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Hepatic Hypertransaminasaemia of unknown Etiology Aclinico-pathological study

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Abstract:

Hepatic aminotransferases are sensitive indicators of liver cell injury. In some patients with persistent elevation of such enzymes; routine clinical, laboratory and serological data cannot establish the underlying causes.

This study was designed to evaluate such patients both clinically and pathologically as a trial to reach the underlying etiology.

Thirty patients with hepatic hypertransaminasaemia of unknown cause (18 females & 12 males), aged 18-50 years (mean age 37.7± 4.6 years), together with ten controls (5 males & 5 females) [matched in age and body mass index with patients]; were included in this study. Both patients and controls were subjected to full history taking, clinical examination, estimation of blood glucose and lipid profile, liver function tests, serum iron & ferrtin estimation, hepatitis viral markers (HBs Ag HCV-Ab), anti Epstien Barr (EBV) and cytomegalovirus (CMV) antibodies, abdominal ultrasonography (U/S)and needle liver biopsy (done only for 15 patients who approved undergoing it.

The study revealed that 18 patients had non alcoholic fatty liver disease NAFLD (bright liver on U/S), eleven patients out of them underwent liver biopsy that showed simple hepatic steatosis in four of them and non alcoholic steatohepatitis (NASH) in the other seven patients. Most of the eighteen patients with NAFLD were obese, diabetic and hypertensive. Four patients had positive serology for autoimmune hepatitis and two patients had positive serology for cytomegalovirus infection. All patients had normally ranged serum iron & ferritin. The remaining six patients had normal hepatic U/S and negative serology for different hepatic viruses; four of them underwent liver biopsy that revealed simple hepatic steatosis in two of them and non alcoholic steatohepatitis (NASH) in the other two patients. **Conclusion & recommendation:** Non alcoholic fatty liver disease (NAFLD) was found to be the commonest cause of unexplained hepatic hypertransamina-saemia. However, we must be minded with less frequent causes like autoimmune hepatitis and cytomegalovirus infection. Needle liver biopsy and possibly MR imaging of the liver are important investigational techniques for patients with hepatic hypertransaminasaemia associated with normal serum iron & ferrtin levels, negative serology of (autoimmune hepatitis & various hepatic viruses), normal hepatic ultrasonography; to diagnose those with occult hepatic steatosis among them. Estimation of HBV-DNA & HCV-RNA by (PCR) could be required for precise exclusion of HBV & HCV infection. Large-scale studies are recommended to verify these findings

Introduction and Aim of the work:

Serum aminotransferases levels are sensitive indicators of liver cell injury (Pratt and Kaplan, 1999). In most patients routine clinical, laboratory and serological data allow identification of the disease entity responsible for liver damage. However, in some patients the cause of persistent elevation of liver enzymes cannot be established on the basis of these data (Berasain *et al.*, 2000).

The presence of occult viral infection in cryptogenic liver disease with

hypertransaminasaemia remains controversial. While in some series HBV-DNA cold not be detected in the sera of HBs Ag negative patients, other series found it in 14-85% of such patients (Cacciola *et al*., 1999). On the other hand, while some studies found HCV-RNA in the sera of 44 - 67% of patients with cryptogenic hepatitis, other investigators failed to detect it in the liver or the serum of such patients (Schmidt *et al.,* 1997).

Information about the spectrum of pathological liver changes in-patients with hypertransaminasaemia of unknown etiology remain little and need to be clarified (Mathiesen *et al.,* 1999).

We aimed through this study to evaluate patients with hepatic hypertransaminasaemia: Alanin aminotransferes (ALT) and aspartate aminotransferase (AST) of unknown etiology, both clinically and pathologically as a trial to discover the underlying causes.

Subjects and Methods:

Thirty patients with hepatic hypertransaminasaemia of unknown etiology in addition to ten healthy controls (matched in age, sex and body mass index (BMI) with studied patients) were collected from Al-Hussein and Damietta University hospitals in the time period from October 2004 to April 2005.

