Cerebral venous thrombosis and chronic active hepatitis as part of the antiphospholipid syndrome

Anat Kesler, Itamar S Pomeranz, Moshe Huberman, Ben Novis, Edna Kott

Summary

A case of antiphospholipid syndrome, presenting as sinus vein thrombosis together with chronic active hepatitis, is reported in a 35-year-old woman.

Keywords: antiphospholipid syndrome, cerebral venous thrombosis, pseudotumour cerebri, hepatitis

Specific neurological syndromes have been reported in the presence of antiphospholipid antibodies.^{1,2} Chronic active hepatitis as part of the antiphospholipid syndrome has been described in only two patients.^{3,4} We report the combination of sinus vein thrombosis together with chronic active hepatitis in a young woman with antiphospholipid syndrome. This patient was 13 months post-partum and still lactating; this may have contributed to her hypercoagulable state. Such a rare manifestation of the antiphospholipid syndrome has not previously been described.

Case report

Thirteen months post-partum and while still lactating, a 35-year-old woman, the mother of seven children, was hospitalised because of severe headaches and transient visual obscuration. She had a history of three spontaneous abortions. On physical examination her fever was 38.4°C and papilloedema with exudates and haemorrhages was noted. Visual acuity was 6/15 in the right eye and 6/12 in the left eye, pupils were equal with +4 response and no afferent pupil defect. Eye movements were normal. Goldmann perimetry showed enlarged blind spots. The erythrocyte sedimentation rate (ESR) was 135 mm in the first hour, white cell count $9.7 \times 10^9/l$, haemoglobin 10.3 g/dl, platelets $360 \times 10^9/l$, prothrombin time, partial thromboplastin time and fibrinogen levels as well as liver function tests were completely normal. Immuno-electrophoresis of blood gamma globulin, LE cells, C3 and C4 complement, VDRL were all normal. Cardiolipin antibodies were moderately elevated, 0.119 IgM optical density was above the normal range (<0.075), as was 0.326 IgG optical density (<0.042). Magnetic resonance imaging (MRI) (figure 1) and magnetic resonance angiography (MRA) demonstrated superior sagittal and right sigmoid sinus thrombosis with small periventricular lesions of increased intensity. A diagnosis of sinus vein thrombosis was made. Treatment with intra-

venous heparin 24 000 unit/24 h, later replaced by low molecular heparin twice daily, together with ceftriaxone 1.0 g/day and dexamethasone 24 mg/24 h was begun. Several days later her temperature returned to normal. The ESR dropped to 20 mm in the first hour and the headaches disappeared.

For one month the patient refused to undergo lumbar puncture which, when performed, showed an opening pressure of 90 mmH₂O, protein 37 mg%, glucose 74 mg/dl and no cells or oligoclonal IgG bands. Two months later visual acuity was 6/12 in the right eye and 6/9 in the left eye. Goldmann perimetry showed concentric contraction with a normal blind spot. Examination of the fundus revealed only mild upper and lower swelling of the optic discs with no exudates or haemorrhages. MRI still disclosed superior sagittal and right sigmoid sinus thrombosis with periventricular and brainstem areas of ischaemia. Antiphospholipid antibody values were now within normal limits.

Five weeks from presentation, while on dexamethasone 16 mg/day, abnormal liver function tests were noted for the first time. Her aspartate transaminase reached 224 IU/l (7–37 normal) and alanine transaminase 1150 IU/l (0–40 normal). The other liver function tests were within normal limits. Over the next three months transaminases decreased (aspartate transaminase 44 IU/l and alanine transaminase 157 IU/l). There was no serological evidence of infection with hepatitis A, B or C, cytomegalovirus or Epstein-Barr virus. Antinuclear antibodies, anti-DNA, anti-mitochondria antibodies, anti-M2 mitochondria antibodies and Coombs test were all negative. Ceruloplasmin levels were normal. Liver ultra-

Meir Hospital, Sapir
Medical Center, 44281
Kfar Saba and Tel-
Aviv University
Sackler School of
Medicine, Tel-Aviv,
Israel
Department of
Neurology
A Kesler
M Huberman
E Kott
Gastroenterology Unit
IS Pomeranz
B Novis

