



Erythrocyte sedimentation rate as a marker of inflammation and ongoing coagulation in stroke and transient ischaemic attack

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Objective. Systemic infection and inflammation have been implicated in the aetiology of thrombotic cerebral events, particularly in younger patients. We decided to determine whether those patients with raised D-dimer levels, indicating continuing thrombosis and fibrinolysis, had evidence of concurrent infection or inflammation as manifested by a raised erythrocyte sedimentation rate (ESR) measured after an ischaemic stroke/transient ischaemic attack (TIA).

Methods. One hundred and forty-eight patients who had suffered either single or recurrent cerebrovascular episodes were analysed. The patients were referred to the thrombosis and haemostasis unit at Johannesburg Hospital for evaluation of their thrombotic profiles, including D-dimer levels. Concurrent infection was assessed by measurement of white cell count (WCC) and ESR. The variable time interval between the date of the most recent cerebrovascular event and the date of venesection was determined. A history was taken, a physical and neurological examination was performed, and a cardiology assessment and neuroimaging studies were done.

Results. Raised D-dimer levels correlated significantly with ESR

levels ($p = 0.0094$) in all patients. This was particularly evident when comparing the 70 younger patients (aged less than 45 years) with the 78 older patients (> 45 years) with raised D-dimers ($p = 0.0070$). When analysing other markers of inflammation/infection in association with raised D-dimer levels and ESR, mean fibrinogen levels were significantly raised at 6.56 g/l ($p = 0.0122$). An elevated WCC, as a categorical variable, was significantly associated with an elevated ESR ($p = 0.0092$).

Conclusion. There is a significant correlation between elevated D-dimer levels (indicating abnormalities of coagulation and fibrinolysis) and markers of inflammatory and/or infective processes. This is particularly evident in black patients below the age of 45 years. These patients are believed to be at decreased risk for generalised atheromatous disease compared with older white patients. The ramifications of these findings are potentially important with regard to thrombotic cerebrovascular disease aetiology, investigation, management and prevention.

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Conventional stroke risk factors often explain stroke incompletely, particularly in young subjects.¹ Systemic infection and inflammation have been considered to modify stroke risk independently of conventional risk factors.² Traditional risk factors, genetic predisposition and chronic and acute infection and inflammation appear to be linked tightly to each other and to influence the likelihood of thrombotic events.² It is feasible that inflammation and systemic infection result in activation of the thrombotic system, adding to conventional risk factors and resulting in ischaemic stroke.²

It is possible to assess systemic inflammation and infection indirectly in a number of ways, including using the C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), and

white cell count (WCC).³ Elevated levels of CRP, an acute-phase reactant that acts as a marker for systemic inflammation, have been described among patients with acute myocardial ischaemia^{4,5} and cerebrovascular disease.^{6,7} An elevated ESR is also known to be a nonspecific but reliable marker of infection and inflammation.^{8,9} The CRP is not readily available within the public sector outside major centres in South Africa, while the ESR is easy to perform, inexpensive and readily available even in the most remote areas of the country. It is useful not only as a potential diagnostic tool, but also as a research tool for assessing underlying systemic inflammation, which may predispose to risk of future cerebrovascular events.

D-dimers are a marker of activation of the coagulation and fibrinolytic systems in hypercoagulable states¹⁰ and thrombotic disorders.¹¹⁻¹⁴ They have been shown to be elevated, particularly in those patients who later develop vascular events.¹⁵⁻¹⁷

The aim of this study was to determine whether ischaemic stroke patients with raised D-dimers, indicating continuing thrombosis and fibrinolysis, are more likely to have evidence of concurrent infection and/or inflammation as manifested by a raised WCC and ESR, than ischaemic stroke patients without raised D-dimers. We attempted to correlate a prothrombotic

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state with a background inflammatory process as a potential risk factor for atherothrombotic cerebrovascular disease.

