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VASCULITIS: INFLUENCE OF VIRAL HEPATITIS B AND C COINFECTION IN CASES WITH PAST HISTORY OF SCHISTOSOMIASIS

By

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ABSTRACT

Objectives: To evaluate the relative magnitude of change in indices of hemostatic disequilibria, immune response, and trace element disbalance in selected cases with vasculitis to delineate the impact of mixed hepatitis HBV/ HCV coinfection and past history of schistosomiasis (PHS).

Study Design: Thirty HCV cases with vasculitis volunteered to participate in this study. They were classified into three groups on the bases of the presence of records of PHS with present HBs Ag (Group I), presence of HBs Ag with no records of PHS (Group II) and undetected HBs Ag with no records of PHS (Group III). A normal group of 10 healthy subjects was included (Group VI). Evaluation of serum plasminogen activator inhibitor "PAI-I", thrombin-antithrombin "TAT", von Willebrand factor "vWF", tumor necrosis factor α "TNF α " and its receptor "TNFR-P75" besides serum selenium, copper and zinc levels were performed.

Results and Conclusion: changes in assessed parameters elaborated higher magnitude of change imposed by HBsAg coinfection in HCV cases wit PHS delineating a relative impact complex interactions in cases with va culitis.

INTRODUCTION

In the Middle Eastern countrie the effects of environmental health ha ards implicate the combination of vir hepatitis with *Schistosoma manso* parasitic infection. This appears mo common among the lower socioec nomic classes with non-hygienic li style. Schistosomiasis induces low immune resistance which renders the classes more prone to viral hepatitis i fection mainly hepatitis B virus (HBV and hepatitis C virus (HCV) (El-Dardi et al., 2000).

Chronic liver cell injury relat to viral replication in the hepatocy could be ascribed to either hepatocytol sis or to the consequences of the immu response potentiating multidisciplina mechanisms involved in development vasculitis (Chwla, 2005). The chror HBV infection which is indicated detectable hepatitis B surface antig (HBsAg) in serum and liver with hepatitis B envelope (HBe), or DN indicates that low levels of the virus

the liver or other tissues exist (Michielsen et al., 2005). The persistence of infection, on the other hand, in most HCV-infected individuals occurs despite the presence of HCV-directed antibodies which suggests that such antibodies fail to induce viral clearance (Henderson, 2003). Thus the dominant cause of viral persistence during HCV infection may be due to the development of a week CD4, CD8 and T cell immune response to the viral antigens, with corresponding inability to eradicate infected cell (Kim et al., 2005).

The challenging outcome of multiple risk-factor distribution in parasitic and viral coinfection identifies a common pathway leading to vascular endothelial damage (Rao et al., 2002). This may influence the development of vasculitis among extrahepatic manifestations and the contributing events including hemostatic disequilibria and immunoinflammatory response (Sneller and Fauci, 1997). Also it may be colinked with perturbations of trace elements (Fraga, 2005) which pave the way to thrombogenic (Caprini et al., 2004), atherogenic (Handin, 1998) and fibrogenic potential (Bataller and Brenner, 2005).

In relevance, the present study aims to monitor variable risk factors, (HbsAg and past history of schistosomiasis), in addition to selected biochemical indices in HCV cases that might influence the development of vasculitis and cardiovascular disease. Assessed biochemical indices include, serum von Willebrand factor, plasminogen activator inhibitor-1 (PAI-1), thrombin-antithrombin complex (TAT), tumor necrosis factor α (TNFα) and tumor necrosis factor receptor (TNFR-P75), besides the trace elemer Se, Zn and Cu and liver function tests.

