NAFLD/NASH and AMA issues in AIH

Newcastle, July 3-4, 2017

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www.med.uth.gr/internalmedicine/
Consultation for a 33 years female with acute icteric hepatitis

- No known past history of liver disease
- CHOL/TRIG: normal, No diabetes
- BMI: 48
- No alcohol, drugs/supplements

<table>
<thead>
<tr>
<th>Lab tests</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>INR</td>
<td>1.25</td>
</tr>
<tr>
<td>Bil (mg/dl)</td>
<td>6.1</td>
</tr>
<tr>
<td>AST/ ALT (U/L)</td>
<td>514/ 548</td>
</tr>
<tr>
<td>γ-GT/ ALP (U/L)</td>
<td>144/ 117</td>
</tr>
<tr>
<td>Albumin/ globulins (g/L)</td>
<td>3.4/ 4.7</td>
</tr>
</tbody>
</table>
Consultation for a 33 years female with acute icteric hepatitis

✓ Investigation for HAV, HBV, HCV, HEV: negative; IgG 2550 mg/dl
✓ Autoimmune serology: ANA 1/160, SMA 1/320 (but also AMA by IIF, MIT3 ELISA and Western blotting!!!)
✓ Liver histology: moderate/severe interface hepatitis, emperipolesis, hepatic rosettes. No biliary and steatosis lesions!!!!

Simplified score = 8 (Definite AIH)

Prednisolone 1mg/kg/day IV
Consultation for a 33 years female with acute icteric hepatitis

- Acute presentation of AIH can occur and may manifest as:
  - acute exacerbation form of previously undiagnosed AIH or
  - new onset acute AIH without histological changes suggestive of chronic disease (II-2)

EASL CPG AIH, J Hepatol 2015
AIH: Clinical case 5; Note the presence of emperipolesis (one arrow) and peripolesis (two arrows)
NAFLD/NASH issues in AIH

Why these patients have by definition only NAFLD/NASH?

Is there any "Medical Law" which excludes the co-existence of AIH or even the presence only of AIH?
AIH and NAFLD/NASH issues

1. Do all NASH patients have truly only NASH?
2. NAFLD/NASH in AIH: important player or innocent bystander?

K. Zachou, N. Gatselis, E.I. Rigopoulou, GN Dalekos

Department of Medicine & Research Laboratory of Internal Medicine,
University of Thessaly, Larissa, Greece
NAFLD has become the most common chronic liver disease in the Western world (prevalence: 20-30% - much higher in obese and type 2 diabetes)

NASH is a subset of NAFLD (3–5% of the population) which has to be diagnosed by liver biopsy showing steatosis, hepatocyte ballooning and lobular inflammation

NASH can progress to severe liver fibrosis and cirrhosis

Chalasani et al, Gastroenterology 2012
EASL: The burden of liver disease in Europe, 2013
EASL-EASD-EASO CPG on NAFLD J Hepatol 2017
Background/Introduction II

Do all NASH patients have truly only NASH?

- Liver autoimmune serological markers in NAFLD patients (12%-48%)
- Studies assessing disease severity with Abs presence have reported conflicting results
- To date, all studies included patients with NAFLD and NASH
  - did not test patients for all autoantibodies implicated in AIH
  - did not apply the simplified AIH score (IgG determination??)
  - did not include long term outcome of the patients
  - did not address the proportion of NASH patients with possible presence of histopathological features of AIH

26/54 patients with NASH had autoimmune features → older obese women
1/3 mice NASH models → autoimmune like histology

Adams et al, Am J Gastroenterol 2004; Cotler et al, J Clin Gastroenterol 2004
No mention on IgG determination and liver autoimmune serology according to EASL CPG on AIH !!!!
Prevalence of NAFLD/NASH in AIH patients: is not well-established

Obesity worsens the course of RA, SLE, IBD and psoriasis and also impairs the treatment of these autoimmune diseases

Versini et al, Autoimm Rev 2014

NAFLD potentiates AIH in the CYP2D6 mouse model

Muller et al, J Autoimm 2016

The consequences of NAFLD/NASH on the outcome & treatment response of AIH is not known
Results  Out of a total 73 study patients, 14 % classified as AIH with SS and 16 % as AIH and NASH. Fifty percent of AIH and NASH patients had cirrhosis at index biopsy as compared to 18 % of AIH-only patients \((p = 0.032)\). Patients with AIH and NASH had a relative risk of 7.65 (95 % CI 1.43–40.8) for liver-related mortality and 2.55 (95 % CI 0.92–7.09) for liver-related adverse outcomes, as compared to the AIH-only cohort. No significant difference in outcome measures existed in comparing (AIH only) with (AIH and SS) cohorts.