Subjects and methods

We included all patients with ischaemic stroke referred to the haemostasis and thrombosis unit of the neurovascular clinic at Johannesburg Hospital for analysis of their thrombotic profiles between 1 January 1995 and 31 August 1997. All patients had suffered either single or multiple strokes and/or transient ischaemic attacks (TIAs).

A neurologist took a comprehensive history from each patient or relative. Risk factors for vascular disease were recorded, namely ischaemic heart disease, peripheral vascular disease, diabetes mellitus, hypertension, migraine, gout, smoking, alcohol consumption, hyperlipidaemia, valvular heart disease, arrhythmias, previous cardiac or vascular surgery, previous venous thrombo-embolic disease, family history of atherosclerotic vascular disease, hyperthyroidism and illicit drug abuse. Neurologists also took a current drug history from all patients and noted the use of all anticoagulant and antiplatelet agents. In addition, we assessed the presence and frequency of other known risk factors associated with elevation of plasma D-dimers including increasing age and concurrent infection.

A full neurological and physical examination and review of brain imaging was performed to determine the nature, territory and number of cerebrovascular events. Cardiological evaluation included an electrocardiograph and echocardiography as appropriate. Carotid artery Doppler evaluation was performed routinely.

We evaluated patients for concurrent infection or inflammation clinically and by measurement of their WCC and Westergren ESR. A normal WCC was considered to be between 4 and $11 \times 10^9/l$.

We performed a full thrombotic profile on each patient including international normalised ratio (INR), partial thromboplastin time (PTT), D-dimer levels, protein C assay, protein S assay, antithrombin assay, activated protein C resistance (APCR), polymerase chain reaction for factor V Leiden mutation, lupus anticoagulant (LAC), fibrinogen levels and thrombin time.

We assessed the level of D-dimers in each patient using the BIOPOOL Minutex D-dimer latex kit. Using this method, normal D-dimer levels are below 250 ng/ml.¹² For the purpose of this study we considered elevated D-dimers to be above this level.

Other laboratory parameters assessed were haemoglobin, platelet count, random glucose, total cholesterol, anticardiolipin antibodies (ACLA), antinuclear factor (ANF), syphilis serology (RPR and TPHA) and free T₄. In selected patients in whom there was a clinical suspicion, we tested for human immunodeficiency virus (HIV).

Statistical analysis

We performed statistical analysis using the SAS computer software package. The statistical tests used in order to determine statistical significance were the Kruskal-Wallis test and the Mann-Whitney U-test or Student's *t*-test (depending on the distribution of the dependent variable) for a continuous dependent variable. We used the Fisher's exact test and chi-square for categorical dependent variables. In view of the fact that many of the parameters assessed are non-parametric in distribution, we computed mean values and analysed significant differences using Wilcoxon's rank-sum test. We performed correlation analysis when seeking correlation between continuous variables.

We compared patients who had suffered single or multiple cerebrovascular events in terms of normal or elevated D-dimer levels. In each group we determined whether the time interval between the most recent event and the time of assessment was more or less than 2 and 6 months.

We grouped D-dimer levels as normal or elevated. We then compared ESR levels in individuals with elevated and normal D-dimer levels.

We undertook comparisons between patients younger than 45 years and those 45 years and older, and between gender and racial groups. We assessed fibrinogen levels and WCCs in relation to D-dimer and ESR levels.

Ethics

We obtained ethics approval from the University of the Witwatersrand Medical School Human Research Ethics Committee, clearance number M980130. Obtaining informed consent from patients included in the study was not deemed necessary because all investigations were performed as part of the routine clinical workup for patients suffering stroke-like episodes.

Results

We assessed 148 patients (mean age of 47 years, range 15 - 79 years). Ninety-three patients (63%) demonstrated normal D-dimer levels at the time of testing, whereas 55 patients (37%) had elevated D-dimers. Table I compares the age, gender, racial group, proportion of young stroke patients, and nature of stroke in those people with elevated and normal D-dimer levels. The patients with elevated D-dimers were significantly older than those with normal levels. Seventy per cent of the 70 young patients, i.e. 45 years of age or younger at the time of their stroke or TIA, had normal D-dimer levels. There was no statistically significant difference in the proportion of younger and older patients with normal D-dimer levels. Fifty-seven per cent of older patients had normal D-dimer levels ($p = 0.092$).

