# Antiphospholipid Antibody Syndrome in Autoimmune Hepatitis

Andrea Becker-Merok MD[1] and Hans Nossent MD PhD[1,2]

[1]Department of Rheumatology, Institute of Clinical Medicine, University of Tromsø, Norway
[2]Department of Rheumatology, University Hospital Northern Norway, Tromsø, Norway

**Key words:** antiphospholipid antiobodies, autoimmune hepatitis, thrombosis

*IMAJ 2005;7:268–269*

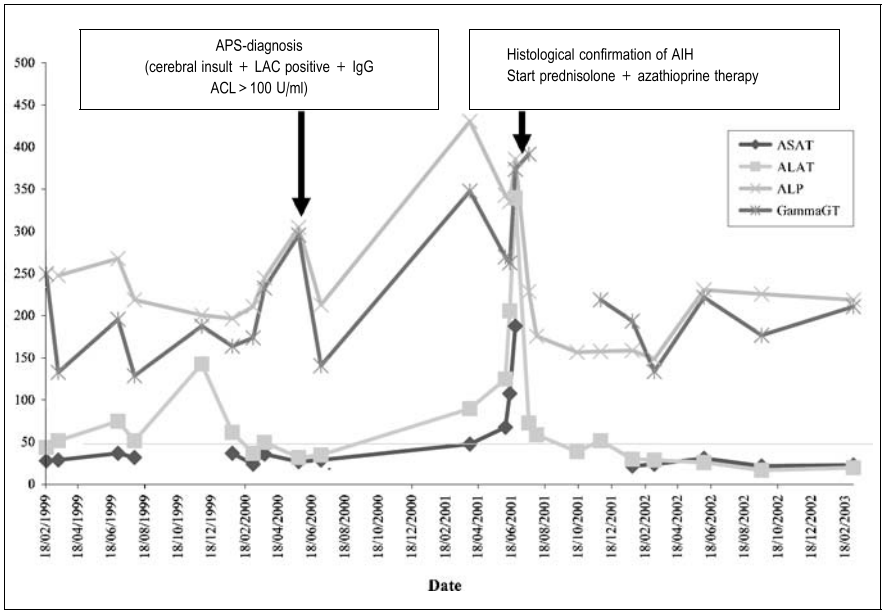
For Editorial see page 264

The antiphospholipid antibody syndrome is a multisystem autoimmune disease in which recurrent arterial and/or venous thrombosis, pregnancy morbidity and a variety of skin, cardiac valve, central nervous system, blood and other organ abnormalities may occur in the sustained presence of serum antibodies against phospholipids, prothrombin and/or $\beta_2$ glycoprotein-1. APS is defined as "secondary" when occurring in the context of another autoimmune disease (most often systemic lupus erythematosus), while "primary" APS refers to APS in the absence of features of other autoimmune diseases. There are few reports on the association between APS and parenchymal liver disease, and these concern mainly patients with APS secondary to SLE. Autoimmune hepatitis is a chronic heterogenic disease characterized by chronic parenchymal liver inflammation in the presence of various autoantibodies, such as anti-smooth antibodies, anti-liver-kidney microsomal-1 antibodies and anti-liver cytosol antibody-1. We describe a rare case in which AIH was diagnosed shortly after the neurologic presentation of APS and discuss the sparse literature on their combined occurrence.

## Patient Description

A previously healthy 46 year old man experienced short periods of clouded vision, although neurologic examination and cerebral magnetic resonance imaging were unremarkable. During the next few years, attacks became more frequent and severe, and began to include scotoma, nausea, headache, reduced consciousness and sometimes postural swaying for about 10 minutes, followed by retrograde amnesia. Routine laboratory tests were normal, except for variable levels of liver enzymes [Figure]. Repeated extensive diagnostic workups – including electromyelography, electroencephalography, cerebral computerized tomography, bone marrow and abdominal ultrasound – revealed no cause for the cerebral symptoms and a tentative diagnosis of basilar migraine was made. Symptomatic treatment with beta-blocking agents, sumatripan and valproic acid did not reduce the persisting attacks, which now also included memory loss, poor concentration, dysarthria, and reduced sensibility in the right facial region.

Fourteen months after presentation the patient developed a stroke in the left occipital hemisphere with a total hemianopsia on the right side, followed by a retinal arterial thrombosis 3 months later despite prophylactic treatment with aspirin and dipyridamol. Diagnostic workup at that time showed a normal blood count, normal liver enzymes, erythrocyte sedimentation rate of 7 mm/hour, INR <1.1, activated partial thromboplastin time 49 seconds (prolonged; normal 25–36 sec), fibrinogen 4.1 G/L (elevated; normal 2.0–4.0 G/L), low protein S (66%; normal 70–140%) and reduced antigen-presenting cell resistance 1.7 (heterozygote type; normal >2.0) and normal levels of antithrombin III and




Time course of liver enzymes and clinical syndromes in a patient with APS and AIH.
AST = aspartate aminotransferase (normal 10–35 U/L), ALT = alanine aminotransferase (normal 10–35 U/L), ALP = alkaline phosphatase (normal 80–275 U/L), gammaGT = gammaglutamyl transferase (normal 5–50 U/L), APS = antiphospholipid syndrome, ACL = anticardiolipin antibody, AIH = autoimmune hepatitis.

