Factor VIII related antigen in the assessment of vasculitis

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SUMMARY Factor VIII related antigen, an endothelial cell product, was markedly raised in systemic necrotising arteritis, reflecting disease activity, but was not raised in active cutaneous vasculitis. In rheumatoid arthritis high levels were only found in systemic vasculitis or Felty's syndrome, but in other connective tissue diseases increased levels were more frequently detected and usually related to disease activity. It did not correlate with C reactive protein. It was also raised in non-inflammatory peripheral vascular disease and after surgery and was not specific for vasculitic endothelial damage. Factor VIII related antigen may be useful in identifying and monitoring systemic necrotising and large vessel arteritis.

Key words: von Willebrand's factor, C reactive protein, endothelium, arteritis, Wegener's granulomatosis, periarteritis nodosa, connective tissue diseases, rheumatoid arthritis, ischaemia.

Vasculitis may arise de novo or as a feature of various connective tissue diseases,¹ its consequences depending on the size, site, and number of blood vessels affected.² Diagnosis is difficult and may require invasive investigation. Small vessel vasculitis rarely causes serious internal organ dysfunction, in contrast with the aneurysmal or occlusive lesions of small and medium muscular arteritis.^{1–6} There is no laboratory investigation that distinguishes between these, nor that consistently reflects disease activity.^{2–6}

Factor VIII related antigen (FVIII RAG) has been proposed as a marker of vascular damage.⁷ It is a high molecular weight glycoprotein,⁸ with a half life of 240–270 min,⁹ present in^{11–13} and synthesised by^{14–16} endothelial cells. Raised circulating levels have been demonstrated after experimental vascular injury⁷ and in a variety of clinical conditions,^{17–31} often in association with overt vascular disease.^{25–29–31} Its usefulness in clinical practice in the assessment of vasculitis has not, however, been established.

We have therefore studied the sensitivity and specificity of changes in the plasma FVIII RAG concentration in detecting the presence of systemic vasculitis and monitoring its treatment.

Patients and methods

PATIENTS

Two hundred and eighty-eight patients were included in the study—51 patients with different types of vasculitis, 99 normal, and 138 disease controls. Most patients were studied prospectively, some were studied serially.

Vasculitis

Patients were subdivided into three different groups depending on the size of the largest blood vessel involved.

Small vessel vasculitis. This group (n=15) of patients had either clinical or histological evidence of vasculitis restricted to small blood vessels such as arterioles, capillaries, and venules. Clinical features included non-thrombocytopenic purpura, maculopapular skin rashes, minor nail edge or nail fold lesions. Clinical diagnoses included Schönlein–Henoch purpura (n=3), cutaneous vasculitis (n=7), and rheumatoid vasculitis (n=5). In 13 patients vasculitis appeared to be restricted to the skin, but two patients with Schönlein–Henoch purpura had systemic disease with renal involvement.

Systemic necrotising arteritis. These patients (n=34) had clinical or histological evidence of vasculitis involving small or medium sized arteries. Clinical

features of arteritis included mononeuritis multiplex, peripheral gangrene, and deep cutaneous ulcers. Histology confirmed an arteritis in 26 patients. In eight patients this histological confirmation of vasculitis was restricted to renal biopsies, which showed microscopic polyarteritis (focal segmental necrotising glomerulonephritis) but negative glomerular immunofluorescence. These patients had clinical polyarteritis nodosa. Clinical diagnoses in the whole group were Wegener's granulomatosis (n=11), polyarteritis nodosa (n=13), and arteritis complicating rheumatoid disease (n=10).

Large vessel arteritis. Two patients had a diagnosis of Takayasu's arteritis confirmed by angiography (n=1) and angiography plus histology (n=1). Both had moderate or severe stenotic changes on angiography affecting many arteries, including the carotid arteries, the aortic arch, and subclavian arteries. One patient had evidence of active systemic disease with a marked acute phase response, whereas the other patient had no systemic symptoms, normal acute phase proteins, and was presumed to be in the 'pulseless' phase of his disease.

Normal controls

These comprised healthy blood donors (n=75) and patients with osteoarthritis (n=24) but without any inflammatory or vascular disease.

