Autoimmune Hepatitis

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AIH - Definition
“Autoimmune hepatitis (AIH) is a chronic self-perpetuating inflammatory disease with a female predominance occurring in all ages and races that may start with an episode of acute hepatitis and may lead to liver cirrhosis, liver cancer, liver transplantation or death”
AIH - Epidemiology
16 to 18 cases per 100,000 inhabitants in Europe - relatively rare
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- 25–30% of all AIH patients are male and may present at any age and in all ethnic groups
AIH - Epidemiology

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- Marked increase in AIH incidence over time
- Affects mainly women
- 25–30% of all AIH patients are male and may present at any age and in all ethnic groups
- Extrahepatic autoimmune disorders are common and occur in all stages of liver disease
AIH – Subclassification
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- AIH-1: (ca. 90% of AIH cases):
  - ANA, SMA
  - rare failure of treatment
  - variable relapse rates after drug withdrawal
  - variable need for long-term maintenance therapy
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- **AIH-2:**
  - **anti-LKM1, anti-LC1 and rarely anti-LKM3**
  - onset usually in childhood and young adulthood
  - clinical and histopathological severity commonly acute and advanced
  - frequent failure of treatment
  - frequent relapse rates after drug withdrawal
  - need for long-term maintenance therapy very common
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► AIH-3: **SLA/LP positive**
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► **AIH-3: SLA/LP positive**
ANA positivity: which pattern do you expect to find?
AIH – Pathogenesis
Genetic associations → genes of the human leukocyte antigen (HLA) region (the human major histocompatibility complex, MHC) located on the short arm of chromosome 6 → involved in the presentation of antigenic peptides to T-cells
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- Strongest association:
  - HLA-DR3 and HLA-DR4 → susceptibility to AIH-1
  - HLA-DR7 and HLA-DR3 → susceptibility to AIH-2
AIH – Pathogenesis

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  - HLA-DR7 and HLA-DR3 → susceptibility to AIH-2

- Development of autoimmune diseases is favored by the breakdown of self-tolerance mechanisms

Manns MP J Hepatol 2015, vol 62, P 100-111
Is there a typical clinical presentation for AIH?
AIH – Diagnosis
Presentation at onset
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Presentation at onset

- Broad range from asymptomatic to acute/severe or even fulminant
AIH – Diagnosis
Presentation at onset

- Broad range from asymptomatic to acute/severe or even fulminant
- 2/3 Patients: insidious onset with non-specific symptoms: fatigue, general ill health, right upper quadrant pain, lethargy, malaise, anorexia, weight loss, nausea, pruritus, fluctuating jaundice and polyarthritis involving the small joints without arthritis, sometimes dating back years
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Presentation at onset

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- 25% of patients → acute onset:
  - acute exacerbation of chronic AIH
  - true acute AIH without histological findings of chronic liver disease: centrilobular zone 3 necrosis (central perivenulitis) usually present in patients with acute presentation; autoantibodies or other classical features can be absent; not always responsiveness to corticosteroids
AIH – Diagnosis
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- One third of patients at diagnosis have already developed cirrhosis irrespective of the presence of symptoms due to delay in diagnosis
AIH – Specific clinical features and presentations

Overlap Syndromes (1)
AIH – Specific clinical features and presentations

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- Lack of internationally agreed criteria defining these variant conditions → difficult to give standardised recommendations
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- AIH-PBC:
  - 8–10% of adult patients with either PBC or AIH
  - in most cases, it is possible to define one primary disorder ("dominant" disease), usually PBC
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AIH-PSC:

- Approximate prevalence of 7–14%
- patients with features of AIH and PSC require immunosuppression
- in AIH patients with remaining cholestasis despite adequate immunosuppression, MRCP for the detection of possible underlying or co-existent PSC is recommended
AIH – Specific clinical features and presentations

Overlap Syndromes (2)
AIH – Specific clinical features and presentations

Overlap Syndromes (2)

- AIH - IgG4: few and unclear data
AIH – Specific clinical features and presentations

Overlap Syndromes (2)

- **AIH - IgG4**: few and unclear data

- **DILI + AIH**
  - DILI with a strong immunoallergic component mimicking AIH
  - AIH mimicking as DILI due to drug exposure in recent weeks and spontaneous improvement after cessation of drug exposure
  - AIH triggered by an offending drug (DILI-induced AIH) → nitrofurantoin, minocycline, statins, anti-TNFalpha
AIH – Laboratory findings

What do you expect to find?
Clinical case

S. G., 63 year-old woman

- Rheumatoid Arthritis diagnosed in 2007
  - Previous treatment: Hydroxychloroquine (suspended for intolerance); Leflunomide (supended for Pancytopenia)
    - since August 2016 under Methotrexate

