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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 with PHS delineating a relative impact of complex interactions in cases with vasculitis.

INTRODUCTION

In the Middle Eastern countries the effects of environmental health hazards implicate the combination of viral hepatitis with *Schistosoma mansoni* parasitic infection. This appears more common among the lower socioeconomic classes with non-hygienic life style. Schistosomiasis induces low immune resistance which renders these classes more prone to viral hepatitis infection mainly hepatitis B virus (HBV) and hepatitis C virus (HCV) (El-Dardi et al., 2000).

Chronic liver cell injury related to viral replication in the hepatocytes could be ascribed to either hepatocytolysis or to the consequences of the immune response potentiating multidisciplinary mechanisms involved in development of vasculitis (Chwila, 2005). The chronic HBV infection which is indicated by detectable hepatitis B surface antigen (HBsAg) in serum and liver with hepatitis B envelope (HBe), or DNA 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 weak 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 (TNF α) and tumor necrosis factor receptor

(TNFR-P75), besides the trace elements Se, Zn and Cu and liver function tests.

SUBJECTS AND METHODS

The study was conducted on thirty volunteer patients with vasculitis and hepatitis C viral infection selected from King Abdul Aziz University Hospital. They were classified into three groups on the basis of the presence of records of past history of *Schistosoma mansoni* (PHS) and presence of hepatitis B surface antigen (HBsAg) as Group I, presence of HBsAg with no records of PHS as Group II and absence of HBsAg with no records of PHS as group III. A normal control group (Group IV), of ten volunteer healthy subjects was included. Selection of cases in I, II, and III was based on the clinical aspects of vasculitis according to Stegeman and Kallenberg (2001). Clinical investigation was done for cases with PHS including abdominal ultrasonography (Abdel-Wahab et al., 1992), stool analysis for absence of viable ova or detection of dead ova (Katz et al., 1997) and haemagglutination test (Madwar and Voller, 1975). All groups were subjected to full clinical investigation, in addition to liver and kidney function testing. A blood samples were withdrawn after overnight fasting and sera were separated by centrifugation. Abdominal ultrasound and liver biopsy were done to confirm diagnosis. The presence of chronic HCV was determined by abnormally elevated serum aminotransferases for more than three months and a positive serological test for HVC-specific antibodies (ELISA3 confirmed with RIBA3 anti-HCV antibodies). Sera were tested quantitatively for HCV-RNA by polymerase chain reaction (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 performed 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 TNF α was estimated by solid phase sandwich ELISA technique using clinical laboratory kits, (Diacalone, 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 performed by atomic absorption spectrometry.

Statistical Analysis:

Results are represented as means \pm S.D. Statistical analysis of the data was carried out using SPSS Package Version

11.5 of "Apache Software Foundation USA. The percentage of change between each group and the control group was determined using the Student t-test between the different groups.

RESULTS

Table (I) shows the results, (mean \pm S.D) and their statistical analysis of the studied indices of hemostatic disequilibrium and immune response of all groups under study. Statistically significant increases above the normal control values were noted for all studied parameters ($p < 0.05$ - $p < 0.01$). However, the comparison of other patient group means with each other has revealed significant low levels of most of the studied parameters for Group III, (HCV only), except PAI-1, TAT and TNFR-P75 of Group (HCV with HBsAg). The effect of PHS has been reflected as significantly high values of most of the studied parameters of Group I (HCV and PHS with HBsAg) over Group II, (HCV with HBsAg) ($p < 0.05$ - $p < 0.01$) with exception of vWF and TNFR-P75 which showed no significant increases.

Table (II) shows the results, (mean \pm S.D) and their statistical analysis of all groups under study. Serum albumin was significantly lower in patient groups as compared to the normal control group (Group VI), ($p < 0.05$ - $p < 0.01$). The same was applied to Group I and II, (HCV and PHS with HBsAg and HCV with HBsAg respectively), when compared of relatively higher values of Group III (HCV only). As for serum bilirubin, the studied groups showed significantly higher values over the normal control group, ($p < 0.05$ - $p < 0.01$). All patient groups were significantly different from

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 \pm 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, TNF α and TNFR-P75 (Table I) reflect the relationship between the magnitude

of vascular injury with critical and complex events. They appeared to be mediated by immuno-inflammatory response involving generation of cytokines modulating the coagulation systems by modifying the balance between procoagulant and anticoagulant activities. Confirmatively, the increments of TAT and PAI-1 in parallel to TNF α and TNFR-P75 verify such an interrelationship. Hence, hypofibrinolysis elaborated by increased PAI-1 levels concurs with magnitude of vascular damage which was reflected by assessed increment of vWF. It was possible by HCV/ HBV coinfection with schistosomal hepatic fibrosis coinciding with reports associated with fibrogen mechanisms (Poynard et al., 2004). Furthermore, reports denoted that thrombogenic potential could be mediated by binding of vWF to platelet specific adhesion receptors to initiate platelet adhesion and aggregation (Ruggeri, 2003). As well, it could event from activation of endothelial cells secreting inhibitors of plasminogen activators as PAI-1 which depresses fibrinolysis and confers an overall procoagulant effect (Thogersen et al., 1998).