SUBJECTS AND METHODS

The study was conducted on thir volunteer patients with vasculitis a hepatitis C viral infection selected fro King Abdul Aziz University Hospit They were classified into three groups bases of the presence of records of pa history of *Schistosoma mansoni* (PH and presence of hepatitis B surface an gen (HBsAg) as Group I, presence HBsAg with no records of PHS as Gro II and absence of HBsAg with no recor of PHS as group III. A normal contr group (Group IV), of ten volunte healthy subjects was included. Selectic of cases in I, II, and III was based on t clinical aspects of vasculitis according Stegeman and Kallenberg (2001). Clir cal investigation was done for cases wi PHS including abdominal ultrasonogr phy (Abdel-Wahab et al., 1992), sto analysis for absence of viable ova or d tection of dead ova (Katz et al., 199 and haemagglutination test (Madwar ar Voller, 1975). All groups were subjecte to full clinical investigation, in additic to liver and kidney function testing. A blood samples were withdrawn aft overnight fasting and sera were separate by centrifugation. Abdominal ultrasour and liver biopsy were done to confir diagnosis. The presence of chronic HC was determined by abnormally elevate serum aminotransferases for more than month and a positive serological test f HVC-specific antibodies (ELISA3 confirmed with RIBA3 anti-HCV ant bodies). Sera were tested quantitativel for HCV-RNA by polymerase chain r action (PCR) (Ravaggi et al.,1992), an

further HBsAg by ELISA technique using commercial kits from Abbott Company USA.

Measurement of plasminogen activator inhibitor-1 (PAI-1), was preformed using the antibody-based enzyme linked immunosorbent assay (Declerck *et al.*, 1988) together with thrombin-antithrombin III complex in plasma (Hoek et al., 1988) and serum von Willebrand factor antigen concentrations (Blann et al., 1992). Moreover, Serum TNFα was estimated by solid phase sandwich ELISA technique using clinical laboratory kits, (Diaclone, France) (Ledur et al., 1995) and serum TNF receptor P75 (TNFR-P75) was analyzed by enzyme amplified sensitivity immunoassay (EASIA) kit (Marinos et al., 1995) provided from Biosource Europe SA, Belgium.

Liver and kidney function test included: serum albumin which was estimated colorimetrically by the method of Doumas and Peters (1997) and liver enzymes, alanine transaminase (ALT) and aspartate transaminase AST which were determined by the colorimetric method of Reitman and Frankel (1957). Also, total serum bilirubin was assessed by the colorimetric technique of Bartels and Doumer (1970) and serum alkaline phosphatase was evaluated according to Kind and King (1954). Moreover, analysis of the trace elements Zn and Cu (Kiilholma et al., 1984), and Se (Gardiner et al., 1995) was preformed by atomic absorption spectrometry.

Statistical Analysis:

Results are represented as means ±S.D. Statistical analysis of the data was carried out using SPSS Package Version 11.5 of "Apache Software Foundatio USA. The percentage of change betwe each group and the control group v determined using the Student t-test l tween the different groups.

RESULTS

Table (I) shows the results, (me ± S.D) and their statistical analysis the studies indices of hemostatic diseq libria and immune response of all gro under study. Statistically significant creases above the normal control val were noted for all studied paramete ($p<0.05$-$p<0.01$). However, the compa son of other patient group means w each other has revealed significant lo levels of most of the studied paramet for Group III, (HCV only), except PAI-1, TAT and TNFR-P75 of Group (HCV with HBsAg). The effect of P has been reflected as significantly hig values of most of the studied paramet of Group I (HCV and PHS with HBs/ over Group II, (HCV with HBsA ($p<0.05$-$p<0.01$) with exception of v and TNFR-P75 wich showed n significant increases.

Table (II) shows the results, (m ± S.D) and their statistical analysis all groups under study. Serum albu was significantly lower in patient gro as compared to the normal control gr (Group VI), ($p<0.05$-p0.01). The sa applied to Group I and II, (HCV PHS with HBsAg and HCV with HBs respectively), when compared of relatively higher values of Group (HCV only). As for serum bilirubin, the studied groups showed significa higher values over the normal con group, ($p<0.05$-p0.01). All pati groups were significantly different fr

each other, with Group I, (HCV and PHS with HBsAg), being higher followed by group II, (HCV with HBsAg), then group III, (HCV only). Serum alkaline phosphatase followed typically the same pattern on statistical analysis of its values. The same applied for serum ALT and AST with the only exception of the non-significant increase in ALT of Group III, (HCV only), over the other patient groups.