When comparing the normal and elevated D-dimer groups no significant difference was found in the number of strokes or



TIAs or the proportion of patients presenting with a TIA rather than a stroke. There was also no significant difference in the proportion of blacks, whites and coloureds in the two groups. Not one of the 9 Asian patients had elevated D-dimers.

Although there was a wide range in the time from stroke or TIA to measurement of D-dimers in both groups, overall the mean time to assessment was shorter in the group with elevated D-dimers ($p = 0.0466$). In 47 patients, D-dimer levels were assessed within 2 months of their most recent cerebrovascular event. Of these 47, 53% had elevated D-dimers. A significantly smaller proportion (30%) of 101 patients assessed at least 2 months after their event had elevated D-dimer levels ($p = 0.010$).

The mean ESR was 8 mm/hour (range 0 - 45 mm/hour) in the 93 patients with normal D-dimer levels. This was significantly lower than the mean ESR of 16 mm/hour (range 1 - 100 mm/hour) found in the patients with elevated D-dimer levels ($p = 0.0094$) (Fig. 1).

There was no significant difference between the ESR in younger and older patients with normal D-dimers ($p = 0.7588$). In the group with elevated D-dimers, however, the ESR was higher in younger than in older patients (Fig. 2a and b). The ESR was higher in the presence of raised D-dimers irrespective of gender (Fig. 3a and b). We found a significant difference

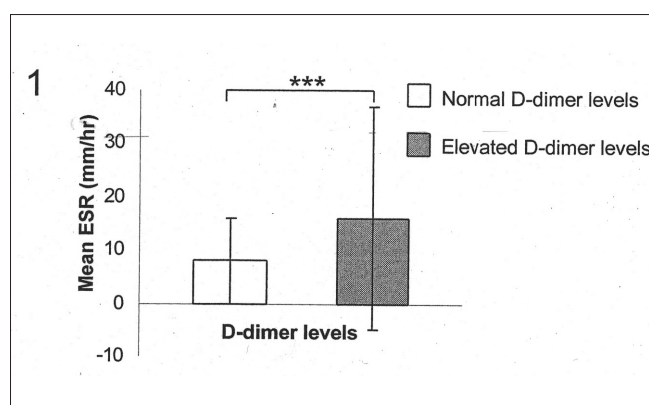


Fig. 1. Mean ESR versus D-dimer levels in all patients (N = 148). Patients with normal D-dimers (N = 93) had a significantly lower mean ESR of 8 mm/h (SD 8) than those with elevated D-dimers (N = 55), mean ESR 16 mm/h (SD 21), $p = 0.0094$ (***) = $p < 0.01$.

between ESR levels in the 48 black and 82 white patients ($p = 0.007$). In the presence of elevated D-dimers, black patients had higher ESRs than white patients ($p = 0.008$) (Fig. 4a and b).

We correlated the level of fibrinogen, an acute-phase reactant that increases in some inflammatory and hypercoagulable states, with the ESR. In patients with normal D-dimers there was no correlation with fibrinogen levels (Pearson's correlation coefficient 0.05). However, in patients with elevated D-dimers

Table I. Characteristics of stroke patients with normal and elevated* D-dimer levels

	Normal D-dimer levels	Elevated D-dimer levels*	Statistical significance
Total patients (N)	93	55	
Gender (N)			
Male	58	27	NS
Female	62	28	NS
Age (mean) (yrs)	45	50	$p = 0.0403$
Number of patients with more than one stroke or TIA (%)	42 (45)	27 (49)	NS
Number of patients who presented with TIAs (%)	26 (60)	17 (40)	NS
Population group (%)			
Black	29 (60)	19 (40)	$p = 0.123$
Indian	9 (100)	0 (0)	
Coloured	5 (56)	4 (44)	$p = 0.123$
White	50 (61)	32 (39)	$p = 0.123$
Mean time to assessment (standard deviation) (yrs)	2 (3.2)	1.7 (3)	$p = 0.0466$
Time to assessment (range) (yrs)	0.01 - 22.8	0.03 - 14.4	

*Elevated D-dimers defined as more than 250 ng/ml (Heaton *et al.*¹²)
NS = non-significant.