Discussion  Patients with coincident AIH and NASH were more likely to present with cirrhosis and more likely to develop adverse clinical outcome with decreased survival as compared to AIH-only patients. These findings suggest that simultaneous exposure confers a clinically significant increased risk, which may warrant closer follow-up and surveillance.
Nonalcoholic Fatty Liver Disease in Patients with Autoimmune Hepatitis: Further Reason for Teeth GNASHing?

Christina Weiler-Normann¹ • Ansgar W. Lohse¹

Dig Dis Sci
DOI 10.1007/s10620-016-4258-3

Suspected NAFLD/NASH + symptoms or signs of AIH

Suspected AIH
- elevated IgG/immunoglobulins
- elevated ANA, SMA and/or presence of SLA/LP
- strong history of autoimmune diseases (personal or family)
- presence of arthralgias

LIVER BIOPSY

AIH

NASH + AIH

Counsel for lifestyle adjustments (e.g. Diet, weight loss, exercise)

Treat AIH using lower doses prednisolone (depending on inflammatory activity), add azathioprine up to 2mg/kg early, try to taper out steroids completely

Response?

NASH

Counsel for lifestyle adjustments (e.g. Diet, weight loss, exercise)

Response?

Continue treatment, ideally steroid free

Consider Re-Biopsy

Standard immunosuppression (e.g. 0.5 - 1mg/kg Prednisolone, tapering down + 1mg/kg azathioprine)
HEPATIC STEATOSIS AND/OR STEATOHEPATITIS IN PRIMARY BILIARY CHOLANGITIS: AN INNOCENT BYSTANDER OR A GUILTY PLAYER?

N.K. Gatselis1, V. Ligoura1, K. Zachou1, K. Azaraidil, P. Arvaniti1, E.I. Rigopoulou1, G.K. Koukoulis2, G.N. Dalekos1

1Department of Medicine & Research Laboratory of Internal Medicine, Medical School, University of Thessaly, Larissa, Greece
2Department of Pathology, Medical School, University of Thessaly, Larissa, Greece

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) ± non-alcoholic steatohepatitis (NASH) is an entity with rising prevalence (25% of the adult population worldwide), so co-existence of NAFLD/NASH with other liver diseases is inevitable. On the other hand, primary biliary cholangitis (PBC) has an increased prevalence in Central Greece with 582 cases/million residents. Previous studies in PBC patients have shown:

• 40-50% co-incidence of steatosis & 6-15% co-incidence of steatohepatitis,
• association of the presence of NAFLD/NASH with increased AST, ALT and histologically more advanced disease in terms of fibrosis stage and biliary duct damage.

AIM

To investigate the prevalence and significance of NAFLD/NASH in patients with PBC.

MATERIAL & METHODS

During the last 15 years, 482 patients were appropriately diagnosed with PBC in our centre. A liver biopsy was performed in 281 patients (245 females, 87.2%; median age 54 years) at the time-point of initial evaluation.

We evaluated the importance of NAFLD/NASH co-existence in PBC patients in terms of demographic, presence of symptoms, liver function tests, autoantibodies, liver biopsy staging, response to treatment according to the Globe score and outcome.

