Short report

Beta-thromboglobulin in cerebral infarction

E Woo, C Y Huang, V Chan, Y W Chan, Y L Yu, T K Chan

From the Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong

SUMMARY Plasma beta-thromboglobulin (BTG) was significantly elevated in the acute phase of 116 atherosclerotic thrombotic (p < 0.0001) and 36 cardioembolic (p < 0.005) infarcts but normal for 96 lacunes compared with controls. This elevation persisted into the 6th week after the acute event. Among atherosclerotic thrombotic infarcts, the acute beta-thromboglobulin level showed a tendency to correlate with infarct size on CT and predicted mortality at 6 weeks. These results suggest that platelet aggregation plays a primary role in the pathogenesis of atherothrombosis.

Platelet aggregation plays a significant role in normal haemostasis by sealing defects in the vessel wall. Pathological extension of platelet aggregation may, on the other hand, contribute to the development of occlusive vascular diseases. Recent studies have shown that antiplatelet agents are effective in improving the outcome of patients with cerebral1,2 or coronary arterial diseases.3,4 It seems likely that these antiplatelet agents would be most effective in those patients with increased platelet reactivity.

Platelet aggregation is associated with the release of a number of proteins including beta-thromboglobulin (BTG), which is a small protein stored in the alpha-granules of platelets. Its function is unclear but it is possibly a "granule packing protein" stabilising the active constituents in the alpha-granules. Measurement of this platelet released material provides an index of platelet activation in vivo in atherosclerotic vascular disease and arterial thrombosis.5

We hypothesise that the role played by platelet aggregation in cerebral infarct varies with the pathological nature of the ischaemic insult. Thus, atherosclerotic thrombotic infarction, a large-vessel disease that arises as a result of artery-to-artery embolism of platelet thrombi from the main carotid arteries or following thrombotic occlusion of a major cerebral artery, should be associated with significant platelet activation and hence an elevated BTG level. Lacunar infarction, on the other hand, is a small-vessel disease with lipohyalinosis of the penetrating end-arteries with in situ thrombosis.6 Platelet aggregation does not play any role in its pathogenesis and thus the BTG level should remain normal. Cardioembolic infarction arises from fibrin-platelet clots in the heart so that platelet activation may be expected to be present. We tested the hypothesis by measuring the BTG level in a consecutive series of ischaemic stroke patients.

Patients and methods

Patients

All Chinese patients with acute cerebral infarction or transient ischaemic attack admitted to the University Department of Medicine, Queen Mary Hospital over a 6-month period were studied. Patients were examined within 7 days of onset of ictus and classified as transient ischaemic attacks (TIAs), atherosclerotic thrombotic infarcts (AIs), cardioembolic infarcts (EIs) or lacunar infarcts (LIs) by clinical criteria and computed tomographic (CT) or necropsy confirmation.

Transient ischaemic attacks (TIAs) required complete resolution of the neurological deficit within 24 hours; Atherosclerotic thrombotic infarcts (AIs) required clinical evidence of cortical deficits (dysphasia, dyspraxia, visual field defects, gaze paresis) and CT or necropsy evidence of recent cortical infarction, sinus rhythm and no source for cardiac emboli; Cardioembolic infarcts (EIs) were clinically the same as AIs except that all these patients had either a cardiac arrhythmia or a definite embolicigenic abnormality;7 Lacunar infarcts (LIs) required the clinical lacunar syndrome (pure motor hemiparesis, pure sensory stroke, ataxic-hemiparesis, dysarthria-clumsy hand syndrome, sensorimotor stroke) without cortical deficits in whom CT was normal or showed a lacunae characteristic of a lacune.

The cardiac status of each patient was assessed by history.
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Sex had no effect on BTG level. The mean (SD) value for the 36 male normal controls was 26.0 (6.7) ng/ml, and that for the 37 female normal controls was 25.3 (6.8) ng/ml (p > 0.1). Similarly, no difference was found between the male and female patients of each stroke subtype, although there were significantly more male LI and more female EI patients.

