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The Main Causes of Hemorrhagic Stroke in Patients

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Abstract

Haemorrhagic stroke is a severe stroke subtype with high rates of morbidity and mortality. Although this condition has been recognised for a long time, the progressing haemorrhagic stroke has not received adequate attention, and it accounts for an even worse clinical outcome than the nonprogressing types of haemorrhagic stroke. In this review article, we categorised the progressing haemorrhagic stroke into acute progressing haemorrhagic stroke, subacute haemorrhagic stroke, and chronic progressing haemorrhagic stroke. Haematoma expansion, intraventricular haemorrhage, perihaematomal oedema, and inflammation, can all cause an acute progression of haemorrhagic stroke. Specific 'second peak' of perihaematomal oedema after intracerebral haemorrhage and 'tension haematoma' are the primary causes of subacute progression. For the chronic progressing haemorrhagic stroke, the occult vascular malformations, trauma, or radiologic brain surgeries can all cause a slowly expanding encapsulated haematoma. The mechanisms to each type of progressing haemorrhagic stroke is different, and the management of these three subtypes differs according to their causes and mechanisms. Conservative treatments are primarily considered in the acute progressing haemorrhagic stroke, whereas surgery is considered in the remaining two types. Haemorrhagic stroke, which accounts for 10–20 % of all of the new strokes that occur every year [8], has a 1-month mortality rate of approximately 40 % [14]. Although it has drawn the attention of researchers because of the high rates of morbidity and mortality, the outcomes and prognosis of intracranial haemorrhage have not improved significantly during the last several decades.

Keywords: *development, diseases, causes, occurrence, treatment Progressing stroke, also known as progressive stroke, stroke-in-progression, stroke-in-evolution, and deteriorating stroke, has been a clinical concept for a long time [7, 4]. Progressing stroke happens often within 36–72 h, with marked deterioration in clinical manifestations measured by the Scandinavian Stroke Scale or the Canadian Stroke Scale [4]. This concept was traditionally limited to ischaemic stroke [16], and haemorrhagic stroke was often ruled out in the initial studies of progressing stroke [4]. However, evidence has shown that a progression also exists in the haemorrhagic stroke [3]. Several researchers have shown that primary haemorrhagic stroke is more often associated with progression than ischaemic stroke [8] and that early deterioration is associated with a poorer outcome [3].*

1. Introduction

Early neurological deterioration of intracerebral haemorrhage has been recognised in many patients with haemorrhagic stroke,. As with progressing ischemic stroke, a deterioration of clinical signs and symptoms often happens within 24–72 h with intracerebral haemorrhage and is associated with haematoma expansion [20], perihaematomal oedema [6], intraventricular haemorrhage [10], and inflammation [1]. The expansion of haematoma may account for most of the progression [3]. Additionally, in the second to third weeks after the onset of intracerebral haemorrhage, many patients may undergo a deterioration of symptoms after the initial alleviation by conservative management, which indicates a subacute progression [2]. Furthermore, the progression of haemorrhage may appear to be a chronic form, in which the gradual formation of an encapsulated intracerebral haematoma may

cause progressive neurologic deficits over weeks or months [3]. Therefore, the concept of progressing haemorrhagic stroke should be separated from the progressing ischaemic stroke, because the causes, pathogenesis, mechanisms, manifestations and management of the former all differ from the latter.In this review article, we proposed the concept of progressing haemorrhagic stroke and summarised the three categories of progressing haemorrhagic stroke, which are as follows: acute progressing haemorrhagic stroke, subacute progressing haemorrhagic stroke and chronic encapsulated intracerebral haematoma. We explored several aspects of their causes, mechanisms and management.

Acute Progressing Haemorrhagic Stroke

Clinical Features

Intraventricular extension of haemorrhage is another deteriorating factor of early ICH Intraventricular extension may occur simultaneously with ICH or within 24–72 h after the onset of initial ICH, in 20–55 % of all ICH patients. Steiner et al. and Bhattathiri et al. [16] all showed that ICH patients with intraventricular haemorrhage had a worse functional outcome compared to those without intraventricular hemorrhage. Adjusting for the ICH score and haematoma expansion, intraventricular haemorrhage is still associated with a higher mortality rate within the patients' hospitalisation stay [6].

Perihaematomal Oedema

Perihaematomal oedema volume increases significantly after onset within the first 24 h after spontaneous ICH [6]. The chronological CT images showed that perihaematomal oedema increased rapidly within 3 days after onset and reached its initial peak in the fourth or fifth day [9]. The highly evident initial mass effect could also contribute to the initial haemorrhagic stroke progression [6].