RESULTS

• 38% of PBC patients had histological findings of NAFLD/NASH (26% simple steatosis, 12% steatohepatitis) (Figure 1).
• Univariate analysis showed that co-incidence of NAFLD/NASH in PBC patients was associated with lower ALP (P=0.001), γGT (P<0.01), bilirubin (P=0.02), IgM (P=0.001), and higher albumin levels (P=0.001). Advanced liver biopsy stage III-IV was less frequent in patients with the presence of steatosis ± steatohepatitis (P=0.001).
• Multivariate analysis showed that co-existence of NAFLD/NASH was associated only with lower IgM levels (OR=0.996, 95% CI 0.994-0.999, P=0.01) (Table 1).
• Mayo Risk Score at baseline was significantly lower in patients with NAFLD/NASH (P<0.01).
• Response to treatment according to the GLOBE score was significantly higher in patients with NAFLD/NASH (P<0.03) (Figure 2).
• No significant difference was found regarding the presence of NAFLD/NASH and the frequency of liver-related death or liver transplantation during follow-up (P=0.142) (Figure 3).

Table 1

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adjusted OR</th>
<th>95% CI</th>
<th>Adjusted P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP</td>
<td>0.997</td>
<td>0.991-1.001</td>
<td>0.111</td>
</tr>
<tr>
<td>γGT</td>
<td>1.080</td>
<td>1.040-1.123</td>
<td>0.663</td>
</tr>
<tr>
<td>bilirubin</td>
<td>0.800</td>
<td>0.760-0.847</td>
<td>0.738</td>
</tr>
<tr>
<td>IgM</td>
<td>0.546</td>
<td>0.489-0.611</td>
<td>0.002</td>
</tr>
<tr>
<td>albumin</td>
<td>0.983</td>
<td>0.976-0.989</td>
<td>0.144</td>
</tr>
<tr>
<td>advanced liver stage III-IV</td>
<td>0.562</td>
<td>0.298-1.071</td>
<td>0.176</td>
</tr>
</tbody>
</table>

Table 1. Lower IgM levels was the only predictive factor for the co-existence of NAFLD/NASH in our PBC patients.

CONCLUSION

Despite the high prevalence of NAFLD/NASH in more than one-third of PBC patients, this did not seem to act as an aggravating factor for unfavorable outcome.

DISCLOSURES

Nothing to disclose.

REFERENCES


Contact information

gatselis@me.com
Aim of the study

A multi-centre retrospective analysis in order to assess:

1. The possibility that some patients with NASH may also have AIH features

2. The prevalence of (i) NAFLD/NASH in AIH patients and (ii) clinical and laboratory parameters of the metabolic syndrome in AIH patients

3. The possible impact of NAFLD/NASH diagnosed by liver biopsy and/or parameters of the metabolic syndrome, in the clinical course and response to treatment in AIH patients
Inclusion criteria

Arm 1
- Patients with NASH diagnosed by liver biopsy and fulfilling the following criteria:
  - Available liver biopsy for review by one experienced pathologist
  - Available sera in order to test the whole AIH autoantibody panel
  - Available clinical and follow up data including outcome and response to treatment

Arm 2
- Patients with definite/probable AIH fulfilling the following criteria:
  - Available liver biopsy for review by one experienced pathologist
  - Available sera in order to determine parameters of the metabolic syndrome
  - Available clinical and follow up data including outcome and response to treatment
Exclusion criteria

- Patients with alcohol consumption > 20 g/day for men and >10 g/day for women
- Coexistence of other liver disease (viral hepatitis, PBC, PSC etc.)
<table>
<thead>
<tr>
<th>Demographics</th>
<th>Clinical data</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Name</td>
<td>9. Alcohol consumption (g/day)</td>
</tr>
<tr>
<td>2. Code (center initials-001 etc)</td>
<td>10. Age at NASH diagnosis (years): first NASH diagnosis</td>
</tr>
<tr>
<td>3. Date of end of follow up: Death or LT/ Last visit</td>
<td>11. Date of NASH diagnosis (month/year): first NASH diagnosis</td>
</tr>
<tr>
<td>4. Date of birth</td>
<td>12. NAFLD diagnosis (1. liver biopsy, 2. U/S, 3. other: define)</td>
</tr>
<tr>
<td>5. Gender</td>
<td>13. Duration of FU (months): till the end of FU</td>
</tr>
<tr>
<td>6. Weight (kg)</td>
<td>14. Simplified AIH score (at diagnosis)</td>
</tr>
<tr>
<td>7. Height (m)</td>
<td>15. Presence of cirrhosis at diagnosis</td>
</tr>
<tr>
<td>8. Waist circumference (cm): last visit</td>
<td>16. NAFLD fibrosis score: at diagnosis/ end of FU</td>
</tr>
</tbody>
</table>
### Histology Response to treatment

