Original Article

A Study of Atherosclerosis in Systemic Vasculitis

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Abstract

Introduction: Vasculitides are diseases characterised by inflammation of blood vessels. Systemic Vasculitis exhibits an enhanced cardiovascular morbidity and mortality akin to Rheumatoid arthritis and Systemic lupus erythematosus. In many systemic vasculitides, accelerated atherosclerosis has become a leading cause of death.

Aim & Objectives: To study the correlation of atherosclerosis in patients with different forms of Vasculitis.

Material & Methods: 13 consecutive patients attending the Dept of Medicine were studied along with 10 age and sex matched controls. Information regarding traditional risk factors was obtained. Disease Activity was assessed by BVAS and organ damage by VDI. Plasma lipid concentrations, C reactive protein (CRP) and ANCA were measured and IMT, a marker of early atherosclerosis, was measured by B-mode ultrasound of extra cranial part of common carotid artery.

Results: Out of the 13 cases studied, 3 had Polyarteritis nodosa, 3 Takayasu arteritis, 2 Churg strauss syndrome, 3 Wegener's granulomatosis,1 Microscopic Polyangiitis, and 1 Hypocomplementic urtecarial vasculitis. Baseline characteristics of patients and controls were similar. Mean disease duration was 3.59±2.45 yrs. Active disease was present in 7 patients with a cumulative BVAS of 78±8.83 whereas VDI was 2.2±1.48 (10 patients having damage). IMT was increased (0.93±0.96 mm) in 10 of 13 (76.92%) patients and 3 of 10 (0.76 ± 0.26 mm) (33.33%) controls. Mean CRP level in patients of Vasculitis was 9±3.46 as against a level <6 in the controls. 4 patients were positive for ANCA (C-ANCA: 2, P-ANCA:1, P+C ANCA: 1). Comparison of patients with and without increased IMT and controls revealed a longer duration of illness (3.77±2.63 Vs 3±1.73), more cumulative BVAS (76±8.72 Vs 13±3.6), more damage (14±3.74 Vs 8±2.83), and increased CRP level (12 ±3.46 Vs 6±2.45) in those having increased IMT without any difference in traditional/nontraditional risk factors including lipid levels amongst the groups.

Conclusion: In our study increased IMT, a sign of accelerated development of atherosclerosis in patients with Systemic Vasculitis is present as compared to controls. This cannot be explained by an increased prevalence of traditional risk factors. Whether the rise of CRP values resulted from atherosclerosis or indicated ongoing activity needs to be further analyzed in prospective studies.

Keywords: Atherosclerosis, Intima media thickness, Vasculitis

INTRODUCTION

Vasculitides are diseases characterised by inflammation of blood vessels. Its clinical manifestations are dependent on the localisation and size of the involved vessels as well as on the nature of the inflammatory process. In many systemic vasculitides, accelerated atherosclerosis has become a leading cause of death.

Systemic rheumatic diseases are complicated by excess cardiovascular mortality, suggesting an accelerated atheromatous process, which relates to the vascular inflammation common in such diseases. Atherosclerosis is a complex and progressive disease of the arterial vasculature consisting of fibro-fatty and fibrous lesions preceded and accompanied by inflammation.[1] Patients with different forms of systemic vasculitis experience long-term morbidity and mortality caused by cardiovascular disease due to premature atherosclerosis.

Systemic vasculitis is a clinicopathologic process characterized by inflammation and necrosis of blood vessels.[2] Patients with systemic vasculitis have a higher risk to develop atherosclerosis than healthy controls[3,4] and this view was also supported by animal models.[5] Oxidized low-density lipoproteins are believed to play important role in the progression of the atherosclerosis. Production of oxygen species plays a pivotal role in the pathophysiology

of vasculitis,[6] which would in turn cause increased oxidation of LDL (low density lipoprotein) leading to atherosclerosis.[7]

Autoimmune diseases like RA (Rheumatoid Arthritis) and SLE (Systemic lupus erythematosus) are complicated by excess cardiovascular morbidity and mortality, which cannot be explained by traditional risk factors.[8,9]

Premature and accelerated atherosclerosis, with enhanced cardiovascular morbidity and mortality, occurs in the course of systemic inflammatory diseases such as RA, SLE and vasculitis.[10]

The systemic vasculitides are a heterogeneous group of diseases, with different patterns of organ involvement, size and type of vascular target, and varying pathological mechanisms, such as ANCA associated damage.

