



## RESEARCH LETTERS

### Hepatitis A. An uncommon associated pathology

#### *To the Editor*

Hepatitis A is a usually benign and self-limited disease in paediatric age, however, 15% of the cases can have some kind of complication. Mortality is low (less than 1/1000), and hepatitis A virus infection can be subclinical, anicteric or icteric. This variability is correlated to age, and the forms are milder in children under 6 years in which only 10% are icteric. These figures reach up to 70–80% in children above 14 years.

Atypical (very rare) presentations have classically been described, especially in adults, such as cholestatic, recurring or fulminant hepatitis A and in the last few years it has been associated to different extra-hepatic complications or manifestations such as pleural effusion, thrombopenia, etc., which are more frequent when associated to another type of viral hepatitis and in adults.

The case of a 6-year-old patient with hepatitis A is presented with associated pleural effusion, thrombopenia, leucopenia, hypoproteinaemia, coagulopathy and exanthema with spontaneous evolution to curing, which is commonly described in the literature.

A 6-year-old school child consulting for fever of up to 39 °C, abdominal pain, asthenia and anorexia with an evolution of 6 days. Forty-eight hours after the onset of the symptoms, he presented generalised pruriginous urticarial exanthema with petechial elements prevailing in the lower limbs. He was diagnosed with gastroenteritis and allergic reaction and was treated with diet and dexchlorpheniramine. He was sent to this hospital for thrombopenia. It should be emphasised for the record that he was not born in Spain, although he has lived here since he was a month old. He visited his birthplace 10 months ago. There is no other family or personal history of interest.

His physical examination on admission was: weight 18 kg. Good general condition. Palpable peripheral pulses and normal revascularisation time. Acceptable nutrition and hydration. Cardiopulmonary auscultation: rhythmic, without murmurs, good bilateral ventilation, without pathological noises. Abdomen soft and depressible, hepatomegaly at 4–5 cm under costal margin. Normal pharynx. Normal otoscopy. At skin level, he presented macular exanthema in cheeks and pruriginous trunk. In lower limbs, he presented non-painful purpuric elements with a diameter

of approximately 1 cm, especially on the back of the feet and pretibials. Normal neurological examination.

Supplementary test were done to the child to admission: Haemogram: haemoglobin 11.4 g/dl, hematocrit 34%, leukocytes 2860/microL, (picture: N 54%, L 31.1%, M 9.8%). Platelets 25,000/microL; Biochemistry: Normal ions. Normal creatinine and urea. Total proteins 5.4 g/dl, albumin 2.3 g/dl. C-reactive protein 17 mg/dl. Total bilirubin 3 mg/dl, GOT/GPT 212/83, alkaline phosphatase 67 U/L and GGT 24 U/L; Normal coagulation; Normal chest X-ray upon admission (Figure 1).

He was admitted with fluidotherapy. Antipyretic-analgesic drugs and antibiotics (cefotaxime 11 days) were prescribed due to the rise of C-reactive protein. He was also subjected to isolation enteric. Serial analytical controls were performed with the slow recovery of the platelet figures. Abdominal ultrasound scan (8th day of admission):



Figure 1 Normal chest X-ray upon admission.



**Figure 2** Opacification of the right pulmonary field.

hepatomegaly without evidence of focal lesions and non-partitioned right pleural effusion; the rest is normal.

He suffered a progressive clinical worsening (until the tenth day of admission), with the onset of generalised jaundice, hypoventilation in right pulmonary field, without presenting respiratory difficulty, with a rise of liver enzyme figures of up to GOT/GPT 387/697 and alkaline phosphatase 312, total bilirubin 4.9, with direct bilirubin 3.35 and GGT 273 and coagulation disorder (prothrombin activity 39%). There was evidence of progression of the pleural effusion until the opacification of the right pulmonary field (Figure 2), continuing without any important clinical repercussion (thoracentesis was not authorised) with venous blood-gas (10th day of admission): normal.