<table>
<thead>
<tr>
<th>17. Date of liver biopsy (LB) at diagnosis</th>
<th>21. Kind of treatment for NASH</th>
</tr>
</thead>
<tbody>
<tr>
<td>First LB: staging (F0-F1/ F2/ F3/ F4)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>18. Detailed description of <strong>NASH findings</strong>: 1. amount and location of steatosis, 2. presence of Malory’s hyaline 3. hepatocyte ballooning 4. lobular inflammation 5. zone 3 fibrosis</th>
<th>22. Response to treatment (1.normalization of LFT's, 2. no response)</th>
</tr>
</thead>
</table>


| 20. Pathologist who made the first diagnosis: 1. liver specialist, 2. general | |
## The excel file

**NASH patients (Arm 1)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>History of other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Disease progression: Progression of fibrosis as attested by liver biopsy or non invasive tests e.g. elastography (1. yes, 2. no)</td>
<td>28. <strong>History of autoimmune diseases</strong> other than autoimmune liver disease; name of the disease(s)</td>
</tr>
<tr>
<td>24. End of FU fibrosis: cirrhosis presence (yes/ no)</td>
<td>29. Drugs currently used for this autoimmune disease treatment</td>
</tr>
<tr>
<td>Cirrhosis decompensation (if present): (yes/no)</td>
<td></td>
</tr>
<tr>
<td>25. Liver related death (yes/ no); Death date</td>
<td>30. <strong>History of hypertension</strong></td>
</tr>
<tr>
<td>26. Transplantation (yes/no); LT date</td>
<td>Date of diagnosis/ Drugs</td>
</tr>
<tr>
<td>27. HCC development (yes/no); HCC date</td>
<td>31. <strong>History of diabetes mellitus</strong></td>
</tr>
<tr>
<td></td>
<td>Date of diagnosis/ Drugs</td>
</tr>
<tr>
<td></td>
<td>32. <strong>History of dyslipidemia</strong></td>
</tr>
<tr>
<td></td>
<td>Date of diagnosis / Drugs</td>
</tr>
<tr>
<td></td>
<td>33. <strong>History of cardiovascular disease</strong></td>
</tr>
<tr>
<td></td>
<td>Date of diagnosis/ Drugs</td>
</tr>
</tbody>
</table>
### Serology

#### Autoantibodies (sera in -20 C):
- ANA (1. pos, 2. neg)
  - ANA titre (if pos, IIFL)
- SMA (1. pos, 2. neg)
  - SMA titre (if pos, IIFL)
- anti-F-actin (1. pos, 2. neg)
- LKM (1. pos, 2. neg)
- SLA/LP (1. pos, 2. neg)
- ANCA (1. pos, 2. neg)

#### Lab values
- PLTs (x10^9/ L), INR, AST, ALT, γ-GT, ALP, Alb, IgG, Bil, Creatinin, urea, cholesterol, HDL, LDL, Triglycerides, Glucose, HbA1c
- at diagnosis
- end of FU

#### HOMA-IR (last visit)
- Plasma fasting insulin (µU/ml)
- Plasma fasting glucose (mg/dl)
Same parameters as in Arm 1 with some differentiation

- **AIH duration (months):** from onset of symptoms or first known AST/ALT increase till the end of FU
- **Detailed description of possible NAFLD/ NASH findings in liver biopsy (LB):**
  - First LB and Last LB
- **Response to treatment:** 1. complete response, 2. relapses during treatment, 3. partial response, 4. non-response
- **Response after stopping treatment** (if the treatment was withdrawn): 1. relapse and treatment restart, 2. maintenance of remission
- **Corticosteroid complete withdrawal** during treatment (1. yes, 2. no)/ Date
- **IgG (mg/dl) at the end of FU**
<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 28, 2017</td>
<td>Protocol, Application Form to the Institutional Review Board, excel file for data collection were circulated to all IAIHG members</td>
</tr>
<tr>
<td>April 30, 2017</td>
<td><strong>Deadline for willingness of participation</strong>, by a yes or no e-mail response to <a href="mailto:zachoukalliopi@gmail.com">zachoukalliopi@gmail.com</a> or <a href="mailto:gatselis@me.com">gatselis@me.com</a></td>
</tr>
<tr>
<td>December 31, 2017</td>
<td><strong>Deadline for completeness of the data collection</strong></td>
</tr>
<tr>
<td>EASL 2018</td>
<td>Present the first results during IAIHG meeting</td>
</tr>
</tbody>
</table>
# Participants of the AIH/NAFLD/NASH studies

