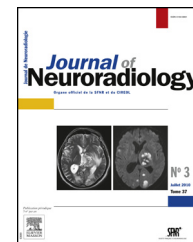




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ORIGINAL ARTICLE

Thrombus composition in acute ischemic stroke: A histopathological study of thrombus extracted by endovascular retrieval



Natasha Simons^a, Peter Mitchell^b, Richard Dowling^b,
Michael Gonzales^c, Bernard Yan^{a,*,b}

^a Melbourne Brain Centre, Level 4, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia

^b Neurointervention Service, Department of Radiology, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia

^c Department of Histopathology, Royal Melbourne Hospital, Parkville, Victoria 3050, Australia

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KEYWORDS

Stroke;
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Thrombus;
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Summary

Background and purpose: The composition of occlusive thrombus in acute ischemic stroke may affect treatment success. Neuroimaging characteristics may correlate with thrombus composition. In this study we aimed to investigate the relationship between the hyperdense artery sign (HAS) on imaging and thrombus composition.

Materials and methods: Acute ischemic stroke patients who underwent endovascular thrombus retrieval from 2010–2012 were prospectively recruited. One blinded pathologist prepared the histology sections of retrieved thrombi whereby staining with haematoxylin and eosin and CD34 immunostain were performed. Histology sections were categorised into 4 phases of thrombus formation: red blood cell (RBC) dominant, RBC proportion equal to fibrin, fibrin dominant and organised fibrin. Computed tomography (CT) brain scans were assessed for HAS. Fisher's exact test was performed to identify an association between HAS and thrombus composition.

Abbreviations: ANOVA, Analysis of variance; CT, Computed tomography; H&E, Haematoxylin and eosin; HAS, Hyperdense artery sign; ICA, Internal carotid artery; IQR, Interquartile range; IV, Intravenous; MCA, Middle cerebral artery; NIHSS, National Institute of Health Stroke Scale; RBC, Red blood cell; SD, Standard deviation; TIA, Transient ischemic attack; tPA, Tissue plasminogen activator.

* Corresponding author. Tel.: +61 3 9349 2477; fax: +61 3 93494489.

E-mail address: bernard.yan@mh.org.au (B. Yan).

Results: Forty patients were included. The mean age was 65.6 ± 12.9 years and 67.5% were male. Atrial fibrillation was detected in 19 (47.5%) patients, diabetes mellitus in 6 (15.0%), hypercholesterolaemia in 11 (27.5%), hypertension in 20 (50.0%) and previous stroke or transient ischemic attack in 8 (20.0%) patients. Of the retrieved thrombi, 11 (27.5%) were RBC dominant, 11 (27.5%) RBC proportion was equal to fibrin, 7 (17.5%) fibrin dominant and 11 (27.5%) organised fibrin pathology. HAS was present in 29 (72.5%) patients and was significantly associated with thrombus early phase pathology ($P < 0.05$).

Conclusion: HAS was significantly associated with early phase thrombus composition. This may enable the prediction of thrombus composition and allow for targeted selection of therapeutic modality.

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Introduction

The most effective treatment for acute ischemic stroke is reperfusion therapy [1,2]. Current guidelines recommend IV tPA as the primary reperfusion therapy, based on randomised controlled studies, demonstrating improved clinical outcomes [1,3,4]. However, IV tPA is associated with high recanalisation failure rates. In particular, recanalisation of an occluded ICA occurs at only 4.4% and recanalisation of the basilar artery occurs at only 4% [5].

It has been postulated that IV tPA is more effective on thrombus in the early phases of formation and organisation, suggesting that thrombus composition may be the mechanism of recanalisation failure. [6–12]. Previous research has demonstrated time dependant histological phases of thrombus formation with the formation of a “white thrombus”, composed mainly of fibrin and platelets, being the first phase [13–16]. In comparison, thrombi of late phase formation, involving the formation of a “red thrombus”, are composed mainly of fibrin and RBC [15,16]. It is possible that the decreased efficacy of IV tPA on late phase thrombus is attributable to the organisation of fibrin within the “red thrombus”. A surrogate marker for organised fibrin is the presence of endothelial cell proliferation which can be detected with CD34 immunostain [17–19]. This novel technique enables the identification of potentially resistant thrombi in the late phases of formation.

Clinical evidence has shown that treatment efficacy for stroke is time-dependant, given that patients demonstrate better clinical outcomes when treatment is administered at the earliest opportunity [1,20–22]. Knowledge of occlusive thrombus composition prior to treatment may enable clinicians to predict the patient’s response to IV tPA and aid in more rapid selection of the most appropriate revascularisation strategy. There is emerging interest in utilising radiologic imaging characteristics as predictors of thrombus composition [23].

Advances in thrombus retrieval technology offers an opportunity to directly examine the occlusive thrombi retrieved from acute ischemic stroke patients [24]. This opens the possibility of correlating thrombus composition with pre-treatment neuroimaging. In this study, we investigated the relationship between radiologic imaging characteristics and thrombus composition. We hypothesised that the presence of HAS, determined by visual asymmetrical increased density of a cerebral artery on plain CT, is associated with the early phases of thrombus formation.

Materials and methods

This study was approved by the Human Research Ethics Committee. Forty acute ischemic stroke patients who underwent thrombus retrieval at our hospital between November 2010 and December 2012 were included in this study. Subjects presented with an acute ischemic stroke, defined by onset < 6 hours, and underwent routine plain CT upon arrival. IV tPA (Alteplase) (Boehringer Ingelheim; Ingelheim, Germany) treatment (0.9 mg per kilogram of body weight) was administered to eligible patients prior to thrombus retrieval being performed. Thrombus retrieval was conducted in the angiography suite by neurointerventionists with the Solitaire™ FR Revascularization Device (Covidien; Mansfield, M.A, USA). Thrombus fragments extracted during the retrieval procedure were immediately fixed in phosphate-buffered formalin (10%). The tissue specimens were then sent to pathology for histopathological analysis. Subjects were excluded from this study if there was no thrombus specimen available for histopathological analysis.

Histopathological analysis

Tissue processing and paraffin embedding of the formalin fixed tissue specimens was performed. The paraffin embedded tissue was sectioned in 10-micrometre thick sections and stained using H&E. The tissue sections were further stained with the immunostain CD34, a marker of endothelial cells. One blinded pathologist performed histological examination of the thrombus specimens. The specimens were qualitatively categorised into one of four phases of thrombus formation – RBC dominant, RBC proportion equal to fibrin, fibrin dominant or organised fibrin pathology. Fibrin organisation was determined by the presence of endothelial cell ingrowth within CD34 immunostained sections. Thrombus pathology was further categorised into early phase (RBC dominant and RBC proportion equal to fibrin) and late phase (fibrin dominant and organised fibrin) pathology.

Plain CT analysis

One neuroradiologist, being blinded to the histopathology results, reviewed the plain CT sequences acquired upon the patients’ presentation to hospital for the presence or absence of HAS. The presence of HAS was recorded by the neuroradiologist by visual inspection and was defined as

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