- Bronchial asthma
Clinical case

- Since **January 2017** progressive elevation of transaminases (up to 2 times ULN)
  - → MTX suspended on February 6th
- Asymptomatic
- Ongoing therapy:
  - Metotrexate 15 mg/week
  - Ipratropium 250 mcg (max 4 times/day)
  - Salbutamol as-needed basis
- No new medication
- No history of alcohol or drug consumption
- No transfusions
- No recent trips
- Negative family history for liver disease
Clinical case

- **February 2017**: Hospitalization in the Rheumatology Department

**ACUTE HEPATITIS**
Clinical case

▶ **February 2017:** Hospitalization in the Rheumatology Department

**ACUTE HEPATITIS**

- Hb 133 g/l (121-154)
- Leuco 4.48 G/l (3.00-10.5)
- PLT 214 (140-380)
- CRP 6 mg/l (<5)
- Glucose 6.05 mmol/l (4.56-6.38)
- Creatinine 65 µmol/l (45-84)
- Bilirubin 32 µmol/l (<17)
- Albumin 30 g/l (35-52)
- AST 2336 U/l (<35)
- ALT 2892 U/l (<35)
- ALP 348 U/l (35-105)
- γGT 370 U/l (5-36)
- PT INR 1.07 (0.8-1.2)
Clinical case

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**Viral serologies:**

- Anti-HBs and anti-HBc positivity (HBsAg neg)
- HCV neg
- HAV IgM neg, IgG pos
- HEV (IgG+IgM+PCR) neg
- CMV IgM neg, IgG pos
- EBV neg
**Clinical case**

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**Viral serologies:**
- Total IgG: 12 g/l

**Autoantibodies:**
- ANA 1:80 (< 1:80)
- LKM-1 < 1:80
- SLA < 1:80
- SMA pending

anti-HBs and anti-HBc positivity (HBsAg neg)
HCV neg
HAV IgM neg, IgG pos
HEV (IgG+IgM+PCR) neg
CMV IgM neg, IgG pos
EBV neg
Next step?
Are the histological findings alone enough to establish the diagnosis?
AIH – Histology
no morphological feature is pathognomonic of AIH
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- Interface hepatitis (hepatitis at the portal-parenchymal interface) with dense plasma cell-rich lymphoplasmocytic infiltrates, hepatocellular rosette formation, emperipolosis (active penetration by one cell into and through a larger cell) and hepatocyte swelling and/or pycnolic necrosis → typical hallmarks of AIH
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- Panlobular hepatitis, bridging necrosis and massive necrosis → signs of severe inflammatory activity (acute disease onset). The characteristic histological pattern is panacinar hepatitis (parenchymal collapse) especially in biopsies performed during an acute onset and closely resembles drug-induced hepatitis.
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Distinction from DILI can be very difficult
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Distinction from DILI can be very difficult

Bile-duct damage is typically not a feature of AIH, but in severe cases it can also be observed
Histologic hallmarks of autoimmune hepatitis:

1) Interface hepatitis (A) occurs when the lymphocytes in the portal triad invade the limiting plate spilling around the hepatocytes.

2) Lymphocytic infiltrate accumulates in the portal triad (B).
Clinical case

Histological findings compatible with DILI

... but:

- Mixed inflammatory cell infiltration (plasma cells and eosinophils)
  - Interphase inflammation
  - Focal apoptosis and necrosis
Clinical case

Histological findings compatible with DILI

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Clinical case

Histological findings compatible with DILI

- Mixed inflammatory cell infiltration (plasma cells and eosinophils)
- Interphase inflammation
- Focal apoptosis and necrosis

No steatosis
No steatohepatitis
Clinical case

Liver histology
Immunohistochemistry
## AIH – Diagnostic criteria

Simplified scoring system for autoimmune hepatitis of the International Autoimmune Hepatitis Group (IAHG)

<table>
<thead>
<tr>
<th>Points</th>
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| **Autoantibodies** | ANA or SMA or LKM > 1:40  
ANA or SMA or LKM > 1:80  
SLA/LP Positive (>20 units) | 1  
2 |
| **IgG** | Upper normal limit  
> 1.10 times normal limit | 1  
2 |
| **Liver histology** | Compatible with AIH  
Typical for AIH | 1  
2 |
| **Absence of viral hepatitis** | Yes  
No | 2  
0 |

≥ 6 probable AIH; ≥7 definite AIH
## AIH – Diagnostic criteria

**Simplified scoring system for autoimmune hepatitis of the International Autoimmune Hepatitis Group (IAHG)**

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| **Points**                            | 1              | 1            | 1               |                           |
| **IgG**                               | Upper normal limit  
                                        | > 1.10 times normal limit |                   |                           |
| **Points**                            | 1              | 2            |                 |                           |
| **Liver histology**                   | Compatible with AIH  
                                        | Typical for AIH           |                   |                           |
| **Points**                            | 1              | 2            |                 |                           |
| **Absence of viral hepatitis**        | Yes            | No           |                 |                           |
| **Points**                            | 2              | 0            |                 |                           |