Table (III) shows serum trace elements results, (mean ± S.D) and their statistical analysis for all the studied groups. As to be expected serum selenium showed significantly lower level on comparison of all patient groups to normal control group, ($p<0.01$), However, Group III, (HCV only), recorded significantly higher level than Group II, (HCV with HBsAg) and Group I, (HCV and PHS with HBsAg), respectively. Typical copy of the above pattern applied to serum zinc, where there was a significant increase of serum copper in all the patient groups over the normal control group, ($p<0.01$). The highest level of serum copper was found in Group I, (HCV and PHS with HBsAg), which was significant from its level in Group III, (HCV only), but non-significantly different from Group II, (HCV with HBsAg). A non-significant increase was also found in Group I, (HCV and PHS with HBsAg) over Group II, (HCV with HBsAg

DISCUSSION

In selected cases with vasculitis under study (Group I – Group III), the assessed data of increments of vWF, TNFα and TNFR-P75 (Table I) reflect the relationship between the magnitude of vascular injury with critical and cor plex events. They appeared to be mec ated by immuno-inflammatory respon involving generation of cytokines mod lating the coagulation systems by moc fying the balance between procoagula and anticoagulant activities. Confirm tively, the increments of TAT and PAI in parallel to TNFα and TNFR-P75 ve ify such an interrelationship. Hence, h pofibrinolysis elaborated by increase PAI-1 levels concords with magnitude vascular damage which was reflected b assessed increment of vWF. It was pose by HCV/ HBV coinfection with schist somal hepatic fibrosis coinciding wi reports associated with fibrogen mechanisms (Poynard et al., 2004). Fu thermore, reports denoted that thron bogenic potential could be mediated b binding of vWF to platelet specific adh sion receptors to initiate platelet adh sion and aggregation (Ruggeri, 2003). A well, it could event from activation endothelial cells secreting inhibitors plasminogen activators as PAI-1whic depresses fibrinolysis and confers a overall procoagulant effect (Thogersen al., 1998).

Concordingly, in cases with vascu litis (Group I-Group III) the monitore activation of the coagulation cascade wa reflected by increased thrombin produc tion and antithrombin III (AT III) cor sumption expressing a higher magnitud of change in cases with mixed HbsAg HCV AND PHS coinfection (Table I Subsequently, the present findings c higher TAT coordinates with lower lev els of the AT III (Schuppan *et al.*, 2003 and those factors which control the function (Carrell et al., 2003) as re ported in HCV cases with hepatic fibro sis. Thus, local intravascular clotting an

Table (1): Indices of hemostatic disequilibria and immune response in normal (the c trol) and patient groups, (mean± S.D.)

Parameters	HCV cases with vasculitis			Contr
	Group I	Group II	Group III	Group
Plasminogen Activator inhibitor type-1 (PAI-1 ng/ml)	25.2±5.1	19.7±4.4	16.9±4.1	11.7±3
t_1	6.96** (p<0.01)	4.55** (p<0.01)	3.09** (p<0.01)	
t_2	4.01** (p<0.01)	1.47 (NS)		
t_3	2.58* (p<0.05)			
Thrombin-Antithrombin Complex (TAT μg/L)	3.84±0.9	2.99±0.7	2.91±0.4	1.86±0
t_1	6.60** (p<0.01)	4.69** (p<0.01)	6.64** (p<0.01)	
t_2	2.99** (p<0.01)	0.31 (NS)		
t_3	2.36* (p<0.05)			
von Willebrand Factor (vWF %)	271.0±49.0	234.0±44.0	192.0±34.0	158.0±2
t_1	6.70** (p<0.01)	4.93** (p<0.01)	2.69* (p<0.05)	
t_2	4.19** (p<0.01)	2.39* (p<0.05)		
t_3	1.78 (NS) (p>0.05)			
Tumour Necrosis Factory (TNF-α Pg/ml)	248±5.9	203±4.8	186±3.9	43.7±1
t_1	47.05** (p<0.01)	37.89** (p<0.01)	34.62** (p<0.01)	
t_2	27.72** (p<0.05)	8.69** (p<0.01)		
t_3	18.71** (p<0.01)			
Tumour Necrosis Factor Receptor P-75 (TNFR-P75 μg/ml)	24.7±8.4	19.8±6.2	16.1±5.3	4.33±1
t_1	7.55** (p<0.01)	7.66** (p<0.01)	6.75** (p<0.01)	
t_2	2.74* (p<0.05)	1.43 (NS)		
t_3	1.48 (NS)			

