The prognostic value of tissue factor levels in acute ischaemic stroke

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ABSTRACT

Introduction: There is no biological marker that can accurately predict the prognosis after an acute ischaemic stroke. The main objective of this study was to evaluate the prognostic value of tissue factor (thromboplastin) levels in first ischaemic stroke.

Methods: This was a prospective study of all patients with first ischaemic stroke conducted from October 2003 to February 2004. Plasma for tissue factor levels was kept at -80 degrees Celsius and was analysed at the end of the study period by an independent person. The activities of daily living (ADL) were assessed by using the Barthel index (BI) on admission and at one month after the stroke onset. Any death or recurrent events were recorded.

Results: 50 patients were recruited into the study. The median tissue factor level was 184.5 +/- 97.3 pg/ml. Only age (p-value is 0.027) and middle cerebral artery (MCA) infarcts (p-value is 0.038) were found to be significant independent predictors for severe disability at one month with BI equal to or less than 9. There was no correlation of tissue factor level with BI at one month post-stroke (r equals -0.028, p-value is 0.846) and there was also no significant relationship between levels of tissue factor and recurrent events (p-value is 0.41).

Conclusion: There is no correlation between tissue factor levels with acute ischaemic stroke outcome.

Keywords: brain infarction, middle cerebral artery infarction, stroke, tissue factors, thromboplastin

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INTRODUCTION

Acute ischaemic stroke is one of the leading factors of morbidity and mortality worldwide. In fact, stroke is the third most common cause of death in many countries after cardiovascular disease and cancer[1]. Two-thirds of stroke death occurs in the less-developed countries. Stroke caused three percent of the world disability burden in 1990, and by 2020, stroke mortality will double because of the increased proportion of older people[2]. There is no single sensitive diagnostic biochemical test for acute ischaemic stroke in the event of normal initial brain computed tomography (CT). Currently, the diagnosis solely depends on the history and clinical signs. However, other potential causes of acute neurological disturbance, including complex migraine, post-ictal paresis, demyelinating disease, transient ischaemic attack (TIA), or even metabolic disturbances like hypoglycaemia, may be difficult to differentiate from acute stroke[3]. Unlike stroke, in acute myocardial infarction, troponin T, a biochemical marker, is diagnostic.

There is also presently no biochemical marker that can be used as a prognostic tool in acute ischaemic stroke. Although acute stroke has been associated with elevations of inflammatory and anti-inflammatory mediators, e.g. C-reactive protein[4], interleukin 6[5], matrix metalloproteinase[6], the lack of specificity prevents their wide acceptance and usage. Thus, the absence of a rapid, objective, accurate, diagnostic and prognostic biochemical tool remains the major obstacle to the optimal care of ischaemic stroke patients. Tissue factor (TF) is a membrane-bound procoagulant glycoprotein. It is the initiator of the extrinsic clotting cascade, which is the predominant coagulation pathway in-vivo[7]. The TF-FVIIa complex is the most potent trigger of coagulation yet known and has been considered as playing a "prima ballerina" role in the initiation of haemostasis[8].

Despite the elucidation of TF structure and function, no human disease has been attributed to the deficiency of this factor. In contrast to a deficiency state, over-expression of TF can be ascribed to a variety of human diseases. Inappropriate intravascular expression of TF triggers the thrombogenic cascade that underlies the often lethal thrombotic

complication of coronary artery disease [9], ischaemic heart disease[10], the consumptive coagulopathy of septicaemia[11], the haemorrhagic diathesis of Rickettsia rickettsii infection[12], the hypercoagulable state in antiphospholipid syndrome[13] and severe preeclampsia[14].

It has been shown that TF level is significantly elevated in patients with cerebrovascular accident (CVA)[15]. There are three reasons why TF can be elevated in CVA. Firstly, TF has been demonstrated to be one of the plaque constituents that participate in the thrombogenicity of atheroma[16]. Secondly, as mentioned above, TF is abundant in the brain and when necrosis occurs, TF may be shed from this reservoir into the circulation[17]. Finally it has been widely recognised that TF expression in the endothelial cells and monocytes can induce pro-inflammatory cytokines that mediate atherogenesis[17]. This study aimed at determining the importance and the prognosticating power of TF in acute ischaemic stroke.