During admission serology was done: Brucella, Salmonella, Rickettsia Chlamydia negative. Cytomegalovirus IgG positive. Hepatitis B and C virus, HIV, toxoplasma, varicella-zoster and parvovirus negative. Rubella, cytomegalovirus and herpes simplex 1 and 2 virus IgG positive. Hepatitis A virus IgM positive; Supplement: C3 47 mg/dl and C4 0.72 mg/dl; Autoimmunity: antiphospholipid and anticardiolipin antibodies positives: 1/320; Normal ammonium. Normal renal function study. Abnormal and normal urine sediment. Urine culture, haemoculture and pharyngeal smear culture negative. Mantoux negative. Normal cardiological study (cardiopulmonary auscultation, electrocardiogram and Doppler echocardiography).

Around the 12th day of admission he presented a progressive improvement, and had no fever, with a fast reduction of the pleural effusion, disappearance of fever and improvement of hepatopathy and jaundice. When he was discharged, the liver enzymes had decreased, coagulation and the chest X-ray were normal and he was asymptomatic.

Our diagnosis was: Hepatitis A, Pleural Effusion, Thrombopenia, Hypoproteinaemia and Coagulopathy.

In subsequent controls, the normalisation of all the clinical and analytical parameters was observed. In the last check-up, the autoimmunity studies showed normal results.

Pleural effusion has been described as a rare extra-hepatic complication of acute viral hepatitis<sup>1-5</sup>, but it is considered to be a rarer complication in the case of hepatitis A<sup>1</sup>. There are very few published cases, especially

in children, and nine cases have been found in the literature search conducted. In most of the reviewed cases, it does not cause any important clinical features and is usually spontaneously resolved<sup>1,3</sup>, despite the fact that the actual hepatitis causes mortal liver failure<sup>2</sup>. As the main characteristics: its onset is usually in the pre-icteric stage or at the end of the icteric stage<sup>1,2</sup> (as in the case presented), it usually relates to transudates (especially in relation to hepatitis A), in which anti-VHA<sup>2</sup> IgM has been detected; it is occasionally also associated to ascites, even pericarditis<sup>4</sup> (not in this case) and frequently located in the right hemithorax<sup>1</sup>. The mechanism through which it occurs is unknown but it does not seem to be correlated to clinical evolution or to a worse prognosis of the disease; some authors defend autoimmune etiology (mediated by immunocomplexes)<sup>3</sup>, other authors defend parainflammatory etiology (as a result of liver inflammation).

Association between infectious disease (viral, bacterial or parasitic) and presence of autoantibodies in individuals who do not have autoimmune disease, but genetically predisposed, has been described<sup>6</sup>. HAV infection with lupus-like syndrome has also been associated with arthralgia, exudative pleural effusion and cells and antibodies of lupus erythematosus (antinuclear antibodies, anti-ds-DNA and anticardiolipin antibodies) also associated with impaired liver function with liver biopsy and diagnosis of acute hepatitis with submassive hepatic necrosis with hepatic function recovery and disappearance of antibodies after a short course of steroids. It has also been observed after measles and Epstein-Barr virus infection<sup>7</sup>. Others articles discuss the frequency which antiphospholipid antibodies are found, mainly anticardiolipin, associated with viral infections<sup>8</sup> (as in our case) and the presence of anti-cytoplasmic antibodies associated with HAV infection<sup>9</sup>. In all cases, these autoimmune features disappeared after treatment with steroids<sup>6,7</sup>.

Thrombopenia has been described in relation to some types of hepatitis, especially hepatitis B and C, however it is uncommon in hepatitis A; its evolution is benign and self-limited<sup>5</sup>. A peripheral platelet destruction is proposed to explain it, since normal megakaryocytes have been found in bone marrow<sup>4</sup>; this destruction can be explained by an autoimmune mechanism (by circulating immunocomplexes, antiplatelet antibodies or by the development of antiphospholipid or transient anticardiolipin antibodies)<sup>5</sup>. Six cases of thrombocytopenic purpura associated to hepatitis A have been described in children and adolescents up to 2005. Some of them needed transfusions<sup>4</sup> or treatment with intravenous immunoglobulin<sup>5</sup>, with a favourable evolution of the disease in all of them.