Accepted 24 January 1996

Figure 1 MRI, axial T1WI (TR 520 TE 25) post-gadolinium. Note the absence of flow void in the right sigmoid sinus

sonography and Doppler ultrasound were both normal. Anti-smooth muscle antibodies were detected at 1/20 titer. Two months later, when steroids were completely withdrawn, her aspartate transaminase increased to 709 IU/l, alanine transaminase to 718 IU/l, γ -glutamyl transpeptidase to 203 IU/l (7–49 normal), alkaline phosphatase to 220 IU/l (53–128 normal) and serum bilirubin to 20.6 μ mol/l. On repeat Doppler ultrasound and abdominal computed tomography (CT) there was no evidence of hepatic vein thrombosis. A needle liver biopsy showed enlarged portal spaces with a heavy lymphocytic infiltration and piecemeal necrosis as well as bridging hepatic necrosis. There were no granulomata or fatty degeneration. The bile ducts appeared normal (figure 2). A diagnosis of chronic active hepatitis was made and treatment with steroids was planned. Two weeks after performing the liver biopsy, however, levels of transaminases spontaneously returned to normal and therefore treatment with steroids was deferred. Ten months after presentation severe headaches and transient visual obscuration recurred. Moderate papilloedema was found and the MRI showed superior sagittal and right sigmoid sinus thrombosis with recanalisation. Antiphospholipid antibody levels were again high, with increased IgG 37 plu (normal <23 plu) and normal IgM (ELISA, Reads anti-cardiolipin semi-quantitative test). On lumbar puncture the opening pressure was elevated (320 mmH₂O). Treatment with steroids was resumed, but as severe headaches continued a lumbo-peritoneal shunt was performed. Following shunt procedure the headaches disappeared and a few weeks later the papilloedema subsided. The antiphospholipid antibody level transiently returned to normal for one month, but subsequently antiphospholipid antibody IgM rose to 14 plu. For more than three months, until the time of the lumbo-peritoneal shunt, normal levels of transaminases were observed. Thereafter a mild elevation of aspartate transaminase to 169 IU/l and alanine transaminase to 140 IU/l was noted. Two weeks later jaundice developed with serum bilirubin of 147.1 μ mol/l (direct 102.6), aspartate transaminase 1654 IU/l, alanine transaminase 1378 IU/l, alkaline phosphatase 391 IU/l and γ -glutamyl transpeptidase 186 IU/l. Treatment with prednisone 40 mg/day was begun and all the liver function tests returned to normal.

Discussion

The diagnosis of the antiphospholipid syndrome was made in this patient on the basis of recurrent spontaneous abortions, pseudotumour cerebri due to sinus vein thrombosis, and the laboratory detection of antiphospholipid antibodies. These antibodies carry an increased risk for cerebral ischaemic events and may therefore serve as a marker for impending strokes or transient ischaemic attacks, particularly in young patients.^{1,5} We assume that the hypercoagulability state present in this patient during lactation, together

Learning/summary points

- antiphospholipid syndrome may cause cerebral venous thrombosis
- habitual abortion is one of the manifestations of the antiphospholipid syndrome
- hepatic vein thrombosis may be part of the antiphospholipid syndrome
- rarely, chronic active hepatitis can be part of this syndrome

Figure 2 The portal spaces are widened and fibrotic piecemeal necrosis and heavy lymphocytic infiltration are present. The bile ducts appear intact

with the high titre of antiphospholipid antibodies, may explain her cerebral venous thrombosis. It is of particular interest that, following cessation of lactation and the administration of heparin and steroids for two months, the clinical symptoms as well as the antiphospholipid antibodies, disappeared.

At the same time, this patient developed chronic active hepatitis, which responded to steroids. The course of her disease is unusual, as the time of onset of the hepatitis is exactly defined and, despite the severe abnormalities on liver biopsy, she went into spontaneous biochemical remission for almost four months. The type of chronic hepatitis, however, remains obscure, as it does not fully conform to the classic type I autoimmune chronic active hepatitis, as she has anti-smooth-muscle antibodies and anticardiolipin antibodies, but no other auto-antibodies. Although the relationship between the antiphospholipid syndrome and Budd–Chiari syndrome has been previously described,^{6,7} there was no evidence of hepatic vein thrombosis either on Doppler ultrasound or CT or on liver biopsy. The relationship between the antiphospholipid syndrome and chronic active hepatitis, as in this patient, has been previously noted in only two other patients.^{3,4}

The association of the antiphospholipid syndrome with chronic hepatitis, as in this patient, is extremely rare. The combination of cerebral sinus vein thrombosis and chronic active hepatitis, as a part of this syndrome, has not been previously described.⁸ Both manifestations of her disease, the sinus vein thrombosis and the chronic hepatitis, responded to treatment with steroids combined with anti-coagulants.