METHODS

This was a prospective observational study of all patients with a first ischaemic stroke from October 2003 to February 2004. All patients with a first ischaemic stroke who were admitted to the medical wards within 72 hours of stroke onset were enrolled in this study. This study was approved by the Ethics Committee of the Medical Faculty of this university. Informed consent was taken from the patient or their immediate relatives. All patients were managed in accordance with the critical pathway of acute ischaemic stroke. Plasma for TF was taken within 72 hours of the stroke onset and was stored at -80° Celsius. At the end of the study period, an independent person blinded to the clinical characteristics measured the TF concentrations.

The activities of daily living (ADL) were assessed by using the Barthel index (BI) on admission and at one month after the stroke onset. Following discharge, patients were seen in the clinic one month after the stroke onset, and their functional ability was assessed. Tissue factor levels were measured using IMUBIND Tissue factor ELISA Kit (American Diagnostica Inc, Stamford, CT, USA). The lower detection limit is approximately 10 pg/ml, and the mean plasma TF level in healthy subjects is 124.9±31.8 pg/ml and shows no sex or age dependence. TF has a short half-life of about one and a half hours. This assay is designed such that there is no interference from other coagulation factors or inhibitors of procoagulant activity. Two duplicate readings of TF levels were taken, and the mean values were taken as the true TF levels.

Univariate analyses were performed on the demographical characteristics and the risk factors, admission parameters, type of stroke, TF levels, and outcome. These were followed by multivariate analysis and logistic regression and the covariates were adjusted for each independent variable. The dependent variables were any recurrent stroke, TIA, death, cardiovascular events and ADL (BI) at the end of one month. The BI was dichotomised into two categories, namely: functionally severe dependent (BI 0-9) and functionally less dependent (BI 10-20) for the statistical analyses of functional outcome. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 11.0 (Chicago, IL, USA), and a p-value of <0.05 was deemed statistically significant.

RESULTS

During the four-month study period, 50 patients with acute ischaemic stroke were identified, the majority of whom were female (30 patients, 60%). The majority of patients presented with lacunar infarcts (25 patients, 50%), followed by middle cerebral artery (MCA) territory infarcts (seven patients, 14%). In this study, four patients (8%) had other types of stroke and 14 patients (28%) had normal brain CT. The demographical data is summarised in Table I. Over the one-month follow-up study period, two patients (4%) died, four patients (8%) developed recurrent stroke and one patient (2%) developed TIA. After performing logistic regression analysis, only age ($p= 0.027$) and MCA infarcts ($p=0.038$) were found to be significant independent predictors for severe disability at one month with BI ≤ 9. There was no correlation of TF level with the BI at one-month post-stroke ($r=-0.028$, $p=0.846$) and there was also no significant relationship between levels of TF and recurrent events ($p=0.41$). (Fig. 1).

DISCUSSION

In this study, the female:male ratio was 1.5:1, and the mean age of the patient in this study was 65.74 ±10.02 years. By using multivariate regression analysis, we demonstrated that age was a significant predictor for functional disability ($p=0.027$). 14% of patients were found to have MCA infarcts, and it was also noted to be a significant independent predictor of functional disability ($p=0.038$). Other variables were not found to be significantly associated with functional disability. This study had failed to show any correlation of TF levels with stroke outcome, either in functional disability or ADL at one month (BI), or in the rate of recurrent events. This is obviously disappointing when the search for a rapid serum diagnostic test

Table I. Baseline characteristics of the study population.