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raul J. Andrade/ Maria Isabel Lucena</td>
<td>University of Malaga, Spain</td>
</tr>
<tr>
<td>Youssef Barbour</td>
<td>Alaska Native Tribal Health Consortium, Anchorage, USA</td>
</tr>
<tr>
<td>Dominique Debray</td>
<td>Hôpitaux Universitaires Paris-Sud, France</td>
</tr>
<tr>
<td>Tomoo Fujisawa</td>
<td>Yokohama City Tobu Hospital, Japan</td>
</tr>
<tr>
<td>Dermot Gleeson</td>
<td>University of Sheffield, UK</td>
</tr>
<tr>
<td>Bart van Hoek</td>
<td>Leiden University Medical Center, The Netherlands</td>
</tr>
<tr>
<td>Pietro Invernizzi</td>
<td>University of Milan-Bicocca</td>
</tr>
<tr>
<td>Marco Lenzi / Paolo &amp; Luigi Muratori</td>
<td>University of Bologna, Italy</td>
</tr>
<tr>
<td>Ansgar Lohse/ Christoph Schramm</td>
<td>University Medical Center Hamburg-Eppendorf, Germany</td>
</tr>
<tr>
<td>Aldo J. Montano-Loza</td>
<td>University of Alberta, Canada</td>
</tr>
<tr>
<td>Dominique Muzzillo</td>
<td>Federal University of Parana, Brazil</td>
</tr>
<tr>
<td>Ye Htun Oo</td>
<td>University Hospital Birmingham, UK</td>
</tr>
<tr>
<td>Atsushi Takahashi</td>
<td>Fukushima Medical University, Japan</td>
</tr>
<tr>
<td>Atsushi Tanaka</td>
<td>Teikyo University School of Medicine, Japan</td>
</tr>
<tr>
<td>Kidist Yimam</td>
<td>California Pacific Medical Center, USA</td>
</tr>
</tbody>
</table>
Statistical analysis – end points

- **Arm 1:**
  - Determination of prevalence of AIH diagnosis in patients diagnosed as having NASH and
  - Determination of demographic, clinical and laboratory characteristics of patients with features compatible with AIH

- **Arm 2**
  - Determination of prevalence of NAFLD/NASH in patients with well defined AIH
  - Determination of prevalence of the components of the metabolic syndrome in AIH
  - Determination of the outcome of patients with AIH and either of the above (NAFLD, metabolic syndrome)

- Defining histological criteria for distinction between AIH, AIH/NASH, NASH
Main outcome measures

• Which are the mean levels of IgG in real NASH cases?

• Should Abs detection according to EASL CPG be done or not in all “supposed” NASH cases?

• Are portal inflammation and interface hepatitis common in cases with only real (true) NASH?

• Which are the characteristics of the inflammatory portal and lobular infiltrates in NASH and NASH with autoimmune features?

• How we could discriminate these conditions at the histological level?
Limitations......

- Retrospective analysis of a prospectively collected data
- Liver biopsies will not be evaluated centrally (ethical issues, logistics, etc.)
- No support from pharmacy industry or other parties
- Histological criteria –if any- for distinction between AIH, AIH with NAFLD/NASH and pure NASH will need an external validation in a prospective manner
Case Presentation 2
Greek-Australian female patient of 55 ys with icteric hepatitis

- Cholestatic enzymes and U/S: Normal
- Viral hepatitis markers negative; no drugs/supplements; no alcohol consumption
- IgG: 2500 mg/dL (<1550 mg/dL)
- ANA 1/640; SMA 1/1280 (F-actin ELISA high pos) but also AMA high positive by IFL and ELISAs (confirmation by WB)
- Liver biopsy: Severe lobular hepatitis accompanied by emperipolesis; no biliary lesions
AMA in AIH
Is this a case of AIH/PBC variant??
No! not at all

Development of antimitochondrial antibodies in patients with autoimmune hepatitis: Art of facts or an artifact?