APS = antiphospholipid syndrome
SLE = systemic lupus erythematosus
AIH = autoimmune hepatitis

protein C. Protein electrophoresis was normal, immunoglobulin G anticardiolipin antibody was strongly positive (>100 U/ml; normal 0–10 MPL U/ml), IgM anticardiolipin antibody weak positive (13 U/ml; normal 0–10 GPL U/ml) and lupus anticoagulant strongly positive. Anti-$\beta_2$ GP1 testing was not done, but anti-dsDNA antibodies were present (enzyme-linked immunosorbent assay, titer 61; normal 0–55 IU/ml) with normal levels of complement C3/C4. Cardiac ultrasound showed a thickening of the mitral valve and a slight mitral insufficiency.

"Primary" antiphospholipid syndrome with cerebral manifestations was diagnosed and treatment with warfarin was instituted. While this led to a significant decrease in frequency and severity of attacks, liver enzymes again became elevated. With negative viral serology, a liver biopsy was performed, which showed chronic active hepatitis (periportal lymphocyte infiltration, piecemeal necrosis) and fibrosis without regeneration. Test results for ASMA were positive (titer 1,250) and negative for antimitochondrial antibodies. Subsequent treatment for AIH with corticosteroids and azathioprine was followed by rapid normalization of liver enzymes and disappearance of ASMA, antinuclear antibodies and anti-dsDNA antibodies, although ACL IgG remained strongly positive.

## Comment

We describe a rare case where ischemic neurologic symptoms preceded the histologic confirmation of AIH. The short-lived attacks with clouded vision, tremor, migraine and later aphasia and thickened, insufficient mitral valve can in retrospect be linked to antiphospholipid antibody-induced small vessel disease. The sparse findings in the literature indicate that APS usually precedes AIH [1–3], but given the prior fluctuations in liver enzymes we cannot exclude that AIH may have been present already at the time of onset of cerebral symptoms in our patient. In other reports, APS and AIH occurred mostly in patients with established SLE, but we were unable to make the clinical diagnosis of SLE in this patient, despite the presence of several non-organ-specific autoantibodies and even with prolonged follow-up.

ApLa has been detected in 3–14% of AIH patients, but this figure is largely similar to that in control patients with viral hepatitis (type B and C, and human immunodeficiency virus infections) [4]. Furthermore, most ApLa in viral hepatitis do not seem to result in a strong thrombotic tendency [5], which makes the relationship between APS and AIH puzzling. Ischemic tissue injury due to APS may have induced a localized inflammatory response of the liver with consequent release of intracellular antigens followed by tissue-specific autoantibody production, such as ASMA. Such antibodies often persist until the cells involved in antigen production are either completely destroyed or the process is controlled by drugs, as in our patient [5]. The fact that antinuclear antibodies and ASMA disappeared with immunosuppressive treatment, while ACL IgG persisted, would support such a view.

Despite these uncertainties regarding the etiologic relationship between AIH and APS, this report suggests that patients with primary APS and abnormal liver enzymes should be screened for AIH in order to prevent the development of subsequent liver failure with appropriate immunosuppressive treatment. Also, screening patients with type I AIH for ApLa may prove beneficial, as prophylactic treatment in ApLa-positive AIH patients can reduce morbidity, even though the precise risk for APS development in these patients is not known.

## References


1. Barak N, Orion Y, Schneider M, Bernheim J, Mekori YA. Case report: Hepatic involvement in antiphospholipid syndrome. *J Gastroenterol Hepatol* 1999;14(11):1124–8.
2. Benten D, Widjaja A, von Depka M, et al. Autoimmune hepatitis associated with coagulation disorders and immune thyreopathy. *Z Gastroenterol* 2001;39(10):837–40.
3. Dourakis SP, Michael AE, Papanikolaou IS, Nomikou E, Thalassinou P, Hadziyannis SJ. Autoimmune hepatitis associated with the antiphospholipid syndrome. *Eur J Gastroenterol Hepatol* 2001;13(5):591–3.
4. Klein R, Goller S, Bianchi L. Nodular regenerative hyperplasia (NRH) of the liver –a manifestation of 'organ-specific antiphospholipid syndrome'? *Immunobiology* 2003; 207(1):51–7.
5. Pathmakanthan S, Kay EW, Murray FE. Autoimmune chronic active hepatitis associated with the presence of antiphospholipid antibodies. *Eur J Gastroenterol Hepatol* 1998; 10(2):155–7.



**Correspondence:** Dr. A. Becker-Merok, Dept. of Rheumatology, University Hospital Northern Norway, N-9038 Tromsø, Norway.
Phone: (47-776) 27294
Fax: (47-776) 27258
email: Andrea.Becker-Merok@unn.no


Ig = immunoglobulin
Anti-$\beta_2$ GP1 = $\beta_2$ glycoprotein1
ASMA = anti-smooth muscle antibodies
ACL = anticardiolipin antibody
ApLa = antiphospholipid antibody