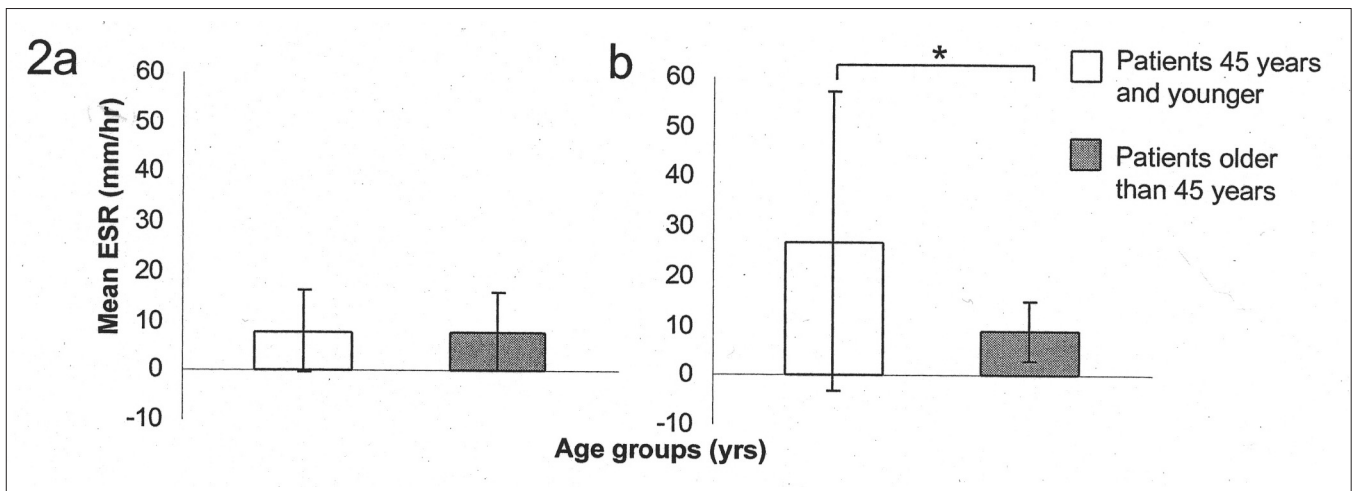


Fig. 2. Mean ESR in younger and older patients (> 45 years) with: (a) normal and (b) elevated D-dimer levels. (a) Of the 93 patients with normal D-dimers, 49 were 45 years or younger, mean ESR 8 mm/h (SD 8.4), and 44 were older than 45 years, mean ESR 8 mm/h (SD 7), $p = 0.75$ (non-significant). (b) However, significant difference was observed in 21 of the 55 patients 45 years and younger with elevated D-dimers, mean ESR 27 mm/h (SD 30), compared with the 34 patients who were older, mean ESR 9 mm/h (SD 6), $p = 0.0493$ (* = $p < 0.05$).

