Elevated platelet-derived growth factor AB/BB is associated with a lower risk of recurrent vascular events in stroke patients

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Background Platelet-derived growth factor (PDGF)-AB and BB have been shown to possess angiogenic properties in vivo, and decreased levels have been linked to plaque instability in atherosclerosis. Little work has been done to determine if PDGF is associated with outcomes after stroke, in particular cognitive outcomes. Therefore, in this study, we investigated the association between PDGF and both vascular and cognitive outcomes in a cohort of patients with recent nondisabling ischemic stroke.

Methods Three hundred nine patients recruited within six-months of a transient ischemic attack or nondisabling ischemic stroke [modified Rankin Scale (mRS) ≤ 3] were followed for up to five-years. Cox proportional-hazard regression analyses were performed to investigate the association of PDGF levels with the risk of death, recurrent vascular events, dependency, and incident dementia, while logistic regression analyses were performed to investigate the association of PDGF levels with the risk of significant cognitive decline. Significant cognitive decline was defined as: (a) a decline of cognitive status from no cognitive impairment or mild cognitive impairment with no dementia to moderate cognitive impairment with no dementia or (b) conversion to dementia.

Results Patients (mean age 60 years) were mostly male (64%) and of Chinese ethnicity (85%) and had posterior circulation or lacunar infarcts (73%). In univariate analysis, PDGF was significantly associated with a lower risk of recurrent vascular events [hazard ratio (HR) 0·61; 95% confidence interval (CI) 0·44–0·84]. In multivariate analysis adjusting for treatment, PDGF was independently associated with a lower risk of recurrent vascular events (HR 0·62; 95% CI 0·46–0·85). PDGF levels were not associated with the risk of the other outcomes of interest.

Conclusions Higher levels of PDGF-AB/BB were independently associated with a lower risk of recurrent vascular events in a cohort of convalescent nondisabled stroke patients. Our findings suggest that PDGF-AB/BB may potentially serve as a prognostic marker for outcomes post-stroke and, if this result is validated in larger samples, a potential therapeutic target.

Key words: growth factors, outcomes, prognosis

Introduction

Platelet-derived growth factor (PDGF) is a dimeric glycoprotein composed of two A chains (PDGF-AA), two B chains (PDGF-BB), or a combination of both chains (PDGF-AB). The AB and BB combinations, but not AA, have been shown to possess significant angiogenic effects (1). Moreover, the PDGF B-chain has been found to be up-regulated in neurons and macrophages of rat brains after cerebral ischemia (2) and to induce formation of capillaries, thereby increasing microcirculation in mice (3). As such, it was postulated as a potentially modifiable target in vascular disease.

In the clinical setting, PDGF B-chain has been found to be up-regulated in brains of patients who died after cerebral ischemia (4), and PDGF-BB has been reported to be elevated in the plasma of patients treated with tissue plasminogen activator compared with normal controls (5). Serum PDGF-AB/BB levels were found to be lower in patients with symptomatic carotid disease at risk of plaque instability compared with asymptomatic patients (6). Nevertheless, thus far, no prospective study has evaluated the prognostic value of PDGF-AB/BB in stroke survivors.

Given the increasing prevalence of vascular cognitive disease, PDGF may also play important roles in cognitive function. Laboratory evidence in PDGF receptor-β knockout mice has exhibited decreased number of neurons and cognitive deficits (7). Therefore, in the present study, we investigated the association between PDGF-AB/BB levels and the risk of death, recurrent vascular events, dependency, incident dementia, and significant cognitive decline in a cohort of convalescent stroke patients.

Materials and methods

Patient population

All patients within six-months of a transient ischemic attack (TIA) or ischemic stroke seen in the Singapore General Hospital between 1999 and 2005 were screened for eligibility to enter the European Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT). The methodology and selection criteria of the ESPRIT study have been reported previously (8). Briefly, the recruited patients were within six-months of a TIA (including transient monocular blindness) or nondisabling ischemic stroke [grade ≤ 3 on the modified Rankin scale (mRS)] (9) of presumed arterial origin. Singapore General Hospital’s Institutional Review Board and Ethics Committee approved the protocol of this study.