Patients:

All patients had elevated hepatic aminotransferases > 1.5 times the upper normal limit (40 u/l), exclusion criteria were: (i) children less than 18 years old (ii) history of hepatotoxic drugs or alcohol abuse. (iii) patients positive for HBs Ag or HCV-Ab.

Controls:

All were healthy volunteers on normal diet with no history of medication or alcohol intake.

Methods:

Both patients and controls were subjected to:

1 –Full history taking and clinical examination

2 – laboratory investigations that included.

(a) Full liver function tests and serum iron, estimated by colorometric technique (larry & Karicka 1996)

(b) Prothrombin time (PT) and concentration, using coagulometer (Larry & Karicka 1996).

(c) Hepatitis viral markers (HBs Ag & HCV-Ab), cytomegalovirus antibo-dies (CMV - lgM & CMV - lgG), Epstein Barr virus antibodies (EBV-lgM & EBV- lgG) and serum ferritin, estimated by enzyme linked immunosorbent assay (ELISA) [Larry & Karicka, 1996]; by fully automated ETI STAR Diasorin, using comme-rcial kits from human Inc. Germany.

(d) Autoantibodies of autoimmune hepatitis (classic type) ie, antinuclear antibody (ANA) and antismooth muscle antibody (ASM), estimated by immunoflurescent technique using commercial kits from Diasorin Inc. USA (Larry & Karicka, 1996).

3 – Abdominal ultrasonography (U/S):

Using Medison Co, LTD SA 6000 C set with convex abdominal probe 3.5 MHZ and aquasonic gel film between the transducer and the skin of the patient who was fasting for at least 7 hours and was examined in supine and lateral positions, measurement were taken on quite inspiration.

4 – CT guided needle liver biopsy (only for patients):

We used automatic liver biopsy needle (16 swg) guided by Samaton CT apparatus.

Biopsy was done for fifteen patients (15/30) who approved undergoing it. The patients were fasting for < 8 hours and their prothrombin concentration was > 60 % and their platelets count was >80% of normal values. The biopsy site was determined and sterilized. The patient was lying in supine position. 5 ml of 2% zylocaine was injected locally and the biopsy was taken while the patient holding his breath in inspiration. After the biopsy, they patient was asked to lie on his right side for 6 hours with one hourly monitoring of vital signs (Rawford *et al*., 198).

5 – Histopathological study:

The specimens were fixed in 10% formalin and processed into paraffin blocks, cut by microtome, stained with Hematoxylin and Eosin, Masson trichrome and Prussian blue staining for image analysis and histologic diagnosis of hepatitis, hepatic steatosis, fibrosis, cirrhosis or hemochromatosis.

6 -Statistical method:

Data were analyzed by computer using (a) mean value, (b) standard deviation: SD ± and (c) Chi-Square test. Significant value were considered at P > 0.05.

Results:

** Results obtained were statistically analysis and tabulated in (table 1-12).

Table (1): Summary of studied patients regarding diagnosis:

	Autoimmune Hepatitis	**CMV** Infection	**NAFLD**	**Unknown (prior to liver biopsy)**	**Total**
Patients	4(13.3%)	2 (6.6%)	18 (60%)	6 (20%)	30

*CMV = cytomegalovirus. *NAFLD = non alcoholic fatty liver disease.

Table (2): Statistical Comparison between patients and controls regarding sex, age and BMI

	sex				Age		BMI	
	Male		Female					
	No	%	No	%	Mean	SD ±	Mean	SD ±
patients	12	40%	18	60%	38.06	9.15	28.76	5.31
Control	5	50%	5	50%	37.70	4.08	25.91	1.85
Total	17	42.5%	23	57.5%	37.97	8.14	28.5	4.83
					P >0.05 (NS)		P >0.05 (NS)	

The mean age in patients group was 38.06 ± 9.15 years and in control group was 37.70 ± 4.08 years with a statistically insignificant difference between both groups (p > 0.05). The mean BMI was 28.76 ± 5.31 in patients group and 25.91 ± 4.83 in control group with statistically insignificant difference between both groups (p>0.05) [NS = nonsignificant].