Disease controls

As vasculitis may accompany many connective tissue diseases, including systemic lupus erythematosus, rheumatoid arthritis, and polymyositis, it was important to examine patients with these diseases in the absence of clinical or histological evidence of vasculitis to compare and contrast them with patients with active vasculitis. In addition, we also examined patients with non-inflammatory vascular diseases (Raynaud's disease—23 patients, peripheral vascular disease without rest pain—24 patients) and patients with vascular damage directly attributable to operative trauma (arthroplasty for osteoarthritis—five patients).

Rheumatoid arthritis. These patients (n=51) fulfilled the criteria of the American Rheumatism Association for definite or classical rheumatoid arthritis³² and had no clinical or histological evidence of vasculitis. They could be subdivided further into patients with active arthritis but no extra-articular manifestations (n=29), arthritis complicated by typical subcutaneous rheumatoid nodules (n=15), and seven with Felty's syndrome.

Connective tissue diseases. These included patients with systemic lupus erythematosus (n=13), mixed

connective tissue disease (n=7), polymyositis (n=4), and scleroderma (n=11). Patients were divided into active or inactive disease on clinical criteria.

METHODS

Clinical assessment

In cross sectional studies patients were examined at a time when their vasculitis was considered most active. This was based on clinical features such as new arteritic or vasculitic lesions, recent neuropathy, or active systemic illness. In some patients there was confirmation of active systemic disease by laboratory assessments such as urine microscopy and measurements of haemoglobin, white cell count, erythrocyte sedimentation rate (ESR), and reactive protein by radial immunodiffusion.³³

FVIII related antigen assay

Circulating factor VIII related antigen was assayed by an enzyme linked immunosorbent assay³⁴ using commercially available antisera. The test was performed in microtitre plates. The first layer was rabbit antihuman FVIII RAg (DAKO), followed by diluted sample or standard, and the third layer was rabbit antihuman FVIII RAg conjugated with horseradish peroxidase (DAKO), which was then developed with *O*-phenylenediamine and hydrogen peroxide and read at 430 nm. Results were expressed as a percentage of a normal control. The normal range was defined as within two standard deviations of the mean level detected in healthy blood donor controls. The coefficient of variation between batches was 5%.

STATISTICAL ANALYSIS

The Mann-Whitney U test was used to look for significant differences, comparing healthy blood donors with the patient groups unless stated otherwise. The paired *t* test was used in the comparison of serial data.

Results

CROSS SECTIONAL DATA

There was no significant difference between healthy blood donors and the older osteoarthritic controls (mean (SD) 103 (59)%).

Vasculitis (Fig. 1)

FVIII related antigen was raised in 32 of 34 patients with active systemic necrotising arteritis (mean (SD) 311.3 (137.1)%, *p*<0.001), independent of the underlying clinical disease. Only two patients with microscopic polyarteritis had normal levels of FVIII

Fig. 1 Factor VIII RAg levels in patients with vasculitis and in controls. * $p < 0.001$.

RAg: one had relatively minor systemic symptoms, but the other had classical multisystem disease with skin, joint, and lung symptoms as well as renal involvement. In contrast, FVIII related antigen levels were normal in all patients with small vessel vasculitis (mean (SD) 110.3 (35.7)%, NS). These results were repeatable and remained within the normal range in serial studies in a number of patients. FVIII RAg levels were also normal in the two patients with Schönlein-Henoch purpura with systemic involvement (renal disease). In the two patients with large vessel vasculitis (Takayasu's arteritis) increased levels of FVIII RAg were detected (189%, 280%).

Disease controls (Fig. 2)

Rheumatoid arthritis. FVIII RAg was not raised in patients with rheumatoid arthritis without distinct

extra-articular features, though most had active synovitis (mean (SD) 112.1 (35.1)%, NS). Two of the three patients with raised levels (184%, 198%) had marked weight loss and acute phase responses but little synovitis and no other definable extra-articular features. FVIII RAg was not raised in patients with rheumatoid nodules (124.9 (36.6)%, NS), but was increased in Felty's syndrome in the absence of clinical vasculitis (435.7 (54.9)%, $p < 0.005$).

