HEPATIC IMPAIRMENT IN TYPE 1 DIABETES MELLITUS

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Abstract

Key words: Children – type 1 diabetes mellitus - hepatic affection

The aim of this study was to determine the prevalence of hepatic impairment in children with type-1 diabetes and to investigate the underlying etiology. The study was carried out on 692 children with type-1 diabetes. Their mean age was 9.65± 4.2. They were 333 (48.1%) males and 359 (51.9%) females. Sixty (8.7%) children showed liver affection. Clinical hepatomegaly was present in 12 (1.7%) children, elevated ALT in 25 (3.6%) children, positive HCV in 25 (3.6%) children and abnormal hepatic ultrasound in 31 (4.5%) children.

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List of abbreviations

A1C: glycosylated hemoglobin
AAP: American Academy of Pediatrics
ACE: angiotensin converting enzyme
ADA: American Diabetes Association
AFP: alpha-fetoprotein
AGEs: Advanced glycation end products
AIC: autoimmune cholangitis
AIH: autoimmune hepatitis
AIRE: autoimmune regulator gene
ALP: alkaline phosphatase
ALT: alanine aminotransferase
AMA: antimitochondrial antibodies
ANA: antinuclear antibody
anti-ASGPR: asialoglycoprotein receptor
anti-LC-1: anti-cytosol antibodies type 1
APCs: antigen-presenting cells
APECED: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
Apo: apolipoprotein
APS-1: autoimmune polyglandular syndrome type 1
AST: aspartate aminotransferase
BCG: bacillus Calmette Guerin
BMI: body mass index
CDC: Centers for Disease Control and Prevention
CHB: chronic hepatitis B
CMV: Cytomegalovirus
Co: cut-off
CRP: C-reactive protein
CT: computed tomography
CYPs: cytochrome P450
DEMPU: Diabetes Endocrine Metabolic Pediatric Unit
DKA: diabetic ketoacidosis
DM: Diabetes Mellitus
DNA: deoxyribonucleic acid
EBV: Epstein-Barr Virus
e.g.: for example
ELISA: enzyme-linked immunosorbent assay
FDA: Food and Drug Administration
FFA = free fatty acids
FPG: Fasting plasma glucose

GAD65: autoantibodies to glutamic acid decarboxylase
GDM: Gestational Diabetes Mellitus
GGT: Gamma glutamyl transpeptidase
gm/kg: gram /kilogram body weight
HAI: histological activity index
HAV: hepatitis A virus
HBc Ag: hepatitis B core antigen
HBe Ab: hepatitis B e antibody
HBe Ag: hepatitis B e antigen
HBIG: hepatitis B virus immunoglobulin
HBs Ab: hepatitis B surface antibody
HBs Ag: hepatitis B surface antigen
HBV: hepatitis B virus
HCC: hepatocellular carcinoma
HCV: hepatitis C virus
HCV Abs: HCV antibodies
HDL: high density lipoprotein
HDV: hepatitis D virus
HDV Ag: hepatitis D virus antigen
HEV: hepatitis E virus
HIV: human immunodeficiency virus
HLA: human leukocyte antigen
HSV: Herpes Simplex Virus
IA-2 & IA-2 ß: autoantibodies to the tyrosine phosphatases
IAAs: autoantibodies to insulin
ICAs: islet cell autoantibodies
i.e.: that is to say
IFG: impaired fasting glucose
IFNα: interferon alpha
IGT: impaired glucose tolerance
Ig A: immunoglobulin A
Ig G: immunoglobulin G
Ig M: immunoglobulin M
IL: interleukin
ISPAD: International society for pediatric and adolescents diabetes
KICA: ketoisocaproic acid
LDL: low density lipoprotein
LKM: liver kidney microsomal antibodies
mg/dl: milligram /deciliter
MHC: major histocompatibility complex
mmHg: millimeter mercury
MMR: measles, mumps and rubella vaccine
MODY: maturity onset diabetes of the young

MRI: magnetic resonance imaging
n: number
NAFLD: nonalcoholic fatty liver disease
NASH: nonalcoholic steatohepatitis
ng/mL: nanogram /milliliter
OGTT: oral glucose tolerance test
pANCA: perinuclear antineutrophil cytoplasmic antibodies
PAS: periodic acid-Schiff
PBC: primary biliary cirrhosis
PC: prothrombin concentration
PCR: polymerase chain reaction
PEG IFN: pegylated interferon
PNL: polymorph nuclear leucocytes
PT: prothrombin time
PSC: primary sclerosing cholangitis
RIBA: recombinant immunoblot assay
RNA: ribonucleic acid
RT-PCR: reverse transcriptase- polymerase chain reaction
S/Co: sample optical density / cut-off value
SD: standard deviation
SLA/LP: soluble liver antigen/liver-pancreas antibody
SMA: smooth muscle antibodies
SVR: sustained viral response
Tc: technetium
TGs: triglycerides
TNF-α: tumor necrosis factor alpha
t-RNA: transfer ribonucleic acid
tTG: tissue transglutaminase
UDCA = ursodeoxycholic acid
UDP: uridine diphosphate
UGTs: uridine diphosphate glucuronosyltransferases
U/mL: unit/milliliter
U.S.: United States
VDR: vitamin D receptor
VLDL = very low-density lipoproteins
VZV: Varicella-Zoster Virus
µg/min: microgram/minute
+ve: positive