Table (3) Statistical Comparison between patients and controls regarding ANA, ASM, and CMV antibodies

		patients (3)		Control (10)		Total (40)	
		No	%	No	%	No	%
ANA	Negative	26	86.67%	10	100%	36	90%
	Positive	4	13.33%	0	0%	4	10%
ASM	Negative	26	86.67%	10	100%	36	90%
	Positive	4	13.33%	0	0%	4	10%
CMV	Negative	28	93.33%	10	100%	38	95%
	Positive	2	6.34%	0	0%	2	5%

ANA = Antinuclear antibody. ASM = Antismooth muscle antibody.
CMY = Cytomegalovirus.

Table (4): Statistical comparison between NAFLD group (diagnosed by ultrasound) and controls regarding liver function tests.

	Group	Mean	S.D	Min	Max	P
AST	NAFLD	95.22	29.22	65.00	177.00	<0.001
(0-40)U/L	Control	29.40	4.29	22.00	35.00	H.sig
ALT (SGPT)	NAFLD	101.11	63.99	49.00	190.00	<0.001
(0-40)U/L	Control	29.30	8.43	22.00	45.00	H.sig
Total serum bilir-	NAFLD	1.69	1.18	0.80	5.10	<0.001
ubin: (0.2-1) mg/dl	Control	0.54	0.048	0.50	0.70	H.sig
Prothrombin time	NAFLD	14.83	1.97	12.00	18.00	<0.001
12-14 second	Control	10.40	0.48	9.00	12.00	H.sig
Serum albumin	NAFLD	3.83	0.53	2.90	5.00	<0.001
(3.5 – 5) mg/dl	Control	4.23	0.21	4.00	4.50	H.sig

There were statistically significant higher levels of AST, ALT, total bilirubin, and prothrombin time in patients with NAFLD in comparison to control group (P < 0.001); while there was a significant decrease in serum albumin in patients with NAFLD in comparison to control group non [H.sig = highly significant].

Table (5): statistical comparison between NAFLD group (diagnosed by ultrasound) and controls regarding BMI, fasting & postprandial blood sugar, cholesterol and triglycerides.

	Group	Mean	S.D	Min	Max	P
BMI	NAFLD	32.0587	4.1587	25.91	42.97	<0.001
	Control	25.9189	1.8511	23.89	29.38	H.sig.
FBS	NAFLD	147.66	47.33	86.00	220.00	<0.001
(70-110) mg/dl	Control	75.00	4.08	70.00	80.00	H.sig.
PPBS	NAFLD	186.33	60.57	110.00	288.00	<0.001
(up to140)mg/dl	Control	123.00	14.94	100.00	150.00	H.sig.
T. cholesterol	NAFLD	255.94	47.25	164.00	351.00	<0.05
(150-250) mg/dl	Control	178.50	51.74	100.00	240.00	Sig.
Serum	NAFLD	344.00	87.73	144.00	410.00	0.05
triglycerides	Control	265.00	28.77	200.00	300.00	Sig.

There were statistically significant higher levels of BMI, FBS, PPBS, T. cholesterol and serum triglycerides in-patients with NAFLD in comparison to control group (p <0.05).

* BMI = body mass index * T. cholesterol = Total serum cholesterol
* FBS = Fasting blood glucose. * PPBS = post prandial blood glucose.

Table (6): Statistical comparison between diabetics and non diabetics patients with NAFLD regarding liver function tests, and lipid profile.

