Autoimmunity and the Liver: Mechanistic insights

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Institute of Liver Studies, King’s College Hospital, London, UK
Autoimmune Hepatitis

- Progressive inflammatory disorder
- Positive AAB and high IgG
- Exclusion of other pathology (Wilson, HCV, HBV, NASH)
Autoimmune Hepatitis

Interface hepatitis
Autoimmune Hepatitis - Type 1

- Anti-smooth muscle (SMA) &
- Anti-nuclear (ANA) autoantibodies
Autoimmune Hepatitis - Type 2

Liver Kidney Microsomal antibody

Liver Cytosol Type 1 antibody
Homogenous anti-nuclear pattern on HEp2 cells
AASLD PRACTICE GUIDELINES

Diagnosis and Management of Autoimmune Hepatitis

Michael P. Manns, Albert J. Czaja, James D. Gorham, Edward L. Krawitt, Giorgina Mieli-Vergani, Diego Vergani, and John M. Vierling
Anti-nuclear (ANA) antibodies

No single AIH-1 specific ANA antigen

Targets: Centromere
Histones
Chromatin
dsDNA
Ribonucleoproteins
Ann Rheum Dis 2010;69:1420–1422

ANA screening: an old test with new Recommendations

Pier Luigi Meroni, Peter H Schur
Box 1  Recommendations of the American College of Rheumatology (ACR) Antinuclear Antibody (ANA) Task Force

- Immunofluorescence ANA test should remain the gold standard for ANA testing.
Anti-smooth muscle (SMA)

VGT (actin) pattern
Actin filament - atomic model

Thomas Splettstoesser
Evaluation of F-Actin ELISA for the Diagnosis of Autoimmune Hepatitis

Christian Frenzel, M.D.,^1^ Johannes Herkel, Ph.D.,^1^ Stefan Lüth, M.D.,^1^ Peter R. Galle, M.D.,^2^ Christoph Schramm, M.D.,^1^ and Ansgar W. Lohse, M.D.^1^

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ORIGINAL ARTICLE

Antibodies to filamentous actin (F-actin) in type 1 autoimmune hepatitis

A Granito, L Muratori, P Muratori, G Pappas, M Guidi, F Cassani, U Volta, A Ferri, M Lenzi, F B Bianchi
<table>
<thead>
<tr>
<th>Patients</th>
<th>A-FAA+ (≥20 AU)</th>
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<tbody>
<tr>
<td>AIH-1 (n = 78)</td>
<td>63 (81%)</td>
</tr>
<tr>
<td>AIH-2 (n = 22)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>HCV (n = 51)</td>
<td>15 (30%)</td>
</tr>
<tr>
<td>CD (n = 17)</td>
<td>5 (29%)</td>
</tr>
<tr>
<td>PBC (n = 20)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>BD (n = 50)</td>
<td>3 (6%)</td>
</tr>
</tbody>
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*The same results were obtained using IgG specific secondary antibodies. †A-FAA v SMA: 70.5% v 78%, p = 0.3; A-FAA v SMA-T/G: 70.5% v 60%, p = 0.2.*
18-month old child

- Elevated ALT
- Histology: interface and lobular hepatitis, multilobular collapse
- Hep B, Hep C and other viral infections excluded
- Anti-mitochondrial Ab positive at 1/800
Repeat test confirms: anti-mitochondrial Ab positive at a titre of 1/800

King’s testing: anti-LKM-1 positive, Titre >1:10.240

Elisa: anti-cytochrome P450 2D6, positive out of scale

Correct diagnosis delayed
Antimitochondrial antibody (AMA)
Molecular target: PDC-E2

Commercial kits available
Molecular target: CYP2D6

Commercial kits available

LKM-1
Clinical Case -1

20 yrs old female, Caucasian, Nurse, from Southern California, Non specific symptoms

Hepatomegaly-Splenomegaly
Unexplained increase of IgG
5x upper NV transaminases
ANA, SMA, AMA negative

Liver biopsy: cirrhosis

ReTest: anti-LKM1 (1/640)
Diagnosis: Autoimmune Hepatitis type 2
Outcome: Liver Transplantation - Alive
ANA, SMA, AMA negative
Liver biopsy: cirrhosis

DIAGNOSIS: Cryptogenic hepatitis
Clinical Case -2

16 yrs old female, Hispanic, Student, from Southern California

Unexplained increase of IgG 21X UNV transaminases
Jaundiced (14X  UNV bilirubin)
ANA, SMA, AMA negative
Liver biopsy: cirrhosis

ReTest: anti-LKM1 (1/320)
Diagnosis: Autoimmune Hepatitis type 2
Outcome: Liver Transplantation - Dead
Liver biopsy: cirrhosis

DIAGNOSIS: Cryptogenic hepatitis
They conclude that ‘The diagnosis of type 2 AIH can be overlooked if anti-LKM antibody is not tested’

(they) recommend testing anti-LKM antibodies in all patients with a chronic liver disorder that is otherwise without apparent cause, especially if they are young and female.

They also conclude that: ‘Early referral to a tertiary liver transplant center is appropriate in light of the complexity and difficulty of management of these patients’.

LKM-positive autoimmune hepatitis in the western United States: a case series.

Duchini A, McHutchison JG, Pockros PJ
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Cases/Population</th>
<th>Prevalence</th>
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<tbody>
<tr>
<td>Clifford</td>
<td>1995</td>
<td>2/41</td>
<td>2.4%</td>
</tr>
<tr>
<td>Cassani</td>
<td>1997</td>
<td>18/290</td>
<td>6%</td>
</tr>
<tr>
<td>Dionysos</td>
<td>1999</td>
<td>3/226</td>
<td>1.3%</td>
</tr>
<tr>
<td>Iijima</td>
<td>2001</td>
<td>6/390</td>
<td>1.5%</td>
</tr>
<tr>
<td>Stroffolini</td>
<td>2004</td>
<td>11/502</td>
<td>2.2%</td>
</tr>
<tr>
<td>Monti</td>
<td>2005</td>
<td>48/2675</td>
<td>1.8%</td>
</tr>
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Of the 170 million HCV patients, 2-10 million are LKM1 positive. Does it matter?
ALT flare in LKM1/HCV +ve pts on IFN
Liver kidney microsomal antibody type 1 targets CYP2D6 on hepatocyte plasma membrane

L Muratori, M Parola, A Ripalti, G Robino, P Muratori, G Bellomo, R Carini, M Lenzi, M P Landini, E Albano and F B Bianchi
SLA = SEPSECS
Anti-SLA

- Longer time to achieve remission
- Tendency to relapse
- More severe histology
- Death or OLT
- HLA A1-B8-DR3
- Undetectable by immunofluorescence
Autoantibodies are useful if:

- Laboratory is familiar with different aab patterns
- Physicians request appropriate tests and interpret results correctly
- Physician and laboratory talk to each other