

Application of Newer Diagnostic Modalities for Childhood Autoimmune Hepatitis

THESIS

Submitted For Partial Fulfillment of M.D. Degree

IN
PEDIATRICS
BY

Marwa Mohamed Safey El Deen Abo El Snoon
(M.B.B.Ch., M.Sc.)

UNDER SUPERVISION OF

Prof. Dr. Hanaa El-Karaksy

Professor of Pediatrics
Faculty of Medicine
Cairo University

Prof. Dr. Nehal El-Koofy

Professor of Pediatrics
Faculty of Medicine
Cairo University

Prof. Dr. Mona Aziz

Professor of Clinical Pathology
Faculty of Medicine
Cairo University

Faculty of Medicine

Cairo University

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ABSTRACT

Background: AIH and cryptogenic chronic hepatitis are important causes of liver failure in children. No single clinical or biochemical test proves the presence of AIH.

Aim: The aim of this study was both to apply the IAIHG scoring system and testing for SLA and pANCA in children with AIH and cryptogenic CLD.

Materials and methods: The study included 28 children with AIH, 15 with cryptogenic CLD and 40 healthy age and sex matched children as controls. The patients' clinical, laboratory, and histological data have been analyzed. The IAIHG scoring system was used to score patients both before and after treatment.

Results: SLA antibody was positive in 17.8% and pANCA in 32% of AIH cases. The IAIHG score was applied before treatment to 24 AIH cases as liver biopsy was not available for 4 cases; 14 (58.4%) scored as definite AIH and 10 (41.6%) scored as probable AIH. When score was reapplied after therapy; one out of the 10 cases with probable AIH was shifted to the definite group and vice versa one of the definite AIH cases was shifted to the probable group. Nine (60%) of cryptogenic CLD patients was scored as probable AIH.

Conclusion: No factor by itself can contribute to the diagnosis of AIH in children. SLA is an additional diagnostic marker for type 1 AIH. pANCA is useful for diagnosis of AIH especially in patients seronegative to conventional autoantibodies. The IAIHG score can be used in diagnosis of AIH in children with a need for more simplified scoring system for every day use.

Key words: Autoimmune Hepatitis - AIH Scoring System – Soluble Liver Antigen - Cryptogenic Chronic Liver Disease – Children.

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LIST OF ABBREVIATIONS

AIC	Autoimmune Cholangitis
AIH	Autoimmune Hepatitis
AILD	Autoimmune liver disease
AIRE	Autoimmune Regulator
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
AMA	Antimitochondrial Antibodies
ANA	Antinuclear Antibodies
ANCA	Antineutrophil Cytoplasmic Antibodies
APC	Antigen-presenting cells
APS-1	Autoimmune Polyendocrine Syndrome type 1
ASC	Autoimmune Sclerosing Cholangitis
ASGPR	Asialoglycoprotein Receptor
AST	Aspartate Aminotransferase
CAH	Chronic Active Hepatitis
CCH	Cryptogenic chronic hepatitis
CD	Celiac disease
CLD	Chronic Liver Disease
CMV	Cytomegalovirus
DILI	Drug-induced liver injury
EBV	Epstein Barr Virus
ELISA	Enzyme-Linked Immunosorbent Assay
GGT	Gamma Glutamyl Transpeptidase
HAV	Hepatitis A virus
HBcAb	Hepatitis B core Antibody
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDV	Hepatitis D virus
HEV	Hepatitis E virus
HLA	Human Leukocyte Antigen

HSV	Herpes Simplex virus
IAIHG	International Autoimmune Hepatitis Group
IBD	Inflammatory Bowel Disease
IDDM	Insulin Dependant Diabetes Mellitus
IFN- γ	Interferon-gamma
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IIF	Indirect Immunofluorescence
IL	Interleukin
LE	Lupus Erythematosus
LC-1	Liver Cytosolic Antigen 1
LKM	Liver-Kidney Microsomal
LP	Liver-pancreas Antigen
LSP	Liver specific protein
MHC	Major Histocompatibility Complex
NK	Natural Killer
pANCA	perinuclear Antineutrophil Cytoplasmic Antibodies
pANNA	perinuclear Antineutrophil nuclear antibodies
PBC	Primary Biliary Cirrhosis
PBS	Phosphate buffered saline
PCR	Polymerase Chain Reaction
PSC	Primary Sclerosing Cholangitis
SAIH	Seronegative autoimmune hepatitis
SD	Standard Deviation
SLA	Soluble Liver Antigen
SLE	Systemic Lupus Erythematosus
SMA	Smooth Muscle Antibodies
SPSS	Statistical Package for Social Sciences
Tc	T cytotoxic
TGF- β	Transforming Growth Factor β
TNF- α	Tumour Necrosis Factor Alpha
ULN	Upper limit of normal value

UNL	Upper Normal Limits
UDCA	Ursodeoxycholic acid
VZV	Varizella zoster virus

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تطبيق وسائل جديدة لتشخيص الالتهاب الكبدي المناعي في الأطفال

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مقدمة من

الطبيبة/ مروه محمد صفى الدين أبو السنون

تحت إشراف

الأستاذة الدكتورة/ هناء القراقصى

أستاذ طب الأطفال

كلية الطب - جامعة القاهرة

الأستاذة الدكتورة/ نهال الكوفي

أستاذ طب الأطفال

كلية الطب - جامعة القاهرة

الأستاذة الدكتورة/ منى عزيز

أستاذ الباثولوجيا الإكلينيكية

كلية الطب - جامعة القاهرة

كلية الطب

جامعة القاهرة

٢٠٠٩

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INTRODUCTION AND AIM OF THE WORK

Autoimmune hepatitis (AIH) is a chronic progressive inflammatory liver disease characterized by an inflammatory liver histology, circulating non-organ specific autoantibodies and increased levels of immunoglobulin G (IgG) in the absence of a known etiology (**Mieli-Vergani and Vergani, 2003**).

Autoimmune liver disease (AILD) in children progresses to cirrhosis and liver failure if not diagnosed and managed in time. Early diagnosis and immunosuppressive treatment are essential in preventing severe liver damage. Unfortunately, lack of diagnostic certainty in establishing a diagnosis can lead to delay in treatment and the continued progression of the disease (**Yachha et al., 2001**).

AIH is classified into three serological subgroups: antinuclear (ANA) and smooth muscle antibody (SMA)- positive in type 1, liver-kidney microsomal antibody (LKM) -positive in type 2 and soluble liver antigen (SLA) antibody - positive in type 3 AIH (**Strassburg and Manns, 2002**).

Autoantibodies against SLA show a high specificity for AIH (**Luxon, 2003**). Several reports have shown that many patients with AIH negative for ANA and SMA show positive SLA reactivity, making these antibodies an important diagnostic marker (**Ballot et al., 2000**).

SLA autoantibodies are the only immunologic marker found in 15–20% of hepatitis cases previously considered cryptogenic. In about 13% of cryptogenic hepatitis patients, initially seronegative, detection of SLA autoantibodies contributed to their diagnostic clarification (**Manns and Strassburg, 2001; Ballot et al., 2003**).