Neutrophil-derived myeloperoxidase and its oxidants, T cells and autoantibodies such as antineutrophil cytoplasmic antibodies (ANCA), anti-endothelial cell antibodies and anticardiolipin antibodies play an important pathophysiological role in the acceleration of atherosclerosis in vasculitis.

Several studies have now shown that, during long-term follow-up, cardiovascular disease is a major cause of mortality in patients with ANCA-associated vasculitis.[11] Zaenker *et al.* reported that patients with Wegener's granulomatosis had a higher frequency of cardiovascular diseases compared with healthy controls [odds ratio (OR)6 ·7].[12] In line with these findings, patients with ANCA-associated vasculitis more often had stroke and/or myocardial infarction (OR 3-4).[13]

The atherosclerotic process is further enhanced due to the presence of co-existent diabetes, hypertension, dyslipidaemia, abdominal obesity (metabolic syndrome), impaired renal function, persistent proteinuria and increased production of C-reactive protein.

This current study is aimed at determining if atherosclerosis could be found in vascular beds unaffected by the primary vasculitic process, and whether vasculitis subgroup or ANCA association influenced this. Multisystem disease such as systemic vasculitis is often complicated by secondary problems which are also associated with atherosclerosis, such as uraemia and hypertension.

Systemic Vasculitis exhibits an enhanced cardiovascular morbidity comparable with that seen in SLE and RA. Increased Intima Media thickness (IMT), a tool for atherosclerosis imaging and event prediction[14] was found increased in Wegener's Granulomatosis (WG) patient's, which could not be explained by traditional risk factors.[15]

Diagnosis of Vasculitis carries an independent possibility of cardiovascular risk and has potential implications regarding their treatment and surveillance.[16]

AIM & OBJECTIVES

To study the correlation of atherosclerosis in patients with different forms of systemic vasculitis.

MATERIALS & METHODS

Ethical approval was given by the Local Research Ethics Committee for the study and informed consent was obtained from each patient.

Thirteen consecutive patients attending the Medicine Department of NSCB Medical College Jabalpur, fulfilling the American College of Rheumatology and Chappell Hill Consensus Criteria for different Vasculitides were included in the study. Secondary Vasculitis was excluded from the study. Ten age and sex matched volunteers were recruited as controls.

Information was obtained from all subjects with respect to the traditional risk factors for cardiovascular diseases including blood pressure; lipid levels, smoking status, diabetes and family history of cardiovascular diseases.

Vasculitis Disease Activity[17] was assessed by the Birmingham Vasculitis Activity Score (BVAS) and active disease was defined as BVAS of >1 and organ damage was assessed by Vasculitis Damage Index (VDI).[18] Clinical remission was defined as the absence of significant disease activity for at least one month (BVAS=0-1), active disease was defined as BVAS>1.

Blood Analyses

Cholesterol, Low density lipoprotein (LDL), Very Low density lipoprotein (VLDL), High density lipoprotein (HDL), triglycerides and C-reactive protein (CRP) were measured by routine techniques and MPO and PR-3 ANCA was measured by ELISA and IF (Iimmunoflorecence).

Measurement of Intima-Media thickness (IMT)

IMT was measured by B-mode ultrasound of extra cranial part of common carotid artery and mean IMT was calculated. Adequate data of all 13 patients and 10 controls were available for analysis.

IMT was considered to be increased when it exceeded 0.8 mm at the age of 50 and 0.9 mm when age was over 50.[19]

Statistical Analysis

Comparison between patients and controls were made by Mann-Whitney U tests and chi-square test. A p value of <0.05 was considered significant.