Connective tissue diseases. FVIII RAg was significantly increased in patients with systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and polymyositis (192.9 (134.5)%, $p < 0.001$), but this was variable, often reflecting clinical disease activity (Fig. 2). It was not significantly raised in progressive systemic sclerosis

Fig. 2 Factor VIII RAg levels in rheumatoid arthritis (RA), connective tissue diseases (systemic lupus erythematosus (SLE), mixed connective tissue disease (MCTD), and polymyositis (PM)), peripheral vascular disease (PVD), and postoperative patients. Patients with active connective tissue disease on clinical criteria are represented by o. * $p < 0.005$; ** $p < 0.001$.

(141.7 (73.5)%, NS), apart from one patient with an ischaemic finger (322%). These patients, however, were longstanding cases with clinically inactive disease.

Primary Raynaud's disease. FVIII RAg was not raised in primary Raynaud's disease (100.4 (36.5)%, NS). It was, however, slightly but significantly raised in intermittent claudication in the apparent absence of irreversible ischaemia (134.5 (41.7)%, $p < 0.005$).

Arthroplasty. FVIII RAg was significantly increased 48 h after arthroplasty for osteoarthritis (288.8 (134.8)%, $p < 0.001$).

LONGITUDINAL DATA

Seven patients with systemic vasculitis were studied longitudinally (three with Wegener's granulomatosis, four with polyarteritis nodosa) (Fig. 3). At presentation, all had raised FVIII RAg levels (390 (135)%). Five of the patients showed a good clinical response to treatment and there was a concomitant

significant fall in factor VIII RAg to 148 (27)% ($p < 0.001$), to within the normal range in four cases. Two cases, however, showed no response to therapy: one dying from septicaemia complicating immunosuppression, and the other dying from perforation of the bowel. These patients showed no fall in FVIII RAg during therapy before their final fatal episode.

A direct comparison of FVIII RAg with reactive protein (CRP) shows that the latter was a poor indicator of disease activity in these patients. It was sometimes normal at presentation, and changes did not reflect the clinical response to treatment, remaining either raised or normal throughout in six of the seven patients (Fig. 3).

A patient with polyarteritis nodosa was studied closely over nine months (Fig. 4). Changes in FVIII RAg appeared to mirror clinical disease activity. Raised levels were detected shortly after presentation, which fell with response to treatment, rose just before clinical deterioration, and were unaffected by an episode of intercurrent infection which provoked an acute phase response. Changes in FVIII RAg

Fig. 3 Factor VIII RAg and C reactive protein (CRP) levels in patients with systemic necrotising arteritis at presentation and follow up.

Fig. 4 A patient with polyarteritis nodosa followed up over nine months, with frequent assessments of FVIII RAg, CRP, and clinical disease activity.

were more marked than changes in CRP and appeared to be more specific for variation in disease activity.

FACTOR VIII RAG AND CRP

There was no correlation between CRP and factor VIII RAg in all patients studied with rheumatoid arthritis ($r=0.080$), nor in systemic necrotising arteritis ($r=0.035$). There were often markedly discordant results. In one patient with Takayasu's arteritis an increase of FVIII RAg was the only laboratory abnormality detected, ESR and CRP being normal.

Discussion

Factor VIII RAg is present in¹¹⁻¹³ and synthesised by¹⁴⁻¹⁶ endothelial cells. It is also present in platelets^{35 36} and synthesised by megakaryocytes.³⁷ It is associated with platelet adhesion to the subendothelium.³⁸ It has been proposed as a marker of endothelial cell injury^{7 30 31} and is raised in a variety of diseases,¹⁷⁻³¹ often complicated by vascular damage, but its use in clinical practice has not been established.

We have found markedly increased FVIII RAg levels in patients with active systemic necrotising arteritis and large vessels arteritis, in contrast with those with active small vessel vasculitis, even when complicated by renal impairment, and this is supported by other recent reports.^{31 39 40} The prognosis of vasculitis is related to the size of vessels involved⁶: it is worse with necrotising systemic

arteritis, which leads to either aneurysm formation and haemorrhage or to occlusion and distal infarction. The size of vessel involved may, however, only be determined by investigations such as biopsy or angiography with their subsequent morbidity as there are no discriminating laboratory tests available at present. This distinction between small vessel vasculitis and systemic necrotising arteritis by FVIII RAg level may therefore prove of great value in identifying those cases which require these invasive investigations.