Concordingly, in cases with vasculitis (Group I-Group III) the monitored activation of the coagulation cascade was reflected by increased thrombin production and antithrombin III (AT III) consumption expressing a higher magnitude of change in cases with mixed HbsAg HCV AND PHS coinfection (Table I). Subsequently, the present findings of higher TAT coordinates with lower levels of the AT III (Schuppan et al., 2003) and those factors which control the function (Carrell et al., 2003) as reported in HCV cases with hepatic fibrosis. Thus, local intravascular clotting an

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

Parameters	HCV cases with vasculitis			Contr Group
	Group I	Group II	Group III	
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±0.6
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)			

t₁: Normal control group, (Group IV) vs. other patient groups

t₂: (Group III) vs. other patient groups

t₃: (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)			

t₁: Normal control group, (Group IV) vs. other patient groups

t₂: (Group III) vs. other patient groups

t₃: (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 patient groups, (mean± S.D.)

Parameters	HCV cases with vasculitis			Control
	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)			

t₁: Normal control group, (Group IV) vs. other patient groups

t₂: (Group III) vs. other patient groups

t₃: (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 elsewhere (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 $TNF\alpha$ 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; Neu-

mann-Haefelin et al., 2005) and healing process (Woitas et al., 2002). The monitored increase in $TNF\alpha$ herein (Table I) reflects its potent cytotoxic effector role that appears as a powerful modulator of immune response mediating the granuloma formation (Joseph and Boros, 1993), tissue necrosis (Strader et al., 2005) and fibrosis (Fabris et al., 2006) in many organ system. Evidently, fibrogenesis proceeds only when additional profibrogenic stimuli are present (Wu and Zern, 2000). It may implement the additive effect posed by PHS herein which is known to skew the immune response towards a Th-2T cell reaction (Rao et al., 2002). Moreover, in correlation with fibrogenic mechanisms elaborated by diagnostic indices herein, the regulation of cell-mediated immune response verified increased level of $TNF\alpha$ and TNFR-P75 that reflect disease activity (Fabris et al., 2006). This shows positive relation as noted elsewhere (Friedman, 2003) and herein to increase level of serum transaminases (ALT and AST) and bilirubin vs. decreased serum albumin (Table II) identifying the close link to assessed alteration in the indices of liver function test. Such findings relate a crucial role noted previously (Wu and Zern, 2000) to occur in hepatic necrosis and inflammation than in apoptosis (Arendt et al., 2005) whereby infection with HCV is characterized by inflammatory liver damage with viral persistence (Jamal and Morgan, 2003; Pachiadakis et al., 2005).

In harmony, the assessed magnitude of selenium (Se) decrement observed herewith (Table III) appearing more profound in mixed HbsAg/HCV cases with PHS may exacerbate tissue 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 metallothionein-like protein complex their excess of one is often associated with diminution of the other (Hambic 2003). In alignment, the assessed increments in Cu levels furthermore identify the inflammatory response noted elsewhere (Speich et al., 2001) and heretofore via the influence of dual HBsAg/HCV coinfection to cases with PHS under study.

In conclusion, the assessed alterations in presented data elaborated principal pathogenic mechanisms that have been implicated for possible role in cases with vasculitis under study. From our study, we have suggested impact of potential relationships between human pathogens and vasculitis. As well sustained associations between hepatitis B or C with PHS has led to increased understanding of the pathogenic mechanisms of systemic vasculitis delineating a relative impact of complex interactions. Such an aspect should be carefully considered in planning the development of new therapeutic alternatives, with better potential specificity both the inflammation and immunologic causes of vasculitis.

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إلتهاب الأوعية الدموية : تأثير الكبد الوبائي الفيروسي من النوع بى، سى فى

الحالات السابق إصابتها بالبلهارسيا المعوية

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

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

دتمت التقديرات فى مصل الدم لمثبط منشط البلازمينوجين -١ (PAI-1) ومخثر - مضاد خثر (TAT) ومعامل فان ولي براند (vWF) ومعامل الورم المهلك (TNF) و مستقبله، لإضافة الى العناصر النادرة و تشمل السلينيوم و النحاس و الخاصين.

تائج و الاستنتاج : التغير فى المؤشرات المقيمة توضح عظم معادل التغير الحادث نتيجة إصابة بالالتهاب الكبدى الوبائى سى أو بى المصاحب للإصابة بالبلهارسيا المعويه وتأثير ذلك فى الإصابة بالتهاب الأوعية الدموية.

١. المجلة المصرية للعلوم الطبية ٢٧(٢) ديسمبر ٢٠٠٦: ٥٦١-٥٧٤.