RESULTS

Out of the 13 cases studied, 3 had Polyarteritis nodosa (PAN), 3 TKA (Takayasu Arteritis), 2 Churg-Strauss Syndrome (CSS), 3 Wegener's Granulomatosis (WG), 1 Hypocomplementemic urticarial Vasculitis (HUS) and 1 Microscopic Polyangiitis (MPA) (Figure 1).

Characteristics of Patients and Controls

Baseline characteristics of patients and controls are given as under. The patients and controls were similar with respect to age, sex, blood pressure, smoking habits, body mass index, prevalence of diabetes and a positive family history of cardiovascular disease (Table 1).

DISEASE RELATED FACTORS

Characteristics of Patients with Vasculitis

Table 2 shows the different characteristics of patients related to duration of disease, age, disease activity (BVAS), damage (VDI) and steroid intake.

Intima-media Thickness

IMT was increased in 10 of 13 patients of Vasculitis (76.92%) and 3 in controls (33.33%).

Intima-media thickness of patients and controls

Patients (N=13)	Controls (N=10)	P value
0.93±0.96	0.76±0.26	0.004

Mean disease duration of patients having increased IMT was 6.91 ± 2.63 yrs (2 wks to 29 yrs). 3 out of these 10 patients were a known hypertensive previous to the onset of the disease

Blood Analysis

4 patients were positive for ANCA (C-ANCA: Two, P-ANCA: One, P+C ANCA: one) all of whom had increased IMT. However one among them had preexisting hypertension for 10 yrs.

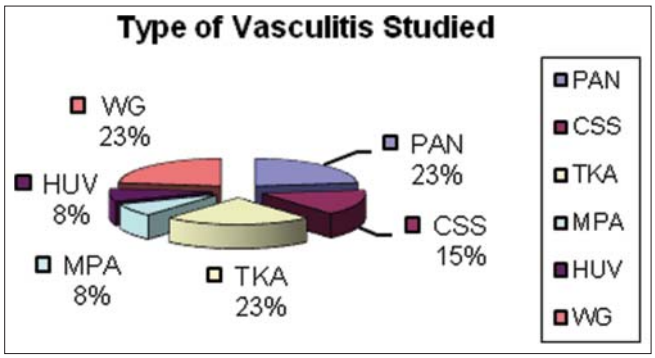

Figure 1: Different Types of Vasculitis Studied.

Mean CRP (C-reactive protein) level in patients of Vasculitis was 9±3.46 as against a level <6 in the controls.

Comparison of Risk Factors for Cardiovascular Disease in Vasculitics Patients with and without Increased IMT

By dividing the patient group in those with (n = 10) and without (n=3) increased IMT, the factors more prevalent in those with increased IMT were evaluated (Table 3).

The patients with increased IMT had a longer duration of illness, higher cumulative BVAS, higher VDI meaning more damage, and increased CRP level as compared to those having normal IMT. The vasculitic patients with increased IMT were also compared with the controls but no difference was found in the traditional risk factors. (Figures 2-4).

DISCUSSION

In this study, it was seen that increased IMT was a sign of accelerated development of atherosclerosis in patients of Vasculitis, assessed during active and inactive disease, compared with controls. This difference could not be explained by traditional risk factors, suggesting that the disease itself contributes to the development of atherosclerosis.

Previous studies have shown premature atherosclerosis in autoimmune diseases such as SLE and RA. Roman *et al* found an association of atherosclerosis with a longer duration of

Table 1: Characteristics of patients and controls

Characteristic	Patients (n=13)	Controls (10)	p value
(yrs)	42.9±6.37	38.7±6.22	NS
Male sex	7 (53.84%)	6 (60%)	NS
Body mass index	25.6±3.3	24.8±2.8	NS
Blood pressure			NS
Systolic	115 (± 17)	116 (± 17)	
Diastolic	69 (± 12)	72(± 8)	
Smoking (n)	1	1	NS
Diabetes	1	0	NS
Family h/o CVD	3	2	NS
Total cholesterol	167.46±12.94	165.1±12.85	NS
LDL	102.69±10.13	102.9±10.14	
VLDL	27±5.20	21.4±4.62	
HDL	48.3±6.95	39.5±6.28	
Triglycerides	119.69±10.94	124.8±11.17	