Long-Term Follow-Up of Antimitochondrial Antibody–Positive Autoimmune Hepatitis

Conor O’Brien,1 Supriya Joshi,1 Jordan J. Feld,2 Maha Guindi,3 Hans P. Dienes,4 and E. Jenny Heathcote1

sion: Patients with overt AIH who test positive for AMAs at initial presentation and are treated with corticosteroid therapy have shown no clinical or histologic evidence of PBC despite the continued detection of AMAs over a follow-up of up to 27 years. (HEPATOLOGY 2008;48:550-556.)
Anti-mitochondrial antibodies

Prevalence of AMA in AIH patients: 5-35%

Their significance is obscure, when identified in patients with other liver diseases, including AIH

Most of the studies so far indicate that AMA in AIH represent simply a bystander phenomenon

Limitations: short FU, infrequent sequential biopsies, small number of patients, different assays employed
Antimitochondrial Antibodies in AIH

Three studies with long term follow up...

Frequency, Behavior, and Prognostic Implications of Antimitochondrial Antibodies in Type 1 Autoimmune Hepatitis
Montano-Loza, J Clin Gastroenterol 2008

Long-Term Follow-Up of Antimitochondrial Antibody– Positive Autoimmune Hepatitis
O’Brien et al, Hepatology 2008

Clinical implication of antimitochondrial antibody seropositivity in autoimmune hepatitis: a multicentre study
Muratori P, Eur J Gastroenterol Hepatol 2017
Antimitochondrial Antibodies in AIH

Frequency, Behavior, and Prognostic Implications of Antimitochondrial Antibodies in Type 1 Autoimmune Hepatitis

- 130 AIH-patients, followed-up for 123 months
- 18% AMA prevalence (n=24)
- No difference on cholestatic histologic features between AMA+ and AMA- patients at presentation (18% vs. 10%, p=0.4)
- Emergence of AMA during follow-up was not associated with cholestatic histologic changes at sequential liver biopsies
- Remission and treatment failures were similar between groups

Montalo-Loza, J Clin Gastroenterol 2008
Antimitochondrial Antibodies in AIH

Long-Term Follow-Up of Antimitochondrial Antibody-Positive Autoimmune Hepatitis

- 126 AIH-patients, followed-up for 27 years
- 12% AMA prevalence (n=15)
- No bile duct damage typical of PBC was seen on initial or follow-up liver biopsies
- Clinical course remained typical for AIH
- No difference on treatment response was noticed

O’ Brien, Hepatology 2008
Clinical implication of antimitochondrial antibody seropositivity in autoimmune hepatitis: a multicentre study

- 47 AMA+ AIH cases from several centres compared with 264 Italian AIH patients
- **Univariate** analysis showed that AMA+ AIH patients
  - were older (46 vs. 36, \( P=0.002 \))
  - more responsive to immunosuppression (74% vs. 59%, \( P=0.05 \))
- **Multivariate** logistic regression analysis using AMA as a dependent variable:
  - showed no differences
- None of AMA+ AIH patients showed signs of PBC features after a median FU up 4 ys

Muratori P, Eur J Gastroenterol Hepatol 2017
Antimitochondrial Antibodies in AIH

Patients With Autoimmune Hepatitis Who Have Antimitochondrial Antibodies Need Long-term Follow-up to Detect Late Development of Primary Biliary Cirrhosis

One patient from the original series from Toronto developed histological features of PBC 29 years after the diagnosis of AIH

Dinani, Clin Gastroenterol Hepatol 2012
Antimitochondrial Antibodies in AIH

Patients With Autoimmune Hepatitis Who Have Antimitochondrial Antibodies Need Long-term Follow-up to Detect Late Development of Primary Biliary Cirrhosis