≥ 6 probable AIH; ≥7 definite AIH
**AIH – Diagnostic criteria**

Simplified scoring system for autoimmune hepatitis

Autoimmune Hepatitis Group (IAHG)

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Female sex</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>ALP/AST (or ALT) ratio</td>
<td>+2</td>
<td></td>
</tr>
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<td>Serum globulins or IgG above normal</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>Autoantibodies (ANA, SMA, or LKM-1)</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>Hepatitis viral markers</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>Drug history</td>
<td>-4</td>
<td>Recent use of known or suspected hepatotoxic drugs</td>
</tr>
<tr>
<td>Average alcohol consumption</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td>Low (&lt;25 g/day)</td>
<td>+2</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>High (&gt;60 g/day)</td>
<td>+2</td>
<td>&quot;&quot;</td>
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<tr>
<td>Liver histology</td>
<td>-3</td>
<td></td>
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<tr>
<td>Interface hepatitis</td>
<td>-3</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Lymphocytic infiltrate</td>
<td>-3</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Portal tract pattern of regeneration</td>
<td>-3</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>None of the above</td>
<td>-3</td>
<td>&quot;&quot;</td>
</tr>
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<td>Bilirubin change</td>
<td>-3</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Other features</td>
<td>-3</td>
<td>&quot;&quot;</td>
</tr>
<tr>
<td>Other autoimmune disorders, in patient or first degree relative</td>
<td>-3</td>
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<td>Optimal parameters in patients who are seronegative for ANA, SMA, or LKM-1:</td>
<td>+2</td>
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<td>Sensitivity for other defined autoantibodies</td>
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<td>HLA DR3 or DR4</td>
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<td>Response to therapy:</td>
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<tr>
<td>Complete</td>
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<tr>
<td>Relapse</td>
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Interpretation of aggregate scores

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<td>Definite AIH</td>
<td>&gt; 15</td>
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<td>Post-treatment:</td>
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≥ 6 probable AIH; ≥7 definite AIH
Who to treat and how to treat
AIH – Treatment
The aim of treatment in AIH is to obtain complete remission of the disease and to prevent further progression of liver disease.
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- Remission induction: start with steroids → prednisolone monotherapy (up to 1 mg/kg/day) or Budesonide 9 mg/d (only in non-cirrhotic patients!)
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  - help to resolve diagnostic uncertainties
  - avoids the diagnostic dilemma of discrimination between azathioprine-induced hepatotoxicity from primary non-response.
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Second line Therapy: MMF, Infliximab, Rituximab
AIH – Treatment

**AIH**

- 0.5-1 mg/kg/d prednisolone

**Good response**
- Add azathioprine gradually up to 1-2 mg/kg/d

**Insufficient response**
- Consider non-compliance
- Consider alternative diagnoses

**Azathioprin-intolerance**
- Second-line therapy (usually MMF)

**Taper steroids (ideally trial of steroid withdrawal)**

- Individualize doses (consider checking AST levels) to achieve and maintain normal ALT and IgG
- Refer to specialist center for confirmation of diagnosis, LTX-evaluation and/or alternative immunosuppressives

**Response**
- Manage alternative disease

**Insufficient response**
- Increase to 100 mg prednisolone i.v.
AIH – Treatment

Treatment requires:

• induction of remission (steroids)
• prolonged maintenance therapy (thiopurines)

Laboratory endpoints:

• normalization of IgG and ALT

Therapy is aimed to obtain complete biochemical and histological remission
AIH – Treatment

When to stop therapy
AIH – Treatment
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- Patients with severe initial presentation and low tolerance of induction treatment should undergo to liver biopsy prior to treatment withdrawal.
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- Flares of AIH activity during maintenance therapy or following treatment reduction require increased doses of immunosuppression and preclude complete drug withdrawal.
Liver Transplantation

- Ultimate rescue treatment
- 4% of OLT are due to AIH (Fulminant AIH and end stage liver cirrhosis)
- Particular risk of infection early after surgery
- Acute rejection episodes occur more frequently
Patients initiated on prednisolone/azathioprine combination therapy should have baseline clinical and laboratory parameters monitored during the first four weeks.

As the steroid dose is tapered → monitoring intervals can be extended to 1-3 months.

During maintenance treatment → patients should be seen in three- to six-month intervals.

Relapse after treatment withdrawal occurs commonly within 12 months → closely monitoring after treatment withdrawal.

Lifelong monitoring → disease flares and relapses are frequent even after complete remission.
Summary

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- Lifelong monitoring of clinical and laboratory parameters.
Thank you for your attention