Delta Virus Infection in Iraq

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Abstract :

Background:

The hepatitis D virus is a defective pathogen that requires the presence of the hepatitis B virus for infection .HDAg can elicit a specific immune response in the infected host.

Patients and methods:

the present study was carried on a total number of 70 patients with chronic HBV infection proved by serological and histopathological methods 40 pt had CAH and 30 were healthy carriers .26 patients (37%) had HDV infection by EIA for total anti-HDV. 9 of them had IgM anti-HDV. All patients groups were studied for The clinical characteristic of chronic HDV infection , the influence of HDV on the progression of chronic HBV infection, the relation between HDV and HBe Ag, the relation of HDV to hepatocellular carcinoma ,microsomal autoantibodies in chronic HDV infection , complement and immunoglbulin profile in HDV infection .

Result:

The ALT,AS,ALP and the TSB were significantly higher in HV group P<0.01,P<0.01 , P <0.001 and P<0.05 respectively . There was higher prevalence of HDV in pts with CAH (44%) than the HBS Ag healthy carriers (25%) although statisting not significant . A competitive inhibition of HBV replication by coexisting Delta infection was demonstrated. There was a negative correlation between HDV and HCC though statistically not significant . LKM3 detected in 27% of pts and there was very high significant association with HDV. The serum complements C3,C4 were significantly lower in HDV while serum immnoglobulins IgA and IgM were significantly higher in HDV .

Conclusion :

delta infection is prevalent in Iraq. Although it has a suppression effect on HBV , it associated with more progressive disease and might induce aggressive immunological response including LKM-3 .

Key wards:

Delta virus, HbsAg, HbeAg, hepatocellular carcinoma , complement and immunoglobulin .

Statistical analysis: The mean value with SD for each value was determined using ANOVA. A p value of <0.05 was considered to be positive .

Original Article

Introduction:

The delta agent was discovered by Rizzetto and colleagues in 197.[1]

Hepatitis D virus (HDV) comprises a 36-nm single-strand positive-sense RAN genome , a single HDV encoded antigen (both LHD Ag& SHD Ag)and lipoprotein envelope provided by hepatitis B virus (HBV) .[2] HDV is closely associated with HBV .[3] A genotypic classification has been proposed , type 1 predominates in most areas of the world , type 2 in Taiwan (less sever disease)and type 3 which found in South America and is associated with a more sever form of hepatitis [4] The modes of transmission of HDV are similar to those of HBV infection, and percutaneous exposures are the most efficient.[5] The pathogenesis of HD-related liver disease appears to be depending on the interplay of three major factors: (1) HDV-associated factors, such as genotype 2 and the expression of specific HDAg species SHDAg, but not LHDAg , is directly ctotoxic to hepatocytes. [6] (2) host associated factors, such as the immune response.[7] Several autoantibodies have been described in association with chronic HDV infection .[8,9]

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The major LKM-3 antigen appears to be a family of uridine diphosphat-glucuronosy 1 transferases (UGTs) , which are hepatic enzyme involved in phase 2-drug metabolism. [8] (3) helper virus-associated factors, such as the HBV genotype and the level of HBV replication .[10] The clinical and libratory findings vary with the type of infection : (1) Coinfection of HBV and HDV result in acute hepatitis B+ D with high incidence of liver failure , however the rate of progression to chronic infection is not different from with progression to chronic is not different from that observed after classical acute hepatitis B. [11,12] (2) Superinfection with progression to chronic HDV infection occurs in almost all patients. [13] (3) helper independent latent infection , which can be rescued by the helper virus at a later time.[14] EIA and RIA are used for detection of total and IgM anti-HDV. High titer anti-HDV of IgG class in present in present chronic HDV infection .[15] IgM anti-HDV is present in high titer during replication and severity of liver disease .[16] Patients with chronic HDV are at risk of developing cirrhosis with portal hypertenstion and hepatic decompensation . the risk of reinfection of the allograft with HBV after transplantation is lower in-patient with HDV coinfection and there is a negative association between HDV and HCC .[17] HBV/HDV coinfection can be prevented by either preexposure or postexposure prophylaxis for behavior modification. The management of HDV infection is supportive .