There was a considerable degree of overlap (fig 1) in the acute BTG levels among the various stroke subtypes. A single BTG level in the acute phase did not predict the nature of the ischaemic disorder although there were no values greater than 70 ng/ml in lacunar infarcts.

By 6 weeks after ictus, 28 patients out of the initial 116 A1 patients had died. Of the 88 survivors, 82 had BTG level repeated (fig 2). The acute BTG level of patients still alive at 6 weeks was 30.5, 14.2 ng/ml, while that of patients who died was 39.9, 20.4 ng/ml (p = 0.05).

The 6-week chronic BTG level in the 82 A1 patients who had the test repeated was 30.9, 13.8 ng/ml. There was no significant difference from their acute BTG levels.

By contrast with A1, there was no significant difference in the acute BTG level between those EI patients who survived 6 weeks (26/36) and those who succumbed at 6 weeks (10/36), and there was no difference between the acute and 6-week BTG levels in the 22 EI patients who had a repeat BTG level taken (fig 3).

Correlation between BTG and infarct size on CT TIAs: All 16 TIA patients had normal CT scans. A1: The infarct size on CT of the 116 A1 patients ranged from 0.5 to 199.8 ml, with a median of 4.35 ml. By dividing into two subgroups according to the median infarct size (4.35 ml), the subgroup with larger infarcts (infarct size above median, n = 58, BTG 35.1, 16.7 ng/ml) had a higher acute BTG level than the subgroup with smaller infarcts (infarct size below median, n = 58, BTG 29.3, 14.1 ng/ml), with a significance level of p = 0.06 (fig 4). Linear regression
analysis between BTG and infarct size in these 116 patients also revealed a borderline significance ($r = 0.25$, $p = 0.08$).

EI: The infarct size on CT of the 36 EI patients ranged from 0.8 to 273.5 ml, with a median of 26.35 ml. By dividing into two subgroups according to the median infarct size (26.35 ml), there was still a tendency for the subgroup with larger infarcts to have a higher mean BTG level (38.4, 20.9 ng/ml vs 32.4, 14.3 ng/ml, fig 4), although it did not reach statistical significance ($p > 0.1$).

II: There was no difference in the acute BTG level between those EI patients with an infarct demonstrated on CT ($n = 46$, BTG 23.1, 8.5 ng/ml) and those with a normal CT ($n = 50$, BTG 23.8, 10.4 ng/ml) (fig 4).

Discussion

Our study showed that in the acute phase after a stroke, the BTG level is significantly elevated among those with a cortical infarct, whether of atherosclerotic or cardioembolic origin, but the level was within the normal range for an age-matched population among those with a lacune. While other workers have reported similar findings, our population is the largest cohort of patients with methodical timing of blood sampling to ensure meaningful results. The finding of elevated BTG levels in atherosclerotic thrombotic infarcts compared with that in lacunes is in keeping with the concept that the former represent large-vessel diseases in which platelet aggregation is important and that the latter represent small-vessel diseases with lipohyalinosis and in situ thrombosis without significant platelet activation. The fact that cardioembolic infarcts also have elevated BTG levels, signifying platelet activation, is not surprising. Pathologically, the hearts of these patients have mural clots consisting of fibrin-platelet mixtures. In addition, it had been shown in a addition of dij in warfarin in pac replacement complications, does have a although it may not element. Our results a overlap in the majority of AI within mean 2 BTG level in the predictive value tively insensitive injury. It has been s cerebral ischaer One may argue stroke is only related to the intensity elevated I suggest that pla and that it is not stimulus. Further elevated BTG le TIA supports tissue destructive invoke platelet r
We thank Ms. Lee Li-Tap and Mr. Chan Po-Tong for

Failure to demonstrate a significant BFG difference in our TIA cohort may be explained by the small number of patients. BFG value was approximately midway between that of patients with intermediate-stage cerebral infarcts and a population of healthy controls.

![Diagram](image-url)
technical assistance and Mrs Shirla Tam for secretarial assistance. This work was supported by grants no. 311-030-8011-21 and 335-041-0029 of the University of Hong Kong.

References
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