Serial data suggest that FVIII RAg levels reflect disease activity in systemic necrotising arteritis and were more useful than C reactive protein. On occasion a rise in FVIII RAg was noted before a clinically apparent flare in disease activity. Persistent increase was associated with a poor prognosis. This may allow more effective monitoring of response to immunosuppressive treatment.

Patients with rheumatoid arthritis (RA) may develop small vessel vasculitis or necrotising arteritis, but it is the latter who have the worse prognosis,² which is improved by aggressive immunosuppression.⁴¹ Their identification by raised FVIII RAg in comparison with the normal levels found in uncomplicated RA, despite active synovitis, nodules, or small vessel vasculitis, may be clinically useful. FVIII RAg was, however, slightly raised in two patients with RA, complicated by weight loss and a marked acute phase response. It was markedly increased in patients with Felty's syndrome in the apparent absence of vasculitis, to 1665% in one case.

FVIII RAg was variably raised in patients with SLE, MCTD, and PM, often, but not always, reflecting clinical disease activity or apparent vasculitis, which may point to pathogenetic differences of the various manifestations of these diseases. We did not find raised FVIII RAg levels in progressive systemic sclerosis (PSS) or primary Raynaud's disease as previously reported,³⁰ but the former had clinically inactive disease, apart from one patient with digital ischaemia who had raised FVIII RAg levels.

An increase of FVIII RAg does not only occur with vasculitic damage as we and others have found it slightly, but significantly, raised in PVD²⁶ without apparent irreversible ischaemia, and following surgical trauma. It has also been reported to be raised after myocardial infarction.^{26, 27}

Although FVIII RAg rises rapidly after trauma, and has a short half life of 240–270 minutes, it may remain raised for 30 days after myocardial infarction.²⁷ It fell within 30 days in parallel with clinical improvement in a patient with polyarteritis nodosa followed up closely (Fig. 4), but the timing of changes in FVIII RAg in response to treatment needs establishing.

The endothelium is the major source of FVIII RAg, but it is also present in platelets.^{35, 36} Platelet-endothelial interactions or platelet destruction by autoimmune thrombocytopenia in connective tissue diseases or by splenic consumption in Felty's syndrome could be important, and the latter could account for increased levels in the apparent absence of vasculitis. We have no data on platelet turnover in these patients.

The increase of FVIII RAg is not simply part of an acute phase response as, although raised after trauma, it was not increased in active articular rheumatoid arthritis accompanied by a raised C reactive protein, and it did not correlate with C reactive protein in systemic necrotising arteritis.

At present, no specific marker of disease activity in systemic necrotising arteritis is available,⁶ though immune complexes are sometimes detected.² C reactive protein levels may be useful in monitoring disease activity,⁴² but these are non-specific, rising in infection, and do not show a normal response in SLE⁴³ or PSS.⁴⁴ We found CRP to be a poor indicator of clinical disease activity in our patients (Figs 3 and 4).

In conclusion, FVIII RAg was raised in systemic necrotising arteritis and large vessel arteritis, but not in small vessel vasculitis. It may therefore prove a useful non-invasive investigation to determine the extent of vasculitis with its therapeutic and prognostic implications. Whether this difference relates to qualitative or quantitative differences in endothelial

cells or platelet turnover is unclear. FVIII RAg levels reflected changes in clinical activity and may be of value in monitoring the response to potentially toxic treatment. Changes in FVIII RAg, however, are not specific to vasculitis as other causes of vascular damage can produce raised concentrations. It is not simply a secondary effect, an acute phase response, but is probably directly reflecting the pathological process in the vessel. To establish fully whether it has a role as a routine investigation procedure requires further experience, but its measurement is simple and appears to offer more than is currently available in the assessment of vasculitis, either occurring de novo or as a feature of connective tissue disease.

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