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Seronegative autoimmune hepatitis in children: Spectrum of disorders

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ABSTRACT

Background: A few children with acute or chronic liver disease display histological features compatible with autoimmune hepatitis, but lack specific serological markers.
Aim: To describe features, management and outcome of childhood seronegative autoimmune hepatitis.
Methods: From 1988 to 2010, 38 children were included under the following criteria: negative virological studies, no serum autoantibodies, exclusion of other causes of liver diseases, and liver histology compatible with autoimmune hepatitis.
Results: Four groups were identified: (1) 12 with increased serum gamma globulin concentrations; (2) 10 with normal or low serum gamma globulins and no combined blood disease; (3) 10 with combined aplastic anemia; and (4) 6 with peripheral thrombocytopenia with/without neutropenia. Immunosuppressive treatment was associated with aminotransferases normalization in all but one child who required liver transplantation. Relapses occurred in 10 children. Lymphocytopenia was found at the time of the diagnosis of hepatitis in 13 children, 12 in groups 3 or 4. All 38 children are alive after 4–17 years, 18 still under immunosuppression.
Conclusions: Childhood seronegative autoimmune hepatitis includes a spectrum of disorders. Early liver histology is recommended and, if compatible with autoimmune hepatitis, immunosuppressive treatment should be started. Initial lymphocytopenia may indicate future hematological complication.
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1. Introduction

In children, there are two main etiological groups of acute or chronic hepatitis: (1) viral hepatitis due to hepatitis viruses or to occasionally hepatotropic viruses; in such cases, the presence of specific IgM antibodies or viral nucleic acid sequences or antigens in the blood allows a precise diagnosis; (2) autoimmune hepatitis, characterized by high titers of organ- and non-organ-specific antibodies, usually increased levels of gamma-globulins, a peculiar histopathological pattern, sensitivity to immunosuppressive treatment and a propensity to relapses [1–5].

In a child presenting with hepatitis, when no specific viral or autoimmune markers are identified, other causes of liver disease are searched for, including drug-induced or metabolic diseases, mostly Wilson's disease in children after the age of 3, and also, among others, biliary diseases or malignant conditions infiltrating

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the liver. There are however instances when none of the known causes are found.

In adults patients who lack exposure to hepatotoxic medication, consume <25 g of alcohol daily, are negative, at presentation, for specific auto-antibodies commonly present in auto-immune hepatitis anti-nuclear (ANA), anti-smooth muscle (SMA), anti-liver-kidney microsome (anti-LKM1), anti-liver cytosol (anti-LC1) and anti-mitochondrial antibodies (AMA), and lack laboratory or histological features of a viral, hereditary, or metabolic disorder, but have histological features of interface hepatitis, the designation of autoantibody-negative autoimmune hepatitis is used. The existence of autoantibody-negative autoimmune hepatitis has been suggested by studies that have shown clinical similarities with the classical disease and corticosteroid-responsiveness [6]. Currently there are no series involving pediatric patients with presumed autoantibody-negative autoimmune hepatitis.

The aim of this study is to describe the clinical, biochemical, histological and evolutionary features of children investigated for acute or chronic hepatitis of apparently unknown origin, but with histological features compatible with an autoimmune origin. For the purpose of this study we will refer to such condition as "seronegative autoimmune hepatitis".

2. Patients and methods

Medical records of all new diagnosis of acute and chronic hepatitis from 1988 to 2010 at the Pediatric Hepatology Unit of Kremlin-Bicêtre Hospital, France and Pediatric Gastroenterology Unit of Pisa University Hospital, Italy were analyzed. Acute hepatitis was defined as a clinically symptomatic liver disease with or without jaundice with raised aminotransferase serum activity. Chronic hepatitis was defined as a liver disease with persisting evidence of active liver damage for more than 6 months.