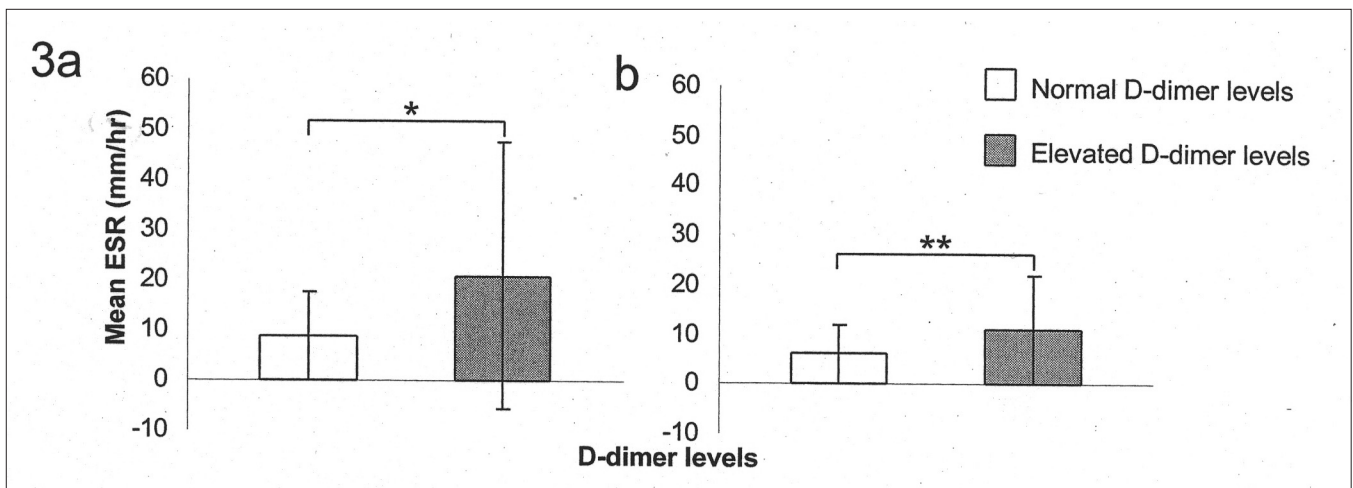


Fig. 3. Mean ESR versus D-dimer levels in: (a) females and (b) males respectively. (a) Ninety-two females were assessed: 62 had normal D-dimers, mean ESR 9 mm/h (SD 9) and 28 had elevated D-dimers, mean ESR 21 mm/h (SD 27), $p = 0.0407$ (* $p < 0.05$). (b) Thirty-one of 58 males had normal D-dimers, mean ESR 6 mm/h (SD 6) and 28 had elevated D-dimers, mean ESR 11 mm/h (SD 11), $p = 0.0235$ (** = $p < 0.03$).

there was a weak correlation between the elevated ESR and increased fibrinogen levels ($r = 0.48$). There was no statistically significant difference in normal and elevated ESR levels versus time interval since cerebrovascular event for young ($p = 0.3$) or older patients ($p = 0.7$).

Only 5 patients had an elevated WCC. We found no correlation between the mean ESR and mean WCC for all patients or within the groups with normal and elevated D-dimers. In those patients with elevated D-dimers, 6 (12%) had a normal WCC with a raised ESR, whereas 2 of the 3 patients with a raised WCC had a raised ESR ($p = 0.052$).

Only 3 patients had identifiable infection at the time of their

cerebrovascular event (bronchopneumonia, meningoencephalitis, pelvic inflammatory disease and tonsillitis). The patient with pelvic inflammatory disease and tonsillitis was the only one to demonstrate an elevated ESR (77 mm/hour) in association with elevated D-dimers. None of the 43 patients tested was found to be HIV-positive.

Twelve patients exhibited clinical features of an autoimmune disease or vasculitis, including rheumatoid arthritis, Takayasu's disease, Raynaud's phenomenon, and systemic lupus erythematosus (SLE). Only 3 demonstrated an elevated ESR at the time of testing and 2 of those 3 had an associated elevation in D-dimer levels. Only 5 patients with an elevated ESR had evidence of autoimmune disease or infection.