AMREEN M. DINANI,* SANDRA E. FISCHER,‡ JEFF MOSKO,* MAHA GUINDI,†,§ and GIDEON M. HIRSCHFIELD*•‖

Patients with autoimmune hepatitis (AIH) who have antibodies against mitochondrial proteins (AMA positive) are believed to have an autoimmune syndrome that should be managed as AIH. Of patients with AMA-positive AIH, we report on 3 individuals to demonstrate how autoimmune liver disease can progress over time. Specific features of primary biliary cirrhosis (PBC) overlapped in time in these patients. Our observations indicate the importance of careful follow up of patients with AMA-positive AIH; health care professionals that treat such patients should therefore be aware of longitudinal clinical changes that might indicate development of PBC in this setting.

Dinani, Clin Gastroenterol Hepatol 2012
Antimitochondrial Antibodies in AIH

Nikolaos K. Gatselis, Eirini I. Rigopoulou, Kalliopi Zachou and George N. Dalekos

Department of Medicine & Research Laboratory of Internal Medicine, School of Medicine, University of Thessaly, Larissa, Greece

*following the International Workshop of the IAIHG (Hamburg, Sep 2106)*
Aim

A multi-centre retrospective analysis of a prospectively collected database in order to assess:

1. Prevalence of AMA in patients with AIH at presentation and during long-term FU

2. Whether AMA positivity in AIH has any significance, in terms of clinical, biochemically and histological characteristics at baseline and during FU

3. Long-term outcome and treatment response of AMA+ AIH-patients compared to age and sex matched AMA- patients with AIH at a ratio 1:4
Antimitochondrial Antibodies in AIH

Methods

• **Inclusion criteria**
  - Patients with established AIH (probable or definite) according to simplified IAIHG criteria
  - Available clinical, biochemical, serological and histological data at the time of diagnosis and during follow-up
  - Available data regarding AMA positivity, by indirect immunofluorescence and/or ELISA and/or Western Blot assays, at baseline and during follow-up (if available)

• **Exclusion criteria**
  - Co-existence of other liver disease
### Antimitochondrial Antibodies in AIH

#### Methods

| Demographics | Date of end follow-up  
Date of birth  
Date of diagnosis  
Age at Diagnosis  
Sex  
Ethnicity |
|--------------|---------------------------------------------------------|
| Liver Histology / Staging | Simplified score  
Revised IAHIG score  
Grading & Staging (Knodell)  
Fibroscan  
Histological characteristics of AIH  
Histological characteristics of PBC |
| Clinical findings | Symptoms PBC-related  
Sign of cirrhosis  
Decompensation for cirrhotics  
Presence of HCC |
| Laboratory | AST, ALT, TBILI, ALP, γGT, ALB, glob, INR, PLT, IgG, IgM |
| Autoantibodies | ANA (IIF on HEp2, rodent, ELISA) anti-sp100, anti-gp210, AMA (IIF, ELISA, WB), LKM (IIF, ELISA, WB), SLA/LP (ELISA, WB), LC1 (IIF, ELISA, WB) |
Antimitochondrial Antibodies in AIH

**Methods**

| Drugs received during follow up for AIH | Initial immunosuppressive treatment
| Date of first treatment administration
| Date of last treatment administration
| Type of treatment during follow-up |
| UDCA specific treatment | UDCA during follow-up
| UDCA dose
| UDCA starting & stopping date |
| Change of immunosuppressive regimen during follow-up | Reason for change (i.e. intolerance, insufficient response, other) |
| Response to treatment (AIH focused) | Response on treatment
| Response after stopping treatment
| Corticosteroids complete withdrawal during treatment |
| ALP changes during follow-up & response to treatment (cholestasis focused) | ALP changes till last follow-up
| GLOBE score
| Barcelona (Pares’s) criteria |
Antimitochondrial Antibodies in AIH