Criteria for inclusion in the study were as follows: (1) a liver disease presenting as acute or chronic hepatitis characterized by an increase in serum transaminase activity with or without jaundice; (2) exclusion at admission or on frozen stored serum collected at that time, depending on the acute or chronic presentation, of hepatitis A (anti-HAV IgM negative), hepatitis B (HBsAg and anti-HBc negative), hepatitis C (negative HCV RNA and/or HCV serology), hepatitis E (anti-HEV IgM negative). Exclusion of recent infection by EBV and CMV, by negative specific IgM and/or blood nucleic acid testing (NAT). HHV-6, Parvovirus B 19, Adenovirus and Enterovirus infections were studied by blood NAT in 25, 28, 23 and 21 children respectively. Herpes simplex virus infection was ruled out by specific IgM and/or NAT in 22 children (Table 1); (3) absence in serum at the time of diagnosis of any of the 4 organ- and non-organ-specific auto-antibodies commonly present in children with auto-immune hepatitis [7] (Table 1); (4) exclusion, by published criteria, liver ultrasonography and liver histology and follow-up of known causes of liver diseases, in particular drug-induced liver disease by patient history, metabolic diseases including Wilson's disease (serum ceruloplasmin > 20 mg/dl, urinary copper < 40 μg/day as well as non suggestive liver histology) and alpha-1-antitrypsin deficiency (serum alpha-1-antitrypsin concentration > 100 mg/dl) (Table 1); (5) available liver histology, at the time of diagnosis (by percutaneous liver biopsy in 27 children, transjugular in 8, surgical in 2 and by examination of the explanted liver in one child). The pathologist was not blinded to the clinical information. In all children, the pathologist's most likely diagnosis was autoimmune hepatitis, based on published criteria [8,9]. Liver histology was scored by METAVIR score [10]. The time of diagnosis was defined as the time when liver histology was performed and decision of immunosuppressive therapy was made. Common liver biochemical tests, prothrombin time and coagulation factor V, serum albumin concentration, serum gamma globulins and/or immunoglobulin G concentrations and blood cell counts with differentials were recorded at the time of diagnosis and during follow-up. Autoantibodies, ANA, SMA with anti-actin specificity, AMA anti-LKM1 and anti-LC1, were searched for by indirect immunofluorescence on rat organ slices and colchicine-treated Hep-2 cell monolayer. The search for anti-soluble liver antigen (SLA) by an inhibition ELISA was negative in all 29 children tested. The same methods were used throughout the period of study and in the two separated centers.

Table 1
Results of blood and urinary tests for viruses, autoantibodies, Wilson's disease and alpha-1-antitrypsin deficiency in 38 children who presented with hepatitis of unknown origin. For each test results indicate the number of times the test was positive in a given group over the number of times this test was performed in this group.

Test	Total (38 pts)	Group 1 (12 pts)	Group 2 (10 pts)	Group 3 (10 pts)	Group 4 (6 pts)
Anti hepatitis A virus IgM	0/37[a]	0/11[a]	0/10	0/10	0/6
HBs Ag and anti HBc	0/38	0/12	0/10	0/10	0/6
Hepatitis C PCR and/or antibody	0/38	0/12	0/10	0/10	0/6
Anti hepatitis E virus IgM	0/32[a]	0/9[a]	0/8[a]	0/10	0/5[a]
Anti CMV IgM and/or NAT	0/38	0/12	0/10	0/10	0/6
EBV anti VCA IgM and/or NAT	0/38	0/12	0/10	0/10	0/6
Anti HSV IgM and/or NAT	0/22	0/4	0/8	0/6	0/4
Human herpes virus 6 NAT	1/25	1/5	0/5	0/9	0/6
Parvovirus B19 NAT	0/28	0/6	0/7	0/9	0/6
Enterovirus NAT	0/21	0/4	0/5	0/9	0/3
Adenovirus NAT	0/23	0/5	0/5	0/10	0/3
Anti smooth muscle	0/38	0/12	0/10	0/10	0/6
Antinuclear	0/38	0/12	0/10	0/10	0/6
Anti liver kidney-microsome 1	0/38	0/12	0/10	0/10	0/6
Anti liver cytosol 1	0/38	0/12	0/10	0/10	0/6
Anti mitochondrion	0/37	0/11	0/10	0/10	0/6
Anti soluble liver antigen	0/30	0/7	0/8	0/9	0/6
Serum ceruloplasmin < 20 mg/dl	0/33	0/8[b]	0/9[b]	0/10	0/6
24 h urinary copper > 40 μg	0/33	0/8[b]	0/9[b]	0/10	0/6
Serum alpha 1 antitrypsin < 100 mg/dl	0/38	0/12	0/10	0/10	0/6

CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; NAT, nuclear acid testing; pts, patients; SLA, soluble liver antigen; VCA, viral-capsid antigen; Group 1, children with increased serum gammaglobulin concentration; Group 2, children with no increase in serum gammaglobulin concentration and no combined aplastic anemia or peripheral thrombocytopenia and/or neutropenia; Group 3, children with combined aplastic anemia; Group 4, children with peripheral thrombocytopenia with or without neutropenia.

[a] Not tested in some children who presented with biochemical signs of unresolving liver disease for more than 6 months before the time of diagnosis.

[b] Not tested in some children who presented with signs of liver disease before the age of 3 years.

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