Several types of exanthemas have been described as prodromes in hepatitis, predominantly in adults and associated to hepatitis B. In this case, it was labelled as an allergic reaction, although he presented characteristics of vasculitis upon admission.

In conclusion, it is very likely that in developed countries the clinical pattern of hepatitis A undergoes important changes, because when the age of presentation increases due to the improvement of the healthcare conditions, the risk of suffering from complications increases.

In this case, it is believed that the complications are due to autoimmune mechanisms, because of the rise of the

antiphospholipid and anticardiolipin antibodies in the acute stage.

Hepatitis A is usually a benign and self-limited disease, but special attention must be paid to its complications when they occur.

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## Prick test: A survey and comparison between Iranian allergic children and adults

### To the Editor:

Allergic respiratory diseases such as asthma and rhinitis are common disorders which have grown considerably during the past 30 years with no doubt due to the world being more industrialised. Allergic rhinitis (AR) may simply affect man during almost any stages of life. Among causative allergens, aeroallergens have received more attention. It seems rational that recognition of high load responsible aeroallergens using a simple and inexpensive method such as skin prick test (SPT) within each specific area may improve the understanding of the pathologic patterns and ultimately give rise to more efficient treatment protocols.

All of the patients with the diagnosis of AR referred to the Research Center for Allergy & Asthma in Rasoul-e-Akram Hospital in Tehran, Iran between March 2007 and March 2008 were recruited in this cross-sectional study. Patients with a history of immunotherapy, dermatographism, chronic steroids use and individuals younger than four years were excluded. After taking written informed consent from patients or guardians, all were provided with the questionnaires for medical records and baseline characteristics (e.g. gender, age, and family history of atopy). Patients were divided into two age categories: children <21 years and adults ≥21 years based on the American Academy of Pediatrics limits.<sup>1</sup>

All patients' sera and nasal smear were obtained for measuring the total IgE (ELISA method, Padtan Elm, Iran) and nasal smear eosinophilia (Gimsa staining), respectively. After enrolment, they were subjected to SPT by prick puncture test and the result was carefully graded for the widest wheal diameter [0 (<3 mm); 1+ (3–3.99 mm); 2+ (4–5.99 mm); 3+ (6–8.99 mm); and 4+ (≥9 mm or pseudopodia)]. The patients under confounding medication such as antihistamines and topical corticosteroids which interfere with SPT interpretation were asked to withhold them for a certain period based on the allergist's discretion.

Allergenic extracts (Allergopharma, Germany) included pollens (weeds, grass and trees), mites and moulds (*Penicillium Notatum*, *Aspergillus Fumigates*). Weeds were *Oxeye daisy*, *Sorrel*, *Lambs quarter* and three weeds mix (*Nettle*, *English Plantain*, *Dandelion Taraxacum Vulgare*). Grasses were *Barley*, *Vernal* and six grasses mix: *Velvet*, *Orchard*, *Rye (Lolium perenne)*, *Timothy*, *Kentucky Blue* and *Meadow Fescue*. Tree extracts provided with early boom sing (*Birch*, *Beech*, *Oak* and *Plane*) and mid-boom sing [*Alder*, *Hazel*, *Poplar*, *Elm (Ulmus Scabra)* and *Willow*].

To test the differences between parametric and non-parametric variable means in groups of the study, Independent T-test and Mann-Whitney U-test were used, respectively. A Chi<sup>2</sup> statistical test was also used to evaluate the possible statistical differences in the distribution of qualitative variables among different groups of the study. A Spearman's rho test was used to assess the correlations between continuous variables. Receiver operating characteristics (ROC) curve analysis was also performed to evaluate the predictability of positive SPT with total serum IgE and a cut-off point was determined. A 5% probability of a type I error (two-tailed), and a power of 80% were