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Review

Do anti-smooth muscle antibodies predict development of autoimmune hepatitis in patients with normal liver function? – A retrospective cohort review

Rebecca Healey [a], Lynsey Corless [b], Pavels Gordins [c], Stephen Holding [d,*]

[a] Hull York Medical School, University of Hull, Cottingham Road, Hull, HU6 7RX, UK
[b] Department of Gastroenterology and Hepatology, Hull Royal Infirmary, Anlaby Road, Hull, HU3 2JZ, UK
[c] Immunology Department, Castle Hill Hospital, Cottingham, HU16 5JQ, UK
[d] Immunology Department, Hull Royal Infirmary, Hull, UK

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ABSTRACT

Background: The presence of anti-smooth muscle autoantibody (SMA) in Autoimmune Hepatitis (AIH) is well established. However, there are no data demonstrating the clinical significance in patients with normal liver function and few showing positive predictive value for AIH when alanine aminotransferase (ALT) is raised.
Methods: We retrospectively established outcomes in a cohort of 251 consecutive patients with positive tubular or glomerular SMA. Patient records were checked for 12 years after the positive SMA result to identify development of AIH.
Results: Of 202 patients with SMA and ALT<55 IU/L, one (0.5%) had a subsequent diagnosis of AIH and this patient probably had abnormal ALT at the time of SMA detection. 22% of 45 patients with raised ALT (>55 IU/L) and 23% of 43 patients with persistently raised ALT (>3 months duration), had a diagnosis of AIH on follow up. Of 10 patients with AIH, 80% were diagnosed within three months of the positive SMA.
Conclusions: Progression to AIH in patients with normal liver function and positive SMA-T/G is rare but patients with positive SMA and raised ALT (>55 IU/L) should be referred to secondary care for investigation. Positive predictive value of SMA with raised ALT for AIH was 22%.

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* Corresponding author at: Immunology Department, Hull Royal Infirmary, Hull, HU3 2JZ, UK. Tel.: +44 1482 607710; fax: +44 1482 607752.
E-mail address: steve.holding@hey.nhs.uk (S. Holding).

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1. Introduction and background

1.1. Autoimmune hepatitis

Autoimmune Hepatitis (AIH) is a chronic progressive inflammatory liver disease of unknown aetiology, characterised histologically by interface hepatitis and lymphocytic infiltrate, serologically by raised immunoglobulins and presence of autoantibodies, and biochemically by raised aminotransferase levels [1–3]. It has a female preponderance (estimated male:female ratio of 1:3.6) [4] and affects both adults and children of all ages and ethnic groups. There is a bimodal peak age distribution (10–20 years and 45–70 years) and recent evidence suggests that it is commoner in older women [5,6]. European prevalence is estimated at 10–17 per 100,000 [7]. A New Zealand population based study found similar incidence and prevalence (1.7 and 18.9 respectively per 100,000 for a WHO age standardised population) [5].

Onset is often insidious; presenting symptoms may be mild and non-specific, including fatigue, generalised malaise, anorexia, jaundice, arthralgia, and right upper quadrant pain [3,8]. Up to 25% of patients may be asymptomatic at presentation [9]. AIH can also present acutely with symptoms similar to those of acute viral hepatitis [10,11], or, more rarely, with fulminant hepatic failure [11–15]. Untreated AIH may lead to liver cirrhosis, liver cancer, or death [1,3,16]. However a positive response to immunosuppressive therapy in most cases leads to remission and extended survival [9,17].

Recent British Society of Gastroenterology (BSG) guidelines [7], showed that a simplified scoring system is useful in diagnosing AIH, with sensitivity and specificity of ≥70% and >95% respectively [18–20] at the recommended cut-off of 7 points. A score of ≥7 points indicates definite AIH and requires the presence of raised IgG, positive SMA ≥ 1:80, typical histology, and absence of viral hepatitis. A score of ≥6 points indicates probable AIH.