t_1: Normal control group, (Group IV) vs. other patient groups
t_2: (Group III) vs. other patient groups
t_3: (Group I) vs. (Group II)
NS: Non-significant difference
Group I: HCV and +ve S.mansoni with HBsAg, Group II: HCV in the HBsAg, Group III: HCV only, Group IV: Normal control.

Table (2): Liver function tests in the normal control and patient groups, (mean± S.D.)

Parameters	HCV cases with vasculitis			Contro
	GI	GII	GIII	GIV
Albumin (g/dl)	2.27±0.37	2.7±0.51	2.97±0.43	3.51±0.5
t_1	5.99** (p<0.01)	3.45** (p<0.01)	2.47* (p<0.05)	
t_2	3.90** (p<0.01)	1.28 (NS)		
t_3	2.16 (NS)			
Total Bilirubin (mg/dl)	0.99±0.07	0.75±0.04	0.59±0.07	0.48±0.0
t_1	14.14** (p<0.01)	8.67** (p<0.01)	3.05** (p<0.01)	
t_2	12.78** (p<0.01)	6.28** (p<0.01)		
t_3	9.41** (p<0.01)			
Alkaline phosphatase (U/dl)	12.8±3.2	9.63±2.2	6.31±2.4	4.61±1.
t_1	7.65** (p<0.01)	6.45** (p<0.01)	2.04* (p<0.05)	
t_2	5.13** (p<0.01)	3.22** (p<0.01)		
t_3	2.58* (p<0.05)			
Alanine transaminase (ALT U/L)	53.9±8.4	44.8±7.1	39.3±5.4	23.7±3.
t_1	10.67** (p<0.01)	8.61** (p<0.01)	7.92** (p<0.01)	
t_2	4.62** (p<0.01)	1.95 (NS)		
t_3	2.62* (p<0.05)			
Aspartate transaminase (AST U/L)	54.8±11.5	36.7±7.1	24.1±6.4	15.4±4.
t_1 (p)	10.21** (p<0.01)	8.22** (p<0.01)	3.62** (p<0.01)	
t_2 (p)	7.38** (p<0.01)	4.17** (p<0.01)		
t_3 (p)	4.24** (p<0.01)			

t_1: Normal control group, (Group IV) vs. other patient groups
t_2: (Group III) vs. other patient groups
t_3: (Group I) vs. (Group II)
NS: Non-significant difference
Group I: HCV and +ve S.mansoni with HBsAg, Group II: HCV in the HBsAg, Group III: HCV only, Group IV: Normal control.

Table (3): Selected indices of serum trace elements in the normal control and patie groups, (mean± S.D.)

Parameters	HCV cases with vasculitis			Contro
	GI	GII	GIII	GIV
Selenium (m mol / L)	0.44±0.09	0.51±0.09	0.62±0.11	0.88±0.1
t_1	6.62** (p<0.01)	5.57** (p<0.01)	3.74** (p<0.01)	
t_2	4.00** (p<0.01)	2.45* (p<0.05)		
t_3	1.74 (NS)			
Zinc (µg/ml)	39.0 ± 9.7	43.7 ± 9.4	58.1 ± 10.3	98.0 ± 17
t_1	9.20** (p<0.01)	8.53** (p<0.01)	6.14** (p<0.01)	
t_2	4.27** (p<0.01)	3.27** (p<0.01)		
t_3	1.10 (NS)			
Copper (µg/ml)	154.0±20.4	142.0±18.6	133.0±17.2	90.1±16
t_1	7.78** (p<0.01)	6.67** (p<0.01)	5.76** (p<0.01)	
t_2	2.49* (p<0.05)	1.12 (NS)		
t_3	1.37 (NS)			

t_1: Normal control group, (Group IV) vs. other patient groups

t_2: (Group III) vs. other patient groups

t_3: (Group I) vs. (Group II)