- 1 Mokri B, Jack CR, Petty GH. Pseudotumor syndrome associated with cerebral venous sinus occlusion and anti-phospholipid antibodies. *Stroke* 1993; 24: 469–72.
- 2 Ribes MF. Des recherches faites sur la phlébite. *Rev Med Fr Etrangere et Journal de clinique de l'hotel Dieu et de la charite de parix* 1825; 3: 5–41.
- 3 Saeki R, Kaneko S, Terasaki S, et al. Mixed types of chronic active hepatitis and primary biliary cirrhosis associated with the anti-phospholipid antibody syndrome: a case report. *Hepatology* 1993; 40: 499–501.
- 4 Beales ILP. An acquired pseudo-Bernard Soulier syndrome occurring with autoimmune chronic active hepatitis and anti-cardiolipin antibody. *Postgrad Med J* 1994; 70: 305–8.
- 5 Karabudack R, Caner H, Oztekin N, et al. Thrombosis of intracranial venous sinus aetiology clinical findings and prognosis of 56 patients. *J Neurosurg Sci* 1990; 34: 117–21.
- 6 Stinson J, Tomkin G, McDonald G, et al. Recurrent disseminated intravascular coagulation and fulminant intra hepatic thrombosis in a patient with the anti-phospholipid syndrome. *Am J Hematol* 1990; 35: 281–2.
- 7 Young N, Wong KP. Antibody to cardiolipin causing hepatic infarction in a post partum patient with systemic lupus erythematosus. *Aus Radiol* 1991; 35: 83–5.
- 8 Martin PJ, Enevoldson TP. Cerebral venous thrombosis. *Postgrad Med J* 1996; 72: 72–6.

Stroke and transient ischaemic attacks in association with substance abuse in a young man

TM Lawson, A Rees

Summary

A 22-year-old man with a five-year history of drug and alcohol abuse presented with a left hemiparesis preceded by three transient ischaemic attacks, two of which occurred whilst smoking cannabis. Substance abuse was the only identifiable risk factor for cerebrovascular disease.

Keywords: substance abuse, stroke, transient ischaemic attack

Substance abuse has now reached epidemic proportions in the developed world and continues to increase. Both emotional and physical illness are common complications and, in particular, a link between acute stroke and substance abuse has been documented.^{1,2} Although relatively uncommon, substance abuse is now considered to be one of the commonest identifiable factors in the aetiology of acute stroke in young people in the US. Its causal link, however, is insufficiently appreciated in contemporary UK practice. Thus, we wish to emphasise this association by reporting a case of major cerebral infarction preceded by three transient ischaemic events in a 22-year-old Caucasian male whose only risk factor was drug and alcohol abuse.

Case report

A 22-year-old man was admitted as an emergency with an abrupt onset of a dense left hemiparesis. In the week prior to his admission, he acknowledged that he had heavily abused both cannabis and LSD, but denied taking any amphetamines or ecstasy. However, in the previous five years, he admitted frequent abuse of amphetamines, LSD, ecstasy and cannabis, but denied parenteral drug abuse. He smoked 20–30 cigarettes a day and consumed approximately 10 units of alcohol per day. There was no significant family history

of cerebrovascular disease. Four days prior to his admission, whilst smoking cannabis with friends, he experienced a transient left hemiparesis. This lasted 30 minutes, but resolved completely. Close questioning revealed similar transient left hemiparesis with subjective hemisensory loss two weeks earlier, which lasted 15 minutes and occurred after taking oral amphetamines. Three months earlier, whilst smoking cannabis, he experienced an expressive dysphasia lasting approximately two hours.

Clinical examination revealed him to be normotensive (140/90 mmHg) with an established left hemiparesis and sensory inattention. Physical examination was otherwise normal. Investigations included full blood count, urea, creatinine and electrolytes, fasting lipid profile, fasting glucose, HbA1, erythrocyte sedimentation rate, clotting screen, anticardiolipin antibodies, lupus anticoagulant, antithrombin III, C3, C4, CH50, protein C and protein S, VDRL, TPHA, autoimmune screen, electrocardiogram, chest X-ray, carotid Doppler studies and both transthoracic and transoesophageal echocardiography. All these investigations were normal.

Computed tomography of his brain was performed 24 hours after admission. This confirmed an infarct involving the right posterior external capsule, upper part of the internal capsule and corona radiata.

The patient was treated with low dose aspirin and entered a rehabilitation programme. He is making reasonable progress with intensive physiotherapy, but still has marked residual left-sided weakness.

Discussion

The first reports of acute stroke secondary to substance abuse were in the 1970s and were initially received with general scepticism, but the number of reported cases has greatly increased since 1983 with the introduction of the cocaine free-base, 'crack'.³ There are

Department of
Medicine, University
Hospital of Wales,
Heath Park, Cardiff
CF4 4XX, UK
TM Lawson
A Rees

Accepted 12 January 1996