Table 2: Characteristics of patients with Vasculitis

Characteristics	All (n=13)
Disease duration	3.59±2.45 (1yr to 8yrs)
Active disease (BVAS>1)	7
Cumulative BVAS	78±8.83
Pt's having damage	10
Cumulative VDI	2.2±1.48
Cumulative prednisolone dose (g)	43.7±6.61

disease, a higher damage index score, and less aggressive immunosuppressive treatment, arguing strongly for chronic inflammation as an atherogenic factor in patient's with SLE.[9]

Endothelial dysfunction, which may lead to atherosclerosis has been demonstrated in systemic Vasculitis.[16] A recent study conducted by Leeuw K de *et al* demonstrated accelerated atherosclerosis in patients with Wegener's Granulomatosis.[12] The present study shows an increased prevalence of atherosclerosis in patient's with all types of Vasculitis.

To measure the extent of atherosclerosis we used ultrasound of the common carotid artery, as the previous study revealed high reproducibility, showing less variability than other segments, and reveal the presence of early atherosclerosis.

In patients with systemic vasculitis, HDL cholesterol levels are decreased, whereas LDL cholesterol levels are not elevated but elevated LDL cholesterol levels occur when moderate to severe proteinuria is present.[20]

To determine predisposing factors for atherosclerosis in our patient group, traditional and non-traditional risk factors were investigated. Although the prevalence of traditional risk factors including lipid profile did not differ significantly between patients and controls, patients tended to be slightly older and tended to have a higher body mass index and were more likely to be male and to have a family history of cardiovascular disease. However, because of the limited number of patient's in our study, no definite opinion could be made.

Atherosclerosis is considered to be a chronic inflammatory disorder, and CRP is a marker of systemic inflammation is described as an independent prognostic marker for cardiovascular disease.[21] In our patient's, plasma concentration of CRP was increased. Several studies have suggested that CRP may contribute directly to the development of atherosclerosis, as it induces the expression of adhesion molecules on the endothelial surface and promotes the adherence of leucocytes.[22] Thus CRP could be a direct link between autoimmune disease, characterized by systemic inflammation, and an increased

Table 3: Characteristics of patients with and without increased IMT and controls

Characteristics	Normal IMT (N=3)	Increased IMT (N=10)	Controls (N=10)
Age (yr)	37.67±6.13	44.5±6.26	38.7±6.22
Male sex n (%)	1 (33%)	6 (60%)	6 (60%)
BMI (Kg/m^2)	24.6(±4.95)	26.2(±5.12)	24.8(±4.98)
Blood pressure			
Systolic	110(±15)	118(±18)	116(±17)
Diastolic	66(±7)	71(±14)	72(±8)
Smoking	0	1	1
Diabetes	0	1	0
Total cholesterol	131±11.44	178.4±13.36	165.1±12.85
LDL	87.67±9.36	107.2±10.35	102.9±10.14
VLDL	20±4.47	29.1±5.39	21.4±4.62
HDL	53.67±7.32	46.7±6.83	39.5±6.28
Triglycerides	106.67±10.33	123.6±11.11	124.8±11.17
Family history of CVD	1	2	2
Duration (yrs)	3±1.73	3.77±2.63	
Patient's with active disease	4 (30%)	6 (46%)	
Cumulative BVAS	13±3.6	76±8.72	
Cumulative BVAS/ Duration (yrs)	4.33±2.08	20.15±3.32	
Patient's with damage	3	7	
Cumulative VDI	8±2.83	14±3.74	
Cumulative prednisolone dose (g)	20±0.1	21.42±0.14	
Pt's with ANCA positive Vasculitis	0	4	
CRP Level	6±2.45	12±3.46	<6