	Diabetics		Non diabetics		p
	Mean	D.S	Mean	DS	
AST(SGOT) (0-40) U/L	100.00	36.63	80.96	63.92	> 0.05
ALT(SGOT) (0-40) U/L	93.40	23.92	83.40	67.80	> 0.05
Total serum bilirubin (0.2-1)mg/dl	2.06	1.47	3.65	7.75	> 0.05
PT (12 – 14 second)	14.60	1.89	13.53	3.29	> 0.05
serum Albumin (3.5-5) mg/dl	3.88	0.60	4.05	0.42	> 0.05
BMI	32.89	3.24	25.51	4.47	<0.001 H.sig
FBS (70-110)mg/dl	176.50	37.32	93.43	22.24	<0.001 H.sig
PPBS(up to 140) mg/dl	221.40	55.19	128.16	20.70	<0.001 H.sig
T. cholesterol (150-250)mg/dl	260.30	54.75	200.50	52.43	<0.01 H.sig
Serum triglycerides (250-350) mg/dl	361.30	83.95	254.30	79.02	<0.001 H.sig

There were statistically significant higher levels of BMI, FBS, PPBS, T.sr. cholesterol and serum triglycerides in diabetic in comparison to non diabetic patients with NAFLD (p value < 0.05). there were no statistically significant difference as regard AST, ALT, total serum bilirubin, prothrombin time and serum albumin.

Table (7): Statistical comparison between patients with autoimmune hepatitis and controls regarding liver function tests.

	Group	Mean	S.D ±	Min	Max	p
AST (SGOT) (0.40)U/L	Autoimmune	134.50	124.44	56.00	320.00	<0.05 H.sig
	Control	29.40	4.29	22.00	35.00	
ALT (SGPT) (0-40)U/L	Autoimmune	144.55	138.36	58.00	350.00	<0.05 H.sig
	Control	29.30	8.43	22.00	45.00	
Total bilirubin (0.2-1) mg/dl	Autoimmune	10.56	15.35	0.40	33.00	<0.05 H.sig
	Control	0.54	0.048	0.50	0.70	
Prothrombin time 12-14 second	Autoimmune	14.11	1.15	13.00	15.00	<0.05 H.sig
	Control	10.40	0.84	9.00	12.00	
Serum albumin (3.5-5)mg/dl	Autoimmune	4.25	0.50	3.50	4.50	>0.05 NS
	Control	4.23	0.21	4.00	4.50	

There were statistically significant higher levels of serum AST, ALT, total bilirubin, and prothrombin time in patients with autoimmune hepatitis in comparison to control group (p <0.05). The difference was statistically insignificant in comparison with controls as regards serum albumin.

Table (8): Statistical comparison between patients with CMV infection and controls regarding liver function tests.

	Group	Mean	S.D ±	p
AST (SGOT) (0-40)U/L	CMV	188.00	82.02	< 0.001 H. sig.
	Control	29.40	4.29	
ALT (SGPT) (0-40)U/L	CMV	118.50	57.27	< 0.001 H. sig.
	Control	29.30	8.43	
Total serum bilinubin (0.2-1)mg/dl	CMV	12.25	11.80	< 0.01 H. sig.
	Control	0.54	0.084	
Prothrombin time 12-14 second	CMV	12.50	0.70	< 0.01 H. sig.
	Control	10.40	0.84	
Serum albumin (3.5-5)mg/dl	CMV	4.15	0.21	> 0.05 NS
	Control	4.23	0.21	

There were statistically significant higher levels of serum AST, ALT, total bilirubin, and prothrombin time in-patients with CMV infection in comparison to controls (p value < 0.01), while there was no statistically significant difference as regard serum albumin.

Table (9): statistical comparison between group patients remained undiagnosed (prior to liver biopsy) and controls regarding liver function tests

	Group	Mean	S.D	p
AST (SGOT) (0-40)U/L	unknown	84.50	18.10	< 0.001 H. sig.
	Control	29.40	4.29	
ALT (SGPT) (0-40)U/L	unknown	84.50	22.07	< 0.001 H. sig.
	Control	29.30	8.43	
Total bilinubin (0.2-1)mg/dl	unknown	4.61	9.01	> 0.05 NS
	Control	0.54	0.084	
Prothrombin time (PT) 12-14 second	unknown	16.66	4.27	< 0.001 H. sig.
	Control	10.40	0.84	
Albumin (3.5-5)mg/dl	unknown	3.96	0.55	> 0.05 NS
	Control	4.23	0.21	

There were highly significant increases in serum AST, ALT and PT in undiagnosed patients in comparison to controls (p <0.001). The difference was not statistically significant as regards total serum bilirubin and serum albumin.