Liver transplant is the treatment of choice for fulminant or end stage liver disease. The only drug that has been examined in randomized controlled trials is infection. [18]

Patients & Method:

The present study was carried on a total number of 70 patients with chronic HBV infection proved by serological and histopathological methods 40 pt had CAH and 30 were healthy carriers. All cases of chronic active hepatitis had more than 6 months of recognized liver disease, were hepatitis B core IgG positive and a percutaneous liver biopsy documented chronic active hepatitis as a result of chronic HBV infection . All cases identified as HBV carriers were symptom-free, hepatic enzyme values that rang from normal to a high of 1.1 times the upper limit of normal and a liver biopsy that was entirely normal. 26 patients (37%) had HDV infection by EIA for total anti-HDV. 9of them had IgM anti-HDV . Each pt was interviewed; detailed history and physical examination were done . Abdominal ultrasongraphy with fine needle aspiration of any suspicious lesion. Blood sample were taken for the following :

1. Liver function test including TSB , liver enzyme ,PT and TSP.
2. Liver kidney microsome type 3 (LKM3) for 26 pt with HDV compared with 44pt with HBV only and 78 pt with autoimmune hepatitis by immune-oflorescence and confirmation by EIA .
3. Serum complements C3 ,C4 by radiali-mmnodiffusion.

The aim of the study :

1. The clinical characteristics of chronic HDV infection
2. The influence of HDV on the progression of chronic HBV infection.
3. The relation between HDV and HBeAg.
4. The relation of HV to hepatocellular carcinoma (HCC).
5. Microsomal autoantibdies in chronic HDV infectin.
6. Complement and immunoglobulin profile in HDV infection.

Results:

We studied a 70 patients (pts) with chronic HBV infection , 50pts were male and 20 were female, their mean age was 38 years (18-65). 50 pts had chronic active hepatitis and 20 were healthy carrier. Delta virus infection was found in 26 pt (37%) , 7 pts of them (27%) had LKM3 antibodies. In this study we compare pts with HDV (26) with HBV only (44), LKM3 antibody positive (7) and 20 healthy controls.

The age of pts within the different groups did not differ significantly .

The ALT ,AST ,ALP and the TSB were significantly higher in HDV group $P<0.01$,$P<0.01$,P0.001 and $P<0.05$ respectively , but their was no significant differences regarding TSP, albumin and prothrombin time as in table (1).

Table (1) Clinical Characteristics of Delta infection

Group parameters	Control (n=20)	HDV (no=26)	HBV only (no=44)	LKM3 (n=7)	P-value
Age (years	40+\-6	40+\-15.4	63+\-12.6	48.8+\-12	P>0.05
Gen.(M\F)	12\8	19\7	30\14	7\0	
ALT(IU\L)	20+\-6	62+\-34.3	30+\-23.8	20.6+\-25	P<0.01
AST(IU\L)	20+\-6	49+\-32.9	22+\-12.8	28+\-23.4	P<0.01
ALP(IU\L)	80+\-5	146+\-64	133+\-75	96.5+\-61	P<0.001
TSP(gm\d)	6.3+\-0.6	6.2+\-1.4	6.6+\-0.38	7.05+\-0.5	P>0.05
Alb.(gm\d)	4.25+\-0.5	2.36+\-1.4	3.55+\-0.3	2.33+\-1.6	P>0.05
TSB mmo\l	17+\-1.5	169+\-179	24.3+\-14	34+\-20.8	P<0.05
P(second)	13+\-0.7	18+\-3.2	15.5+\-2.5	15.6+\-3.8	P>0.5

There was higher prevalence of HDV in pts with CAH (44%) than the HBSAg healthy carries (25%) although statistically not significant as in table (2)

Table (2) the influence of HDV on progression of liver disease

Liver disease	No	HDV	%	P-value
CAH	50	22	44	
Carriers	20	4	25	P>0.0

A competitive inhibition of HBV replication by coexisting Delta infection was demonstrated, HBe Ag was present in 30% (7 out of 26) and 52% (23 out of 44) in delta and non-Delta chronic HBV infection and was statistically significant as in table(3).

Table (3) Relation of HDV to HbeAg

	No.	HBeAg+ve	%	P-value
HBV+HDV	26	7	30	
HBV only	44	23	52	P<0.05

There was a negative correlation between HDV and HCC though statistically not significant as in table (4)

Table (4) Relation of HDV to HCC

	No.	HCC	%	P-value
HBV+HDV	26	0	0	
HBV only	44	4	9	P>0.5

LKM3 detected in 27% of pts and there was very high significant association with HDV as in table (5)

Table (5) Relation of HDV to LKM

	No.	LKM3	%	P-value
HBV+HDV	26	7	26.9	
HBV only	44	0	0	
AIH	78	1	1.28	P<0.0005

The serum complements C3 ,C4 were significantly lower in HDV than the other groups as n table (6)

Table (6) The pattern of complements in HDV

	Control (no=20)	HDV (no=26)	HBV only (no=44)	LKM3 (no=7)	P-value
C3 mg\dl	119+\-20	61+\-34	68.7+\-54	65.5+\-27	P<0.001
C4 mg\dl	30.9+\-3.5	17+\-10.1	68.7+\-54	17.5+\-3.1	P<0.001

