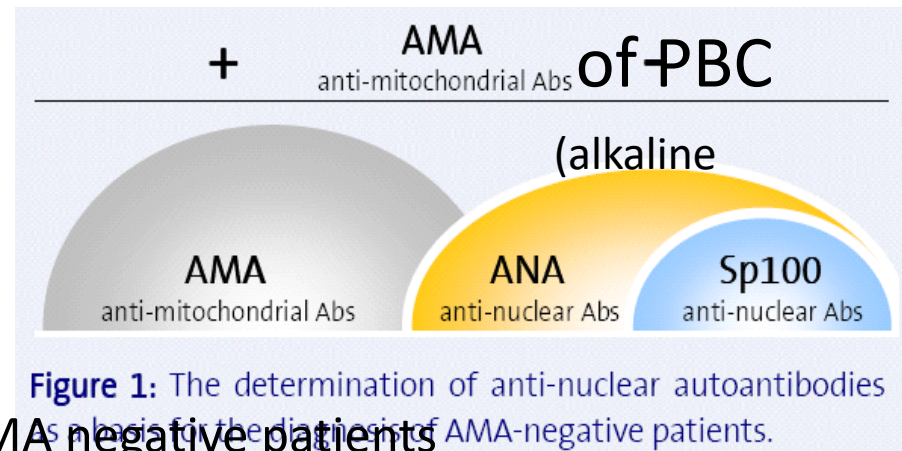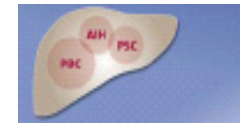
Autoimmune Liver Diseases

Sp100-Antibodies

– Higher Sensitivity and Specificity for PBC compared to IFA (HEp2; multiple nuclear dots)

– Correlation to unfavourable course of disease

– Sensitivity of 31% for PBC
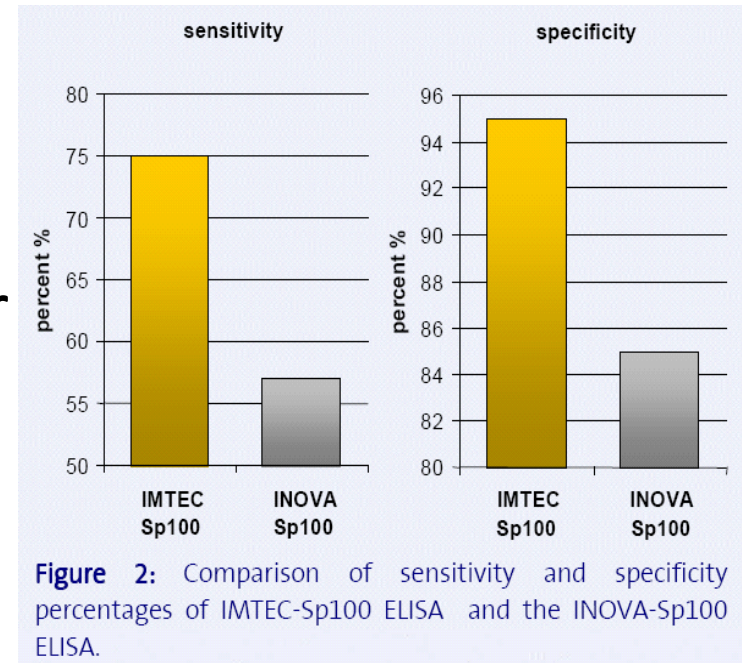
Figure 2: Comparison of sensitivity and specificity percentages of IMTEC-Sp100 ELISA and the INOVA-Sp100 ELISA.
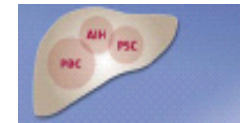
Autoimmune Liver Diseases

•**Sp100 Antibodies**　　　ITC66040

Conclusions. Both methods were highly specific. Sensitivity of ELISA method was slightly better than this of IIF. IIF had lover predictive values for PBC than ELISA. IIF require significant experience in interpreting subjective pattern, but remains an effective assay. ELISA produce a clear quantitative and qualitative results.