Table (10): statistical comparison between patients who remained undiagnosed (prior to liver biopsy) and controls regarding BMI, Fasting & post prandial blood sugar, total serum cholesterol and serum triglycerides

	Group	Mean	S.D	p
BMI	Unknown	23.43	1.47	> 0.05 NS
	Control	23.14	1.73	
FBS (70-110)mg/dl	unknown	94.16	12.89	<0.001 H. sig.
	Control	75.00	4.08	
PPBS (Up to 140) mg/dl	unknown	122.50	8.47	> 0.05 NS
	Control	123.00	14.94	
T. Cholesterol (150-250)mg/dl	unknown	192.50	29.77	> 0.05 NS
	Control	178.50	51.74	
Serum triglycerides (140-160)mg/dl	unknown	166.66	20.56	<0.001 H. sig.
	Control	265.00	28.77	

Highly significant increases in FBS and serum triglycerides in undiagnosed patients in comparison to control group (p <0.001) were recorded. While the difference was not statistically significant as regard BMI, PPBS and total serum cholesterol.

Table (11): comparison between studied groups regarding abdominal ultrasound (before doing liver biopsy).

Group	Liver						Spleen				Total (30)	
	Enlarged Coarse echopattern		Enlarged bright liver		Normal echopatter		Enlarged		Normal Sized			
	No	%	No	%	No	%	No	%	No	%	No	%
Autoimmune hepatitis	0	0%	0	0%	4	100%	0	0%	4	100%	4	13.33%
CMV Infection	0	0%	0	0%	0	0%	2	100%	0	0%	2	6.67%
NAFLD	1	5.6%	17	94.4 %	2	10%	0	0%	18	10%	18	60%
Unknown	0	0%	0	0%	6	100%	0	0%	6	100%	6	20%

Table (12): Liver Biopsy findings of the patients who approval undergoing it (15 patients)

		NAFLD (11/15)		Unknown (4/15)	
		NO	%	NO	%
Simple steatosis	Positive	4	36.36	2	50
	Negative	7	63.64	2	0
Steatohepatitis, (NASH)	Positive	7	63.64	2	50
	Negative	4	36.36	2	50
Steatohepatitis with fibrosis	Positive	3	27.28	0	0
	Negative	8	72.72	4	100
Steatohepatitis with cirhosis	Positive	1	9.09	0	0
	Negative	10	90.90	4	100

From this table we found that 50% of patients of unknown etiology (prior to liver biopsy) diagnosed as NASH, and 50% of them diagnosed as Steatosis by liver biopsy.

** The studied patients aged 18-50 years with mean age 38.06 ± 9.15 years, they were 18 females & 12 males. The controls aged 20 - 49 years with mean age 37.7 ± 4.08 years, they were 5 males and 5 females with no statistical differences in age and body mass index (BMI) between them and patients (table 2).

** Four patients 4/30 (13.3%) had positive serology of classic type of autoimmune hepatitis (positive ANA, ASM with serum gamma globulin > 5 gm/dl) they were 3 females and one males, they all refused liver biopsy, they had normal abdominal U/S (table 11), their aminotransferases levels and prothrombin time were statistically higher than that of controls. (Table 7).

** Two patients 2/30 (6.6%) had positive (CMV) antibodies [CMV. Igm values were 0.860 & 0.878 Au/ml (normally <0.6 Au/ml) and CVM IgG values were 400 & 551 Au/ml (normally < 15 Au/ml)]. Both patients were females, they refused liver biopsy. They both had hepatosplenomegaly with average hepatic echopattern on abdominal U/S (table 11). They had statistically significant higher serum aminotransferases serum bilirubin level and prothrombin time than that of controls (table 8).