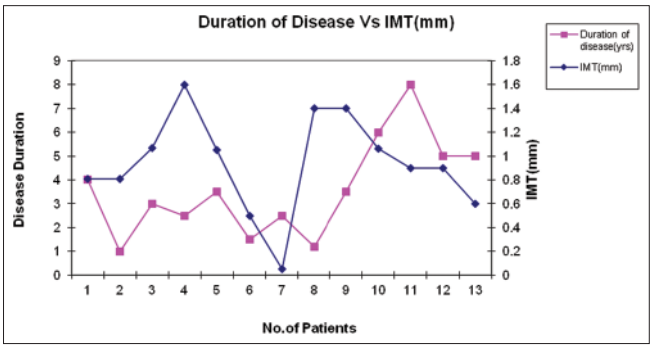

Figure 2: Correlation of the disease duration with the Intima media thickness

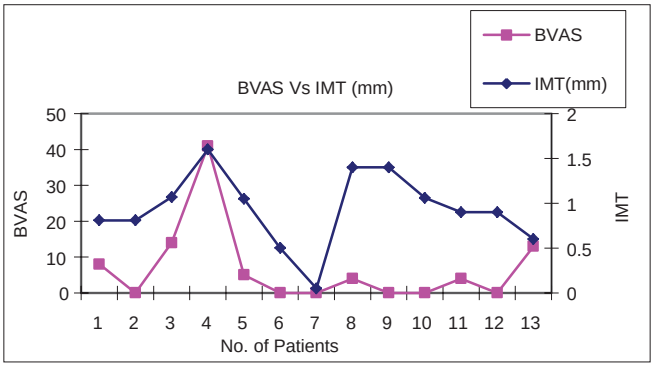

Figure 3: Correlation of the Vasculitis disease activity (BVAS) with the Intima Media thickness

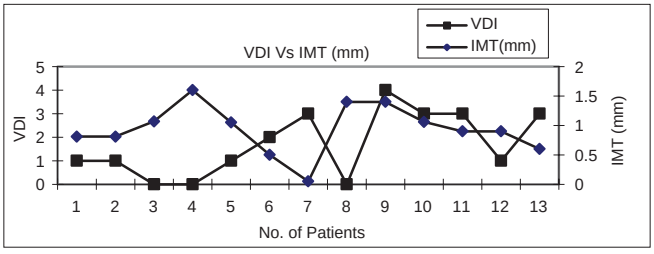

Figure 4: Correlation of the the organ damage (VDI) with the Intima Media thickness

risk for cardiovascular disease. But the question remains as to whether this is a reflection of the greater prevalence of atherosclerotic changes in the vessel wall or of active disease in these patient's resulting in endothelial activation and eventually, in atherosclerosis.

When we divided our patient group on the basis of the presence or absence of increased IMT, it was found that patient's having increased IMT had longer duration of disease, more disease activity, more damage and increased CRP levels. (Figure 5)

No difference was found between age, sex, body mass index (BMI), blood pressure, smoking habits, diabetes, or family history of cardiovascular disease (CVD). Leeuw K de et al neither found any difference in traditional or non-traditional risk factors nor a history of more severe active disease/long duration in patients with increased IMT.

In the present study no difference was found in the cumulative dose of prednisolone between patients with or without increased IMT.

CONCLUSION

In our study increased IMT, a sign of accelerated development of atherosclerosis in patients with Systemic Vasculitis is present as compared to controls. This cannot be explained by an increased prevalence of traditional risk factors.

Whether the rise of CRP values resulted from atherosclerosis or indicated ongoing activity needs to be further analyzed in prospective studies.

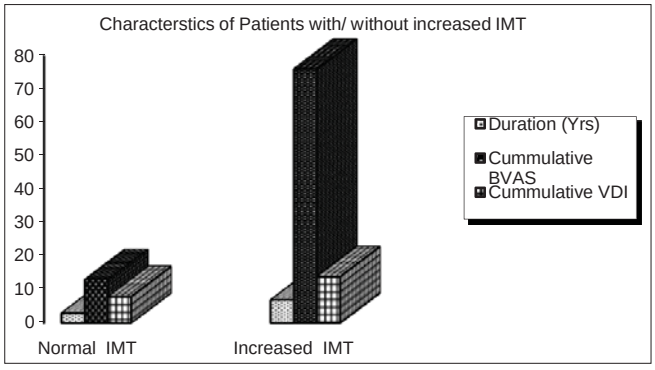

Figure 5: Characteristics of Patients with or without increased IMT

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