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# Clinical features and biochemical data of Caucasian children at diagnosis of autoimmune hepatitis

R. Oettinger, A. Brunnberg, P. Gerner, P. Wintermeyer, A. Jenke, S. Wirth*

*HELIOS Children's Hospital Wuppertal, Witten-Herdecke-University, Heusnerstrasse 40, 43283 Wuppertal, Germany*

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**Abstract**

Objective: Evaluation of systematic epidemiological data regarding clinical characteristics, sex distribution and autoantibody pattern in Caucasian children with autoimmune hepatitis (AIH).

Study design: Data of 142 children presenting with AIH (97 girls and 45 boys) have been analysed for their clinical, serological, and histological profile.

Results: Clinical findings were jaundice (58%), unspecific weakness (57%), anorexia (47%), abdominal pain (38%) and paleness (26%). One hundred and three children (73%) (68 girls, 35 boys, 1.9:1) had AIH type 1 and 35 patients (25%) (27 girls, 8 boys, 3.4:1) type 2 due to specific autoantibodies. Four children could not be classified. Histology of 122 children revealed active hepatitis in 64 (52%), cirrhosis in 46 (38%), and mild inflammatory activity in 12 individuals (10%). The most prevalent HLA type was B8.

Conclusion: In our cohort the prevalence of AIH was half as frequent in boys as in girls. Type 1 was the most frequent diagnosis (73%) and was more prevalent in older children. Type 2 was equally age distributed. The clinical presentation of AIH in children was unspecific and type I and type II could only be differentiated by the determination of the specific autoantibodies. Ninety percent of patients presented with high inflammatory activity or liver cirrhosis.


*Keywords:* Autoimmune hepatitis type 1, type 2; Children; Autoimmune liver disease

## 1. Introduction

Autoimmune hepatitis (AIH) in childhood is a rare chronic progressive liver disorder. Characteristic laboratory findings include the detection of antibodies against certain tissue antigens, elevated serum liver enzymes and gamma globulins [1,2]. Histological examination usually reveals mononuclear cell infiltration in the portal tracts with fibrosis and/or cirrhosis to a variable extent. Despite viral infections as possible trigger factors and the frequent presence of some specific HLA allotypes, reflecting a genetic background, aetiology finally remains unknown [3–7].

According to the pattern of detected antibodies two major forms of autoimmune hepatitis are differentiated. Autoantibodies characterizing type 1 are anti-nuclear antibodies (ANA), anti-smooth muscle antibodies (SMA) and anti-soluble liver protein antibodies (SLA). Type 2 is defined by the detection of liver–kidney microsomal autoantibodies (LKM1) and/or liver cytosol 1 antigen (LC1) autoantibodies [1].

Without immunosuppressive treatment it is only a matter of time until the liver disease proceeds to liver

*Abbreviations:* AIH, Autoimmune hepatitis; ANA, Anti-nuclear antibodies; SMA, Anti-smooth muscle antibodies; SLA, Anti-soluble liver protein antibodies; ESR, Erythrocyte sedimentation rate; LKM1, Liver–kidney microsomal autoantibodies; LC1, Liver cytosol 1 antigen; HAI, Hepatitis activity index.

* Corresponding author. Tel.: +49 202 8963833; fax: +49 202 8963834.

*E-mail address:* s-k-wirth@t-online.de (S. Wirth).

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cirrhosis. Unfortunately many patients do not reveal significant clinical features at least in an early silent phase of the disease. Thus, it may last for months or not seldom for years until the final diagnosis has been established, and a considerable number of patients is going to present with liver cirrhosis. There are only a very small number of reports on larger series of children reflecting upon the allocation of subtype, sex distribution, clinical features and laboratory characteristics in correlation with age. In terms of these issues in most countries systematic epidemiological data are not available to date. Nevertheless, these informations are the basis for synchronization of treatment, determination of prognostic factors and improvement of long-term outcome [2,8].

The aim of this study was both to define the clinical features, biochemical and histological findings and to determine the age and sex related distribution of autoimmune hepatitis type 1 and 2 in a large Caucasian paediatric study cohort.

## 2. Patients and methods

Between January 1995 and December 2003 a nationwide survey on prevalent and incident cases of AIH in children and adolescents under 16 years of age was carried out. During the first 3 years the survey was performed by the ESPED registry for rare paediatric disorders in Germany. Inquiries were mailed to all children hospitals in Germany asking for the occurrence of AIH. For each case reported, a standard questionnaire was sent to the physician. During the second period registration was continued by collecting reports of cooperating paediatric gastroenterologists and paediatricians using the same standard questionnaire.

The questionnaire requested anonymous data on demographic patient characteristics, presented clinical signs and symptoms, biochemical and histological findings and treatment. The study was coordinated by the corresponding author and the data collected were based on the reports of single centres. Deliberately no attempts were made to collect sera and biopsies in the same laboratory.

AIH in children was diagnosed after excluding an infection with hepatitis A-, B- and C-virus, alpha-1-antitrypsin deficiency, Wilson's disease and other metabolic liver diseases and disorders of the biliary tract. A modified scoring system according to Johnson and McFarlane [9] was applied to each patient. The most important criteria of the scoring system include significant titres of autoantibodies (ANA, SMA, SLA, LKM1), hypergammaglobulinaemia with elevation of serum IgG, seronegativity for viral hepatitis infections and positive response to immunosuppressive treatment.

### 2.1. Case registration

The response rate to the general ESPED registry was 94% in 1995–1997. Two hundred and twenty-six cases with unknown hepatopathy or probable AIH were reported and inquiries were sent to the responsible physicians. One hundred and forty-five responded but 47 cases had to be excluded because of age older than 16 or diagnosis of AIH was unlikely. Ninety-eight children were definitively classified as autoimmune hepatitis. Between 1998 and 2003 additionally 44 well-documented cases were reported meeting the criteria for AIH.

### 2.2. Autoantibodies

Tissue autoantibodies were tested with commercially available assays. Immunofluorescence tests (IFT) were used for ANA and SMA and immunoblots were applied to detect SLA and LKM1 antibodies. IFT titres equal or higher than 1:40 were considered positive.

### 2.3. HLA typing

Typing of major HLA types from lymphocytes was performed in 47 children using microcytotoxicity tests according to standard procedures following the recommendations of the manufacturer. As reference population the HLA distribution of 157 healthy adults (94 women, mean age $29 \pm 10$ years; 63 men, mean age $31 \pm 11$ years) of a German district around Halle/Saale was kindly provided by H. K. Machulla, Institut for Medical Immunology, University of Halle/Saale, Germany. The HLA typing of the control population was performed by using both the microcytotoxicity test and additionally the polymerase chain reaction with HLA sequence specific primers.

### 2.4. Statistic evaluation

Statistic calculation of HLA type distribution was done by using the Fisher's exact test.

## 3. Results

Data from 142 children were available, 97 girls and 45 boys (2.2:1) aging from 11 months to 15 years (mean age 9.5 years). One hundred and thirty were of German, 4 of Turkish and 8 of East European origin. Overall, the highest proportion of both males and females had come to observation between 10 and 16 years. The age distribution at the time of diagnosis also stratified by gender and AIH type is reported in Fig. 1.