Eighteen patients 18/30 (60%) had bright liver on abdominal U/S; non-alcoholic fatty liver disease (NAFLD); with negative serology of hepatic viruses (including CMV, EBV) and autoimmune hepatitis. They were nine males & nine females, they had statistically significant higher BM1, fasting and postprandial blood glucose (FBS & BPBS) levels, serum trighycocides, total serum cholesterol serum bilirubin, prothrombin time and amino-transferases (ALT&AST) levels than that of controls (table 4 &5).

Ten patients from these eighteen patients with NAFLD: 10/18 (55.55%) were diabetic and eight patients 8/18 (44,45%) were non diabetic. There were statistically significant higher values of BM1, FBS, PPBS, total serum cholesterol, serum triglycerides in diabetic patients than non diabetic patients with NAFLD (table6).
Eleven patients out of the eighteen patients with ultrasonogra-phically diagnosed NAFLD (11/18) approved liver biopsy. Four patients from them 4/11 (36.36%) showed simple hepatic steatosis, while seven patients: 7/11 (63.64%) showed non alcoholic steatohepatitis (NASH) on doing liver biopsy. Three patients from these seven patients: 3/7 (42.8%) had pure NASH, another three patient had 3/7 (42.8%) NASH associated with fibrotic changes and the remaining one patient 1/7 (14.4%) showed NASH complicated with liver cirrhosis (table 12).

The remaining six patients: 6/30 (20%) had normal abdominal 4/5 and negative serology of autoimmune hepatitis

and hepatic viruses (table 1), they had statistically significant higher ALT &AST levels, prothrombin time, fasting blood glucose (FBS) and serum triglycerides in comparison to control group (table 9&10). Four patients from them 4/6 underwent liver biopsy, two of them 2/4 (50%) had simple hepatic steatosis and the other two patients: 2/4 (50%) showed NASH not associated with fibrotic or cirrhotic changes (table 12). Serum iron and ferritin levels were normally ranged [serum iron was 55-134mcg/dl (mean: 74.82±11.42 for both males and females) & serum ferritin was 65-192 ng/ml (mean: 145.88 ± 58.04) in females and 92-310 ng/ml (mean: 216.73 ± 78.46) in males] without histologic evidence of hemochromatosis in Prussian blue stained liver biopsy specimens in all studied patients (normal serum iron level is < 160 mcg/dl for both adult males & females and serum ferritin level is ≤ 501 ng/ml for males and ≤ 223.5 ng/ml for females.

Discussion:

Hepatic aminotransferases are sensitive indicator of liver cell injury regardless its etiology. They are normally present in the serum at low levels (usually less than 30 u/l). They are mostly elevated above that level in patients with acute or chronic liver disease (Limi and Hyde, 2003).

Raised aminotransferases levels of unknown etiology is a common problem in clinical practice, although ALT elevation doesn't always mean a specific liver disease (Simornovic et al., 2004).

In our study; among 30 patients with unexplained elevation of aminotransferases (ALT&AST) four patients 4/30 (13.3%) had positive serology of classic type of autoimmune hepatitis (ANA, ASM), two patients 2/30 (6.6%) had positive serology of CMV infection (CMV-IgM & CMV-IgG) and eighteen patients 18/30 (60%) had non alcoholic fatty liver disease (NAFLD) on abdominal U/S. The etiology could not be identified through different laboratory findings, serological and ultrasound data (table 1) in the remaining six patients. However, liver biopsy performed for four patients from them, revealed simple hepatic steatosis in two patients of them and nonalcoholic steatohepatitis (NASH) in the other two patients.

This is in agreement with what was published by Deledinghen *et al*. (2004). They found in their study that 10% of patients with elevated ALT levels remained without detectable causes before undergoing liver biopsy; on doing liver biopsy 50% of such patients proved to have NASH.

In contrast to our findings, Mathiesen *et al*. (1999) in a study of 150 asymptomatic patients with mild to moderate hepatic hypertransamin-asaemia found (NAFLD) only in three patents (2%), autoimmune hepatitis in two patients (1.3%). This discrepancy could be explained by the involvement of both symptomatic and asymptomatic patients in our study unlike their study that included only asymptomatic patients.