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INTRODUCTION

Patients with underlying diabetes mellitus (DM) can present with abnormal liver chemistries, which can represent findings as benign as hepatic steatosis or as severe as cirrhosis of the liver ***(Baig et al., 2001).***

Insulin-reversible hepatic glycogenosis is the most common cause of hepatomegaly and raised serum liver transaminase concentrations in children and adolescents with type 1 diabetes ***(Munns et al., 2000).***

Hepatic glycogenosis can occur at any stage of type 1 DM and may even be one of its earliest manifestations. Since long-standing hyperglycaemia and overinsulinisation are metabolic pre-requisites for hepatic glycogen storage, liver glycogenosis should be expected to be not uncommon during the first phases of type 1 DM, especially in the cases who are initially treated with supraphysiological insulin doses ***(Carcione et al., 2003).***

Epidemiologically there seems to be a correlation between DM, the most common endocrinologic disease, and hepatitis C infection ***(Baig et al., 2001).*** Chronic hepatitis C patients have specific host factors that can modulate their fibrogenic response. Obesity, because of its prevalence and diabetes, which seems to occur more frequently in patients infected by the hepatitis C virus (HCV), are often present in patients with chronic hepatitis C. Both conditions result in fatty liver, which in turn is associated with more severe liver damage, especially fibrosis or inflammation. Steatosis can originate either from associated metabolic

alterations or from a direct cytopathic effect of the virus ***(Ratziu et al., 2004, B).***

Autoimmune polyglandular syndrome type-1 (APS-1) is caused by a single gene mutation in autoimmune regulator gene (AIRE). Its onset occurs in childhood with development of organ-specific autoantibodies and the evolvement of multiple autoimmune manifestations including type 1 DM and hepatitis ***(Obermayer-Straub and Manns, 1998).***

The term "nonalcoholic fatty liver disease" (NAFLD) is a clinicopathologic syndrome which includes a wide spectrum of liver injury ranging from simple steatosis to steatohepatitis, fibrosis and cirrhosis. Whereas simple steatosis without inflammation has a benign clinical course (which may not lead to progressive liver injury), nonalcoholic steatohepatitis (NASH) may progress to cirrhosis and liver-related death in 25% and 10% of patients respectively. Liver biopsy is required for definitive diagnosis ***(Mehta et al., 2002; McCullough, 2002).*** The progression from simple fatty liver to more severe forms of NAFLD (nonalcoholic steatohepatitis and cirrhosis) is much less clear but evidence suggests that oxidative stress may preferentially enhance proinflammatory cytokines, which leads to cellular adaptations and dysfunction followed by development of inflammation, necrosis and fibrosis ***(Harrison and Di Bisceglie, 2003).***

Diabetes is a risk factor for the development of NASH. Most of the patients are clinically asymptomatic. This means, that a diagnosis of NASH is a diagnosis of exclusion. Viral induced, autoimmune, metabolic and toxic liver diseases have to be excluded ***(Maier, 2002).***

AIM OF THE WORK

The aim of the present work is to determine the prevalence of hepatic impairment in children and adolescents with type 1 diabetes mellitus and to investigate the underlying etiology whether infectious, autoimmune or metabolic (glycogenosis or fatty infiltration).

DIABETES MELLITUS (DM)

Definition

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. The basis of the abnormalities in carbohydrate, fat and protein metabolism in DM is deficient action of insulin on target tissues (***The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus, 2003).***

Epidemiology

The prevalence of type 1 DM in Egypt is 0.13: 0.4% according to the International Diabetes Federation while the prevalence of type 2 DM is about 9% ***(Elbache, 2003).***

Diabetes mellitus affects 1.7 out of 1,000 people under the age of 20 ***(Caughron and Smith, 2002).***

In Latin America, the prevalence of type 1 diabetes among students was 0.042% and 0.125% among those aged 3-13 years and 13-20 years, respectively, with incidence rates around 6.5/100,000 children/year from 1985-1990 ***(de Sereday et al., 2003).***

Classification

Classification of diabetes according to American Diabetes Association (ADA) (2007) is shown in table I.