Serum immunglobilins IgA and IgM were significantly higher in HDV whle IgG although wa higher than the other group it was not statistically significant as in table (7)

Table (7) The pattern of immunoglobulins in HDV

	Control (no=20)	HDV (no=26)	HBV only (no= 44)	LKM (no=7)	P-value
IgA mg\dl	173+\-33	376+\-151	363+\-131	240+\-44	P<0.001
IgM mg\dl	126+\-54	146+\-64	102+\-71	151+\-34	P-0.001
IgG mg\dl	898+\-304	1244+\-99	1005+\-98	900+\-235	P>0.05

Discussion :

The prevalence of HDV infection among chronic HBV infection in the present study was 37% , in Saudi Arabia 13.6%, [19] n Egypt 23.5% , [20] in Turkey 5.2%, [21] in India 63%, [22] in Cameroon 27.3%, [23] in Yugoslavia 2.8%, [24] and in Mexico 4%, [25] Available data suggest that approximately 5% of the HBV carriers may be infected with HDV. [26] A study from Italy suggested that the prevalence of HDV infection has declined in the past tow decades. [27] Improvements in socioeconomic condition, an increased awareness of the risk of transmitting infectious diseases fostered by AIDS prevention policy , and aggressive vaccination campaigns against HBV infection .[28]

The liver enzymes ALT ,AS ,AL and TSB were significantly higher in HDV than HBV and the control , while TSP , serum albumin and PT were more severely affected in HDV . The PT was abnormal in all clinical groups as compared to the control , except for the carrier group (p>0.05). In super infection with HDV , the presence of established HBV infection provide the ideal substrate for HDV , and , as a

consequence , chronic progressive liver disease develops in over 90% of pts, and the effect of direct cytotoxicity of HDV on hepatocytes may play a major pathogenic role in aggravating illness status to sever type. (29) Certain pts in whom infection with HDV should be considered includes anti-HBe positive pts with chronic hepatitis , HBsAg - positive pts who experience a flare or unexplained rise in serum amnotransferase activity and HBsAg positive pts with rapidly progressive disease or presentation with cirrhosis early after infection .(36)

A competitive inhibition of HBV replication by coexistent delta infection was demonstrated in this study and was reflected on HbeAg in chronic HB pts. This observation might be attributed to the clearance effect of HDV on HBsAg(Ischmura et al.,1988) or due to suppressing effect resulting in low undetectable HBsAg level in serum , (Sherlock , 1989).(20)

LKM-3 detected in 26.9% of delta infection and there was very high significant association ($p<0.0005$) , it was not deyected in chonic HBV without delta infection and it was found in only 1.28% of pts with AIH . The mean age of pts with delta associated LKM-3 was 48.8+\-11.8years and the male to female ratio was 7:0 . Five of them had cirrhosis and two chronic active hepatitis . None of them had anti-nuclear , smooth muscle mytochondial , or reticulin autoantibodies . O. Civelli et al from Italy founded LKM-3 in 13% of 81 pts with chronic HBV infection and suggest as t that delta infection possibly might alter a microsomal component as to rende it antigenic and capable of eliciting an antibody cross reactive with the unaltered parent substance. (32) Strassbug CPet al founded 13% prevalence of HDV; this study indicates a molecular target and titer difference of LKM-3 autoantibodies in German subjects with HDV and AIH . (33) whether LKM-3 has a role in the pathogenesis of liver disease propagated and may explain , in part, the differences in disease severity seen in pts with HDV and HBV coinfection compared with those with HBV infection alone . (8)

Serum complement C3 , C4 was significantly lower ($p<0.001$) while serum immunoglobulins IgA ,IgM was significantly higher ($p<0.001$, $p<0.025$ respectively) in delta group. McFarlane founded that IgA antibody to hepatitis D virus was almost exclusively associate with chronic hepatitis delta virus infection and correlated independently with moderate sever histological activity (with a specificity of 90.5%and a sensitivity of 82.6%) suggest that this IgA antibody might be a useful serological marker of liver damage in chronic delta hepatitis . (34)

We may conclude that HDV may lead to more vigorous inflammatory changes than HBV , alone which ma have pathophysiological significance. It is difficult from this data to identify a specific pattern of immunologic responsiveness that relate to different HBV clinical syndromes. More data needs to be accumulated to resolve this issue. Test examining HDV specific antigen responses by T and B cell subset population might be informative . (35)

Conclusion :-

Delta infection is prevalent in Iraq. Although it has a suppression effect on HBV , it associated with more progressive disease and might induce aggressive immunological response including LKM-3.

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