De Le Dinghena *et al*. (2004) reported that 10% of patients with chronic ALT elevation included in their study had unidentified etiology for such elevation, while 50% of such patients had NAFLD. This goes with our findings (table 6).

Sorbie *et al*. (1999) concluded that elevated aminotransferases (ALT&AST) levels is commonly the only biochemical indicator for NAFLD, this is inconsistent with our findings that revealed elevated serum bilirubin, prolonged prothrombin time and lowered serum albumin in addition to serum aminotransferases elevation in patients with NAFLD in comparison to controls (table 4).

Suzuki *et al*. (2005) found that diabetes mellitus or impaired glucose tolerance was the most important factor for development of NAFLD which was a common cause of unexplained hypertransam-inasaemia in patients involved in their study. They found that ALT elevations in patients with NAFLD is more prominent in patients with metabolic syndrome of (increased BMI, insulin resistance, hypertrigly-ceridemia). This goes with our findings as shown in (table 5).

We also found that ten (10/18) patients with NAFLD were diabetic with significantly higher serum triglycerides and BMI than the remaining eight (8/18) non diabetic patients (table 6). This is consistent with what was published by Younossi *et al.* (2004) who found in a study of 132 patients with NAFLD; 44 patients had established diabetes mellitus (DM), increased BMI with hypertriglyceridemia and high risk for development of aggressive hepatic outcome.

Mathiesen *et al.* (2002) reported that abdominal U/S is of value for detection only moderate to pronounced fatty infiltration of the liver although it cannot be relied upon in diagnosing of hepatic fibrosis or cirrhosis. This goes with our findings that 4/6 patients with unexplained elevation of ALT & AST, negative serology of (hepatic viruses & autoimmune hepatitis) and normal hepatic ultrasonography underwent liver biopsy which showed simple hepatic steatosis in two patients 50% and NASH in the other two patients (50%). So the documented number of patients with simple hepatic steatosis were six 6/15 (40%) and the number of patients with NASH were nine: 9/15 (60%) among the fifteen patients who approved undergoing liver biopsy magnetic resonance imaging may be as valuable as liver biopsy and more precise than ultrasonography as a non invasive procedure for detection of hepatic steatosis Macdonald *et al*. (2000).

In contrast; Daniel *et al.* (2000), found in their study of 81 patients with raised aminotransferases and negative (HCV& HBV) markers; that liver biopsy showed simple hepatic steatosis in 41/81 patients (50.6%) and NASH in 26/81 patients (38.9%). The discrepancy between their findings and our findings may be due to the refusal of some patients with NAFLD in our study to undergo liver biopsy.

Clark *et al.* (2003) reported that unexplained elevation of aminot-ransferases is mostly caused by adiposity associated with frank type 2DM, impaired glucose tolerance, dyslipidemia and NAFLD shown by abdominal U/S. They recommended liver biopsy for such patients particularly those with persistent elevation of aminotransferases levels more than twice the normal value for reassurance of the patients and exclusion of serious pathology.

conclusion

Non alcoholic fatty liver disease (NAFLD) was found to be the most common cause of unexplained hepatic hypertransam-inasaemia. Less frequent causes were autoimmune hepatitis and cytomegalovirus infection. Needle liver biopsy and possibly MR imaging are important diagnostic techniques for patients with normal hepatic ultrasonography and negative serology for detection of patients with occult hepatic steatosis.

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ارتفاع مستوى انزيمات الترانس أمينزالكبدية مجهول الأسباب: دراسة إكلينيكية باثولوجية.

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تعد أنزيمات الترانس أمينيز الكبدية من المؤشرات الحساسة التى تعكس إصابة خلايا الكبد. وقد لوحظ أنه فى بعض المرضى لا يمكن الوصول إلى أسباب ارتفاع هذه الإنزيمات من خلال الأبحاث الإكلينيكية والمعملية والمصلية الروتينية.

وقد أجريت هذه الدراسة للتقييم الإكلينيكى والباثولوجى لهؤلاء المرضى بهدف الوصول إلى معرفة أسباب ذلك الارتفاع.