Autoimmune Liver Diseases
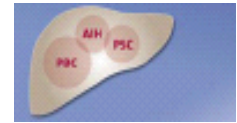
- **Primary Sclerosing Cholangitis**

- **تصلب الأقنية الصفراوية لابتدائى**

- Inflammation of small bile ducts

  - High association with inflammatory bowl diseases

  - Laboratory tests include

    - Perinuclear Antineutrophil Antibodies (pANCA) (70 %)

  - Ursodeoxycholic acid therapy questionable

  - Immunosuppressive therapy questionable
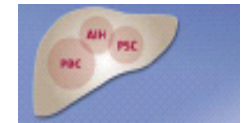
Autoimmune Liver Diseases

- Autoantibodies in
- Autoimmune
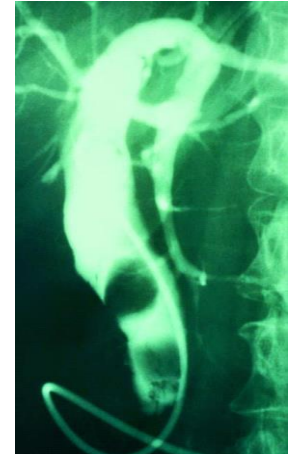- Liver Diseases

	PBC	PSC	AIH Type 1	AIH Type 2	AIH Type 3
ANA Antinuclear Antibodies	(+)	(+)	+	(+)	(+)
ASMA Anti-smooth muscle Ab			+		
LKM1-Antibodies Cytochrome P450 2D6				+	
LC1-Antibodies liver cytosolic antigen				+	
SLA-Antibodies soluble liver antigen					+
ASGPR-Antikörper Asialoglycoprotein-Receptor			+	+	+
AMA-M2 Antimitochondrial Antibodies	+				
Sp100-Antibodies "nuclear dots"	+				
gp210-Antibodies Glycoprotein 210 kD	+				
LBR-Antibodies Lamin B-Receptor	+				
ANCA Antineutrophil Antibodies		+			
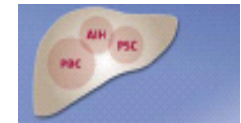
Autoimmune Liver Diseases

- Diagnostic
- Algorithm
- for
- Autoimmune
- Liver
- Diseases

Liver diseases of unknown origin → Tests for Hepatitis B oder C

Negative / Positive → Virus-induced hepatitis probable → virologic tests, optionally liver biopsy, Autoantibody profile (ANA, ASMA, SLA, LKM, ANCA, AMA)

Test for Haemochromatosis or Morbus Wilson

Negative / Positive → Haemochromatosis or Morbus Wilson

Autoantibody test for ANA, ASMA, LKM1, SLA, LC1

Negative / Positive → **Autoimmune Hepatitis** Diagnostic Scoring System of the *International Autoimmune Hepatitis Group*

AIH Typ I Positive for ANA, ASMA "lupoid Hepatitis"

AIH Typ II Positive for LKM1, LC1 poorer outcome, more common in children

AIH Typ III Positiv für SLA früher "non-A-non-B Hepatitis"

HLA-Typing, liver biopsy

Autoantibody test for AMA, Sp100, gp210, LBR

Negative / Positive → **Primary biliary cirrhosis (PBC)** → Röntgenuntersuchung der Gallen-, Bauchspeicheldrüsengangsystems (ERCP), Leberbiopsie

Autoantibody test for ANCA

Negative / Positive → Probably **Primary sclerosing cholangitis (PSC)** → X-ray examination of the bile ducts (ERCP), liver biopsy

Probably Autoantibody negative autoimmune hepatitis or virus-induced hepatitis → Virologic tests, liver biopsy

ANA - Antinuclear antibodies; ANCA - Antineutrophil Antibodies;
AMA - Antimitochondrial Antibodies; ; ASMA - Anti-smooth muscle Antibodies
ERCP - Endoscopic retrograde cholangiopancreatography
gp210 - Glycoprotein 210 kD; LC1 - liver cytosolic antigen; LKM1 - Cytochrom P450 2D6;
SLA - soluble liver antigen; Sp100 - 95-100 kD protein "nuclear dots"