1.2. Smooth muscle autoantibodies

The detection of autoantibodies forms a key element of the AIH diagnostic criteria and allows differentiation between AIH Types 1 and 2 (AIH-1 and AIH-2), with AIH-1 characterised by anti-smooth muscle (SMA) and/or anti-nuclear (ANA) autoantibodies, and AIH-2 by anti-liver kidney microsomal type-1 (LKM1) and/or anti-liver cytosol type-1 (LC1) autoantibodies [7].

According to the Committee for Autoimmune Serology of the IAIHG 2004 guidelines, testing for SMA should be by indirect immunofluorescence (IIF) on fresh, multi organ (liver, kidney, stomach) rodent sections (LKS) [21]. Three different SMA types are defined by the IIF staining pattern in the kidney sections: SMA-V (vascular), SMA-G (glomerular) and SMA-T (tubular). The SMA-G/T patterns mainly react with filamentous actin (f-actin) [22–25] and are considered more specific for AIH-1 than SMA-V [26]. SMA-V is not considered clinically significant as it is commonly found in non-autoimmune liver disease, other autoimmune conditions and viral infections [21].

2. Aims

Although the presence of SMA-T/G with F-actin specificity in patients with AIH-1 has been widely reported and is an important indicator of AIH [24,27–31], there are no data demonstrating the clinical significance of SMA-T/G detected in individuals that have normal liver function at the time of testing. In this study we retrospectively assessed outcomes in a consecutive series of SMA-T/G positive patients with normal liver alanine aminotransferase (ALT). Patient records from these individuals were examined for a period of up to 12 years after the finding of a positive SMA-T/G for evidence of progression to AIH.

3. Methods

3.1. Setting

Hull and East Yorkshire Hospitals serve a population of about 720,000 for LKS and SMA testing. This service covers primary and secondary care. During the period reviewed (April 2003 to December 2005) we performed IIF on LKS as our primary screen for SMA, using a tissue mosaic (HEp2 and rat liver, kidney and stomach; Euroimmun, London, UK). The Pathology Service Laboratory Information Management System (LIMS) contains a database of all pathology patient results generated since December 1999. We utilised this database to identify all SMA-T/G positive results between April 2003 and December 2005. A consecutive series of 252 patients was identified.

Patients with a previous diagnosis of AIH were excluded. Remaining patients were separated into two categories for follow up, based on liver function: Group 1 was those patients with normal ALT (≤55 IU/L), at the time of the positive SMA result. Group 2 were those patients with abnormal ALT (>55 IU/L). Patients with no available ALT measurements were excluded.

Patient NHS numbers (national patient case number) were then used as identifiers to extract data for individual patient assessment against the AIH simplified diagnostic criteria [19], serum aminotransferases as outlined in the revised descriptive criteria [32], and ALP:ALT ratio (ratio of elevations above upper limits of normal) according to the modified criteria [32], to determine if AIH developed during a follow up period of up to 12 years. The data required for each patient therefore comprised ALT, alkaline phosphatase (ALP), immunoglobulin G (IgG), liver histology reports and viral hepatitis serology. Patients were then categorised according to their results.

3.2. Group categorisation

Patients categorised into groups 1 and 2 above were then further stratified according to outcome during follow up:

Subsequent diagnosis of AIH - histology consistent with development of AIH or a clinic letter confirming diagnosis.

No subsequent diagnosis of AIH - no evidence of histological confirmation or clinical diagnosis. These patients were further sub-classified as follows:

ALT persistently normal - ALT results that remained normal (<45 IU/L) or near normal (45–55 IU/L) throughout follow up.

ALT transiently abnormal - raised ALT (>55 IU/L) with subsequent return to normal/near normal within three months. For these patients, AIH scores were calculated according to the simplified diagnostic criteria [19]. Those with a score of 6 or more had case notes examined to ascertain potential explanations for the raised ALT and evidence of AIH.

ALT persistently abnormal - raised ALT (>55 IU/L) lasting more than three months. Case notes for these patients were examined to ascertain potential explanations for the raised ALT.

4. Results

4.1. Patient characteristics

An initial cohort of 252 consecutive patients with positive SMA-G/T was identified. One patient with a previous diagnosis of AIH was