**Methods**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Progression to cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Progression to decompensation</td>
</tr>
<tr>
<td></td>
<td>Liver transplantation</td>
</tr>
<tr>
<td></td>
<td>Development of HCC</td>
</tr>
<tr>
<td></td>
<td>Death (liver related or no)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological characteristics of PBC at sequential liver biopsy or biopsies</th>
<th>Number of sequential liver biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Histological characteristics of PBC at sequential liver biopsies</td>
</tr>
<tr>
<td></td>
<td>Preservation of PBC histological characteristics (preservation, resolution, emergence)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AMA changes during follow-up</th>
<th>AMA changes during follow-up with any method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of AMA emergence for AMA- at baseline</td>
<td></td>
</tr>
<tr>
<td>Date of AMA disappearance</td>
<td></td>
</tr>
</tbody>
</table>
Antimitochondrial Antibodies in AIH

Methods

Statistical analysis and endpoints

- Prevalence of AMA positivity at baseline and variations during follow up visits
- Comparison of demographic, clinical, biochemical and histological characteristics
- Development of bile duct damage over time in sequential liver biopsies
- Response to treatment
- Disease progression (development of cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, liver transplantation or liver related death)
Final call of interest was done on March 28, 2017

<table>
<thead>
<tr>
<th>Date</th>
<th>Event Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 28, 2017</td>
<td>Protocol, Application Form to the Institutional Review Board, excel file for data collection were circulated to all IAIHG members</td>
</tr>
<tr>
<td>April 30, 2017</td>
<td><strong>Deadline for willingness of participation</strong>, by a yes or no e-mail response to <a href="mailto:zachoukalliopi@gmail.com">zachoukalliopi@gmail.com</a> or <a href="mailto:gatselis@me.com">gatselis@me.com</a></td>
</tr>
<tr>
<td>December 31, 2017</td>
<td><strong>Deadline for completeness of the data collection</strong></td>
</tr>
<tr>
<td><strong>EASL 2018</strong></td>
<td><strong>Present the first results during IAIHG meeting</strong></td>
</tr>
</tbody>
</table>
## Participants of the AMA in AIH study

<table>
<thead>
<tr>
<th>Name</th>
<th>Institution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raul J. Andrade/ Maria Isabel Lucena</td>
<td>University of Malaga, Spain</td>
</tr>
<tr>
<td>Benedetta Terziroli Beretta-Piccoli</td>
<td>Epatocentro Ticino CA, Lugano, Switzerland</td>
</tr>
<tr>
<td>Eduardo Cancado</td>
<td>University of Sao Paolo, Brazil</td>
</tr>
<tr>
<td>Annarosa Floreani</td>
<td>University of Padova, Italy</td>
</tr>
<tr>
<td>Dermot Gleeson</td>
<td>University of Sheffield, UK</td>
</tr>
<tr>
<td>Bart van Hoek</td>
<td>Leiden University Medical Center, The Netherlands</td>
</tr>
<tr>
<td>Pietro Invernizzi</td>
<td>University of Milan-Bicocca</td>
</tr>
<tr>
<td>Cynthia Levy</td>
<td>University of Miami, USA</td>
</tr>
<tr>
<td>Marco Lenzi / Paolo Muratori</td>
<td>University of Bologna, Italy</td>
</tr>
<tr>
<td>Ansgar Lohse/ Christoph Schramm</td>
<td>University Medical Center Hamburg-Eppendorf, Germany</td>
</tr>
<tr>
<td>Aldo J. Montano-Loza</td>
<td>University of Alberta, Canada</td>
</tr>
<tr>
<td>Dominique Muzzillo</td>
<td>Federal University of Parana, Brazil</td>
</tr>
<tr>
<td>Ye Htun Oo</td>
<td>University Hospital Birmingham, UK</td>
</tr>
<tr>
<td>Atsushi Takahashi</td>
<td>Fukushima Medical University, Japan</td>
</tr>
<tr>
<td>Kidist Yimam</td>
<td>California Pacific Medical Center, USA</td>
</tr>
</tbody>
</table>
G.N. Dalekos, Professor of Medicine, Head of the Dept.

E.I. Rigopoulou, Associate Professor of Medicine
K. Zachou, Assistant Professor of Medicine
N. Gatselis, Assistant Professor of Medicine
G. Papadamou, Consultant in Internal Medicine
S. Gabela, Consultant in Internal Medicine
S. Saitis, Consultant in Internal Medicine
K. Azariadi, PhD student, P. Arvaniti, PhD student
V. Lygoura, PhD student, A. Lyberopoulou, PhD