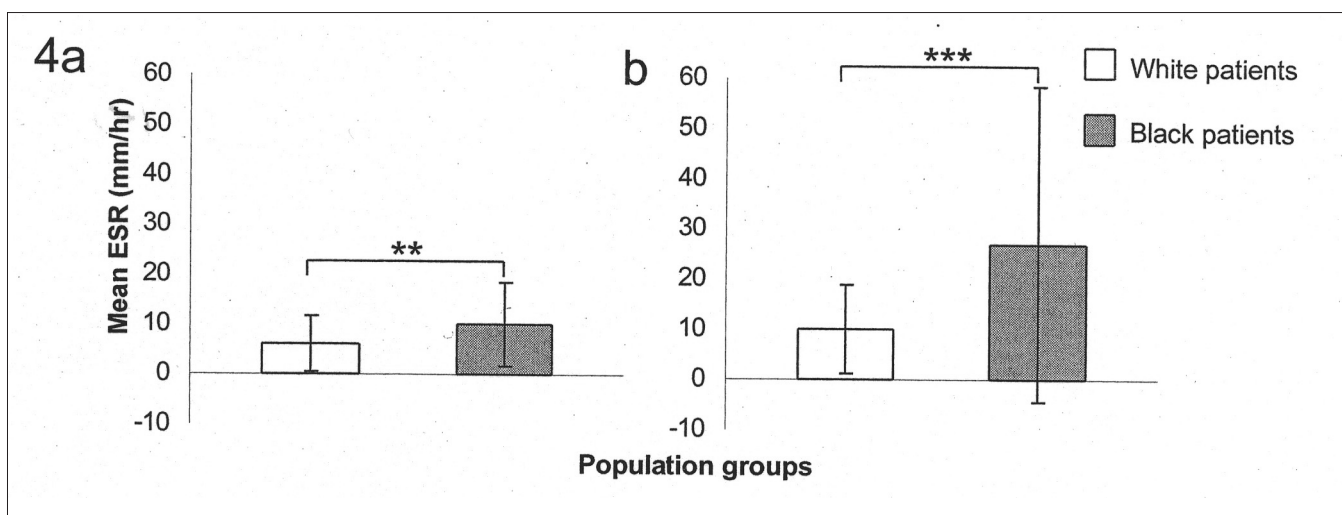


Fig. 4. Mean ESR in black and white patients with: (a) normal and (b) elevated D-dimer levels. (a) There was a statistically significant difference, $p = 0.0217$ (** = $p < 0.03$) observed between mean ESR levels in the 50 white patients, mean ESR 6 mm/h (SD 5) compared with the 29 black patients with normal D-dimers, mean ESR 10 mm/h (SD 9). (b) An even more significant difference was observed when comparing mean ESR levels in the 32 white patients with elevated D-dimers, ESR 10 mm/h (SD 9) versus the 19 black patients, ESR 27 mm/h (SD 32), $p = 0.00803$ (** = $p < 0.01$).

Discussion

Our study found that patients who had had an ischaemic stroke or TIA, and who had elevated D-dimer levels, suggesting ongoing thrombosis and fibrinolysis, were more likely to have laboratory evidence of inflammation as manifested by an elevated ESR than those with normal D-dimer levels. An elevated ESR in the presence of raised D-dimers was most common in young and black patients, and was seldom associated with obvious infection or autoimmune disease.

Infection may precipitate stroke in many ways. Ischaemic stroke has long been known to complicate chronic meningeal infections that cause inflammation and secondary thrombosis.¹⁸ Some viruses can cause peri-arterial inflammation, particularly in people with HIV.¹⁹ HIV itself may precipitate stroke via a vasculopathy or indirectly secondary to opportunistic infections or coagulopathy.^{19,20} Even in the absence of HIV infection, recent or current systemic infection may increase stroke risk by inducing inflammation and creating a prothrombotic state.^{22,21} There has also been much recent interest in the role of infectious agents such as *Chlamydia pneumoniae* and *Helicobacter pylori* in the pathogenesis of atherosclerosis.^{22,24}

We found no correlation between the WCC and ESR. Only 3 of our patients had evidence of infection at the time of stroke and of these only 1 had a raised ESR together with elevated D-dimers. None of our patients who consented for testing were found to be HIV-positive. This is probably influenced by when the study took place (early 1990s) and selection bias, as patients were predominantly referred from a specialist neurovascular

clinic. We may have underestimated the number of people with an elevated WCC at the time of stroke or TIA, as many patients were assessed several months after their cerebrovascular event. Despite this, leucocytosis does not appear to be an important cause of ongoing thrombosis and fibrinolysis in our study.