	Number	Percentage
Sex		
Male	20	40
Female	30	60
Age (in years)		
<40	1	2
41-50	3	6
51-60	8	16
61-70	22	44
71-80	14	28
>80	2	4
Race		
Malay	16	32
Chinese	28	56
Indian	6	12
Hypertension	38	76
Hypercholesterolaemia	37	74
Diabetes mellitus	29	58
Smoking	14	28
Atrial fibrillation	6	12
Ischaemic heart disease	6	12
Type of stroke		
Lacunar	25	50
(Based on brain CT)		
MCA	7	14

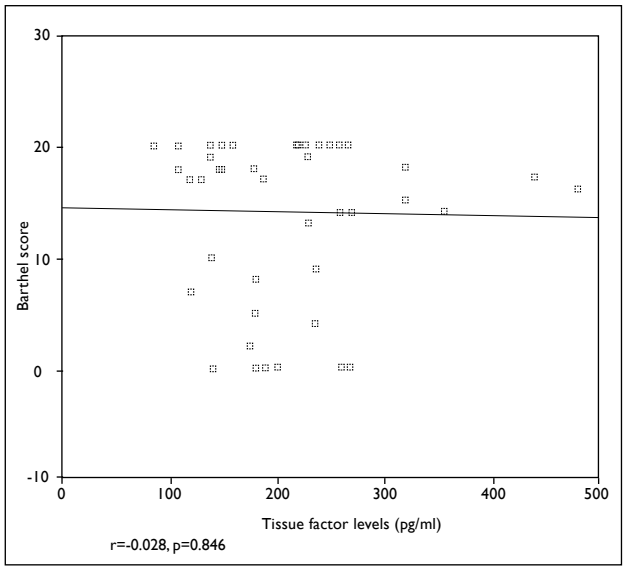

Fig. 1 Severity of functional disability in relation to tissue factor levels.

of acute ischaemic brain injury remains critically important in the management of acute stroke. A reliable biochemical marker of cerebral ischaemia is needed to diagnose, prognosticate and also provide additional information for the primary care providers who may be considering the administration of thrombolytic therapy.

The reason for this lack of correlation is not clear but there are a few possible explanations. First of all, TF is only one of many endothelium and thrombotic markers in our body. Other factors, for example, intracellular adhesion molecule 1 (ICAM 1), thrombomodulin, tissue factor pathway inhibitor (TFPI), von Willebrand factor, protein S, and protein C, will interact with each other in a complex manner to keep our vessels patent[9,18]. By being non-specific to any of the organs, it is difficult to interpret these markers in isolation. It is wiser then to look at a combination of these markers and correlate them to a specific disease. For example, Hassan et al[18] adopted this strategy and showed that patients with ischaemic leukoaraiosis had higher TF:TFP1 ratio compared to patients with isolated lacunar infarction. Thus, future studies should be geared to analyse the combination of biochemical markers rather than a single marker and correlate them with acute stoke outcome.

Stroke is not the only condition and the brain is not the only organ that can express TF. As mentioned earlier, there are numerous conditions that can cause elevation of TF levels. Most of them are associated with atherosclerosis, inflammation or coagulopathy[10-15]. Therefore, TF can be expressed as a consequence of any vascular injury in any other organ bed and at any time, as well as due to events in the brain. Although other conditions that can increase TF levels were excluded in this study, atherosclerosis can be a silent and asymptomatic disease. Atherosclerotic plaques can present occultly in asymptomatic individuals, and at the same time, express TF that makes the relationship between TF levels and specific disease outcome difficult to interpret. Therefore, analysing tissue factor levels in a patient with multiple risks of atherosclerosis can be very disappointing, like in this study.

Another reason for the lack of correlation in this study was because we did not examine serial and the peak tissue factor levels. It is known that tissue factor has a very short plasma half-life and the brain is a large reservoir for tissue factor. Thus, it is may be a better strategy to analyse the correlation between the peak tissue factor levels rather than a random levels to the outcome of acute ischaemic stroke There were few limitations that could influence the results of this study. The small number of patients and the short study period limit the conclusion that can be made from this study. It was also a hospital-biased study that suffered from the referral bias.

In conclusion, this study revealed no correlation between tissue factor levels and acute ischaemic stroke outcome. Larger numbers and studies of longer periods are needed to analyse the correlation of blood-borne markers with stroke outcome. We believe that the answer is not in single biochemical marker but a combination of the markers in view of their complex interrelation in our blood homeostasis.

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