NS: Non-significant difference

Group I: HCV and +ve S.mansoni with HBsAg, Group II: HCV in the HBsAg, Group III: HCV only, Group IV: Normal control.

occlusion may occur by subtle forms of immune or inflammatory activation such as that posed by chronic hepatitis (Safadi et al., 2003). It occurs in relation to alterations of hemostatic factors which serve to balance coagulopathy versus fibrinolysis (Ware et al., 2005). In harmony, the assessed increase in TAT (Table 1) may represent a compensatory mechanism relative to magnitude of hepatic disposition which may become less efficient in the presence of multiple liver insults such as that posed by PHS and HbsAg/HCV. In event, lower synthetic rate of anticoagulants by the liver, occurs with a subsequent greater risk of thromboembolic complications as noted eleswhere (Omran et al., 1994; Josic et al., 2003; Ware et al., 2005). Confirmatively, the present findings identified the outcome of immuno-inflammatory response to viral infection and parasitic hepatic predisposition in association with magnitude of vasculitis in alignment with previous findings (Mogensen and Paludan, 2001; Woitas et al., 2002; Bowen and Walker, 2005; Strader *et al.*, 2005). Hence, the outcome of above mentioned scenario inducing vasculitis via inflammatory involvement of any artery, vein or venule occurs via many clinicopathological entities (Gouwy et al., 2005), distinctive of this condition implementing immunologic aspects (Meister, 2003).

Consistently, the associated increase of TNFα and TNFR-P75 (Group I>Group II>Group III vs Group IV) was observed to represent a mediator of both specific and nonspecific immune response (El-Dardiry et al., 2004). It also elaborates an important link between immuno-inflammatory reaction (Mogensen and Paludan, 2001; Neumann-Haefelin et al., 2005) and healir process (Woitas et al., 2002). The mon tored increase in TNFα herein (Table reflects its potent cytotoxic effector ro that appears as a powerful modulator immune response mediating the gran loma formation (Joseph ar Boros,1993), tissue necrosis (Strader al., 2005) and fibrosis (Fabris et a 2006) in many organ system. Evidentl fibrogenesis proceeds only when add tional profibrogenic stimuli are prese (Wu and Zern, 2000). It may implemer the additive effect posed by PHS herei which is known to skew the immur response towards a Th-2T cell reactio (Rao et al., 2002). Moreover, in correl tion with fibrogenic mechanisms elab rated by diagnostic indices herein, th regulation of cell-mediated immune r sponse verified increased level of TNF and TNFR-P75 that reflect disease activ ity (Fabris et al., 2006). This shows positive relation as noted elsewher (Friedman, 2003) and herein to increase level of serum transaminases (ALT an AST) and bilirubin vs. decreased seru albumin (Table II) identifying the clos link to assessed alteration in the indice of liver function test. Such findings re late a crucial role noted previously (W and Zern, 2000) to occur in hepatic ne crosis and inflammation than in apop tosis (Arendt et al., 2005) whereby infec tion with HCV is characterized by in flammatory liver damage with viral per sistence (Jamal and Morgan, 2003; Pa chiadakis et al., 2005).

In harmony, the assessed magni tude of selenium (Se) decrement ob served herewith (Table III) appearin more profound in mixed HbsAg/HC cases with PHS may exacerbate tissu lesions as reported elsewhere (Fraga

2005). Thus, Se which is a major antioxidant trace element is known to act as the cofactor of glutathione peroxidase (GSHPx) whereby reports related that low Se GSHPx activity may be colinked with thrombosis and cardiovascular complications (Bansal and Kaur, 2005). As Se represents an important component of the endogenous antioxidant defense system, its deficiency has been noted to increase the sensitivity of a living system to oxidative stress. Thus, Se contributes to cellular antioxidant defense against reactive molecules and free radicals, which cause lipid peroxidation (Tapiero et al., 2003). In reference, reports indicated that the biological activities of Cu and Se are strongly associated with the presence of unpaired electrons that allow their participation in redox reactions (Klotz et al., 2003).