ولهذا الغرض تم اختيار ثلاثين مريضاً من هؤلاء المرضى (18 أنثى، 12 ذكر) تراوحت أعمارهم ما بين (18 – 50) سنة ومتوسط أعمارهم 37.5 سنة بالإضافة إلى عشرة من الأصحاء المتطوعين (خمسة ذكور وخمسة إناث) والمتوافقين فى السن ووزن الجسم مع المرضى (مجموعة ضابطة).

أجريت لكل من المرضى والمجموعة الضابطة الفحوص الإكلينيكية والمعملية التقليدية التى شملت مقاييس مستوى السكر فى الدم ومستوى دهنيات الدم ووظائف الكبد ومستوى الحديد والفريتين فى الدم. كما تم إجراء الفحوص المصلية لهم لاستبعاد الإصابة بالفيروس الكبدى من النوع (ب، ج) ومعرفة مدى الإصابة بفيروس الستيوميجالو وفيروس أيبشتين وكذلك لمعرفة مدى الإصابة بالالتهاب الكبدى المناعى الذاتى كما خضع كل من المرضى والمجموعة الضابطة للفحص بالموجات فوق الصوتية. وتم أخذ عينات كبدية لفحصها هستولوجياً لخمسة عشر مريضاً فقط ممن وافقوا على أخذ هذه العينة منهم.

أظهر البحث ما يلى:-

1 – وجود ثمانية عشر مريضاً لديهم كبد متشحم (لامع) عند الفحص بالموجات فوق الصوتية، كان أغلبهم من البدناء المصابين بارتفاع مزمن فى ضغط الدم وسكر الدم مع عدم وجود فارق إحصائى ذو أهمية بالنسبة لجنسهم (من الرجال والنساء على حد سواء). وقد وافق أحد عشر مريضاً منهم على فحص عينات كبدية منهم أظهرت وجود تشحم كبدى بسيط فى أربعة منهم والتهاب كبدى متشحم فى سبعة منهم.

2 - وجود أربعة مرضى لديهم نتائج مصلية إيجابية لالتهاب الكبد المناعى الذاتى.

3 - وجود مريضين لديهم أجسام مضادة إيجابية لفيروس الستيوميجالو.

4 - بالنسبة للستة مرضى الباقين لم يظهروا تغيرات كبدية ذات أهمية عند الفحص بالموجات فوق الصوتية وكذلك لم يظهروا نتائج إيجابية مصلية لفيروس الستيوميجالو أو فيروس أيبشتين بار

أو الالتهاب الكبدى المناعى الذاتى. وقد وافق أربعة منهم على اخذ عينات كبدية منهم لفحصها أظهرت وجود تشحم كبدى بسيط فى اثنين منهم والتهاب كبدى متشحم فى الاثنين الآخرين.

5 - كان مستوى الحديد والفريتين فى الدم فى معدله الطبيعى بالنسبة لجميع المرضى.

وقد خلص البحث إلى الآتى: -

أ - أكثر حالات ارتفاع إنزيمات الترانس أمينيز الكبدية غامضة الأسباب أظهرت من خلال الفحوصات المختلفة وجود تشحم كبدى غير كحولى؛ مع الأخذ فى الاعتبار وجود بعض الأسباب الأخرى الأقل شيوعاً مثل الالتهاب الكبدى المناعى الذاتى والإصابة بفيروس الستيوميجالو .

ب - أهمية فحص عينات الكبد هيستولوجيا وتصوير الكبد بالرنين المغناطيسى بالنسبة لمرضى ارتفاع إنزيمات الترانس أمينيز الكبدية مجهولة السبب الذين لم يظهروا أى تغيرات كبدية واضحة عند الفحص بالموجات فوق الصوتية أو نتائج مصلية إيجابية وذلك لتشخيص مرضى التشحم الكبدى بينهم.

جـ- ضرورة إجراء هذه الدراسة على مجموعة أكبر من المرضى للتأكد من صحة النتائج .