The elevated ESR levels in our patients with raised D-dimer levels, in the absence of an elevated WCC or clinical evidence of infection, is probably the result of ongoing thrombosis and fibrinolysis or occult inflammation. Although 12 of our patients had autoimmune disease or vasculitis, only 3 had an elevated ESR, 2 in the presence of raised D-dimers. Normal ESR values increase marginally with age.⁹ Interestingly in our study, in patients with elevated D-dimers the ESR was higher in younger patients than older patients. Race is also thought to affect the ESR, and in black subjects normal ESR values are at least 2 - 13 mm/hour higher than in whites, even after correcting for age, haemoglobin concentration and chronic disease.^{25,26} However, black patients were if anything over-represented in the group with normal D-dimer levels.

Atherosclerosis is increasingly being accepted as an inflammatory disease,² and is associated with elevated inflammatory markers such as CRP and fibrinogen.³ Acute and chronic infection and inflammation may induce a prothrombotic state with altered coagulation/fibrinolysis and platelet activation² that leads to stroke or myocardial infarction. While atherosclerosis may account for inflammation in some of our patients, it is unlikely that this is an important cause. Our patients with elevated ESR and D-dimer levels were mainly young or black, and neither of these groups is likely to have severe atherosclerotic disease.

The question remains regarding the significance of an



elevated ESR in the absence of an identifiable cause. In 1 000 asymptomatic men aged 18 - 33 years, a persistently elevated ESR increased the likelihood of disease in general from 3.8% to 22.7% and of myocardial infarction from 0.7% to 9% over 15 years. In some of these men the abnormal ESR preceded the clinical manifestations by 2 - 10 years.²⁷ Although previous studies have indicated that an elevated ESR is a poor prognostic marker for those at risk of cerebrovascular disease,²⁸ and inflammation is increasingly thought to be a risk factor for stroke,^{2,3} few if any have explored the use of the ESR as a marker of an ongoing procoagulant state. The correlation of an elevated ESR and blood fibrinogen level in our patients with elevated D-dimers is not surprising. Fibrinogen, the most abundant acute-phase reactant, has the greatest effect on the elevation of the ESR when compared with other acute-phase reactants.⁹ Our findings therefore suggest that the ESR, a readily available and inexpensive bedside test, may highlight patients with ongoing thrombosis/fibrinolysis who are at increased risk of further vascular events.

However, our study has important limitations. The patients assessed were from a potentially biased population that was neither randomly selected nor based on consecutive admissions or referrals. Most patients were referred from a specialist neurovascular clinic and criteria for selection were not determined at the start of the study. Thus patients might have been more likely to be included, for example, if they did not have a clear cause for their stroke or if they were HIV-negative. The positive findings of the study are based on small numbers.

Although there were no major differences between those individuals with elevated and normal D-dimers (Table I), those with elevated D-dimers were more likely to have been assessed slightly earlier following their stroke. As time since the cerebrovascular event affects levels of inflammatory and coagulation markers this may have influenced our results.

Ideally, future research should include careful unbiased patient selection and clinical and laboratory assessment both at the time of stroke/TIA and several months later. HIV-positive and negative patients should be clearly identified and differences investigated. Measurement of CRP and ESR would enable comparison between these two modalities. Finally, long-term follow-up of all patients to determine the prognostic significance of an elevated ESR with and without raised D-dimers would be useful.

In conclusion, infection and inflammation are increasingly being recognised as risk factors for ischaemic stroke. Their role in the pathogenesis of cerebrovascular disease is complex. Inflammation may activate coagulation with or without the presence of atherosclerosis. Our study raises the possibility that

a persistently elevated ESR in someone who has had a stroke or TIA may imply ongoing thrombosis/fibrinolysis. The ready availability and ease of performing this inexpensive bedside test makes further research to clarify its role in our South African setting compelling.

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