Moreover, Zn decrements evident with higher magnitude in Group I >Group II >Group III relative to Group IV (Table III) reflects as noted elsewhere the intensity of vascular injury (Hennig et al., 1999) with impaired healing capacity. This was implemented herewith by mixed HBsAg/HCV cases with PHS. Hence, Zn ions exist primarily in the form of complexes with proteins and nucleic acids and participate in all aspects of intermediary metabolism, transmission and regulation of the expression of genetic information, storage, synthesis and action of peptide hormones and structural maintenance of chromatin and biomembranes (Tapiero and Tew, 2003). Probably, as Zn-dependent enzymes are crucial for many metabolic processes, so the fall in serum Zn-levels may be due to increased uptake of Zn to meet cofactor and substrate requirements with inflammation monitored herein. Moreover, as Cu and Zn may compete for bind sites on metallothionein or me lothionein-like protein complex ther excess of one is often associated v diminution of the other (Hambic 2003). In alignment, the assessed in ments in Cu levels furthermore identi the inflammatory response noted e where (Speich et al., 2001) and he via the influence of dual HBsAg/H coinfection to cases with PHS un study.

In conclusion, the assessed alt tions in presented data elaborated principal pathogenic mechanisms have been implicated for possible r in cases with vasculitis under stu From our study, we have suggested impact of potential relationships betw human pathogens and vasculitis. well sustained associations betw hepatitis B or C with PHS has led to increased understanding of the patho netic mechanisms of systemic vascu delineating a relative impact of comp interactions. Such an aspect should carefully considered in planning the velopment of new therapeutic alte tives, with better potential specificity both the inflammation and immunol causes of vasculitis.

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إلتهاب الاوعيه الدمويه : تاثير الكبد الوبائي الفيروسي من النوع بى، سى في الحالات السابق إصابتها بالبلهارسيا المعوية

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دف من البحث : يهدف البحث لدراسة حجم الإختلال فى معدلات وقف النزف والإستجابة اعية وعدم توازن العناصر النادرة مثل السلينيوم والنحاس والخارصين (الزنك) وذلك فى لات التهاب الأوعية الدموية المصاحبة للإلتهاب الكبدى الوبائى بى ، سى فى المرضى ابق إصابتهم بالبلهارسيا المعوية

لة البحث: أجري هذا البحث على ٣٠ حالة من الكبد الوبائي الفيروسي سى مع التهابات وعية الدموية ليشاركوا في إجراء هذه الدراسة . وقد تم تقسيمهم إلى ثلاثة مجموعات: مجموعه الاولى (١٠ حالات) ذات إصابه سابقة بالبلهارسيا المعوية والأنتيجينات السطحية بد الوبائي بى والمجموعه الثانيه (١٠ حالات) وجود الانتيجنيات السطحية للكبد الوبائي بى م يسبق إصابتها بالبلهارسيا المعويه والمجموعه الثالثه (١٠ حالات) لا يوجد بها أنتيجينات لحية للكبد الوبائي بى ولم يسبق إصابتها بالبلهارسيا المعويه. المجموعه الرابعه وهي جموعه الضابطه وتحتوى على (١٠ حالات) من الاشخاص الاصحاء.

د تمت التقديرات في مصل الدم لمثبط منشط البلازمينوجين -١ (PAI-1) ومخثر- مضاد خثر (TAT) ومعامل فان ولي براند (vWF) ومعامل الورم المهلك (TNF) و مستقبله، لاضافة الى العناصر النادرة و تشمل السلينيوم و النحاس و الخارصين.

تائج و الاستنتاج : التغير في المؤشرات المقيمة توضح عظم معادل التغير الحادث نتيجة صابة بالالتهاب الكبدى الوبائى سى أو بى المصاحب للاصابة بالبلهارسيا المعوية وتأثير ذلك ى الاصابة بالتهاب الأوعية الدموية.

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