Inflammation

Sun et al. [15] reported that a white blood cell above 10,000/mL3 on hospital admission or within the first 72 h of hospital admission was highly associated with deterioration. Leira et al. [10] also showed that a body temperature of above 37.5 °C and increased neutrophil count are predictors of early neurological deterioration. The inflammation response predicts a worse short-term and long-term outcome [2, 6].

Blood Clotting Dysfunction

Continued haemorrhage from the primary haemorrhagic vessel or secondary bleeding into the periphery of the clot from the stretching of the surrounding vessels may account for the initial haematoma expansion or intraventricular haemorrhage [20]. The ceaseless bleeding or re-bleeding in ICH may result from coagulopathy in certain patients. Haematoma expansion is shown to be positively associated with liver disease [7] and the amount of alcohol consumption , and negatively associated with the level of fibrinogen [4]. Warfarin use was associated with both haematoma expansion and intraventricular haemorrhage [7]. Broderick et al. and Yildiz et al. found a correlation between antiplatelet therapy and haematoma expansion [9,]. The low serum LDL cholesterol level was also reported to be associated with a higher haematoma expansion rate; researchers think that this association is related to the function of LDL to maintain vascular integrity .

Hyperglycaemia

Hyperglycaemia on admission is an important predisposing factor for haematoma expansion [19]. Querish et al. [8] analysed the blood glucose of the ICH patients measured repeatedly after hospital admission over 3 days, and the results showed that those with increasing blood glucose had increased haematoma expansion and perihaematomal oedema, compared to those with decreasing blood glucose measurements. A linear correlation of intraventricular haemorrhage and hospital admission hyperglycaemia has also been detected by Appelboom et al. [9]. In an experimental model, Liu et al. [5] showed that hyperglycaemia increased haematoma expansion through the effect of increased kallikrein, which inhibits platelet aggregation. Hyperglycaemia may result from a history of diabetes, or stress reaction of ICH [9]. Many studies have shown that hyperglycaemia at the time of hospital admission is associated with early mortality and poor outcome in ICH patients [10].

Haemorrhagic Location

For patients with lobar ICH, an early mortality was associated with the involvement of the inferior parietal lobule, posterior insula and posterolateral thalamus, whereas for patients with basal ganglia ICH, early mortality was associated with a large region extending from the cortex to the brainstem [7]. Intraventricular haemorrhage extension is correlated with the primary location of ICH [2]. A retrospective study by Hallevi et al. [6] showed that thalamic and caudate locations had the highest intraventricular haemorrhage frequency. Lee et al. [7] also detected a higher incidence of intraventricular haemorrhage in the thalamic and basal ganglia. Intraventricular haemorrhage patients including the third and fourth ventricle or ICH patients with insular involvement are reported to have

lower baroreflex sensitivity than the patients without these involvements, suggesting that involvement of these sites could contribute to impairment of autonomic blood pressure regulation [7, 8]. Hypertensive responses can be exaggerated and additive because of the impaired baroreceptor sensitivity [15].

Vasogenic Oedema

Early perihaematomal oedema could be vascular in origin [2]. Several animal experiments have confirmed that early oedema formation occurs despite an intact blood–brain barrier [8]. The oedema occurrence and the volume in thrombolysis-related patients with ICH are all less frequently observed than those seen in patients with spontaneous ICH, indicating that an existence of a clot is necessary for the presence of hyperacute oedema [5]. Blood clot retraction could force the serum into the perihaematomal space to form vasogenic oedema [6]. Butcher et al. [3] investigated 21 patients with ICH using perfusion-weighted MRI and diffusion-weighted MRI within 10 h; they found that water diffusion in the perihaematomal region was significantly increased and was independently correlated with perihaematomal oedema volume, and they suggested that the hyperacute oedema was, for the most part, plasma-derived.

Cytotoxic Factors and Inflammation

Thrombin, which is formed in the activated coagulation cascade in the early phase of ICH, primarily contributes to the development of early perihaematomal oedema [17] by activating Src kinase phosphorylation to destroy the blood–brain barrier via its protease-activated receptors [13]. Several animal studies have shown that thrombin could induce apoptosis of neurons and astrocytes [8], potentiate glutamate NMDA receptor function [10], activate microganglia [5], activate autophagy process [9] or induce TNF-alpha release [3]. Also, the activated inflammation cascade may contribute to brain damage. Heme oxygenase, cellular fibronectin, interleukin-6, tumour necrosis factor-alpha, matrix metalloproteinase-9 (MMP-9) overexpression are all shown to be associated with haematoma expansion [9]. Lee et al. [9] showed that by blocking the MMP-9 modulations in the experimental ICH of rats, a reduction of haematoma expansion can be observed (Fig. 1).

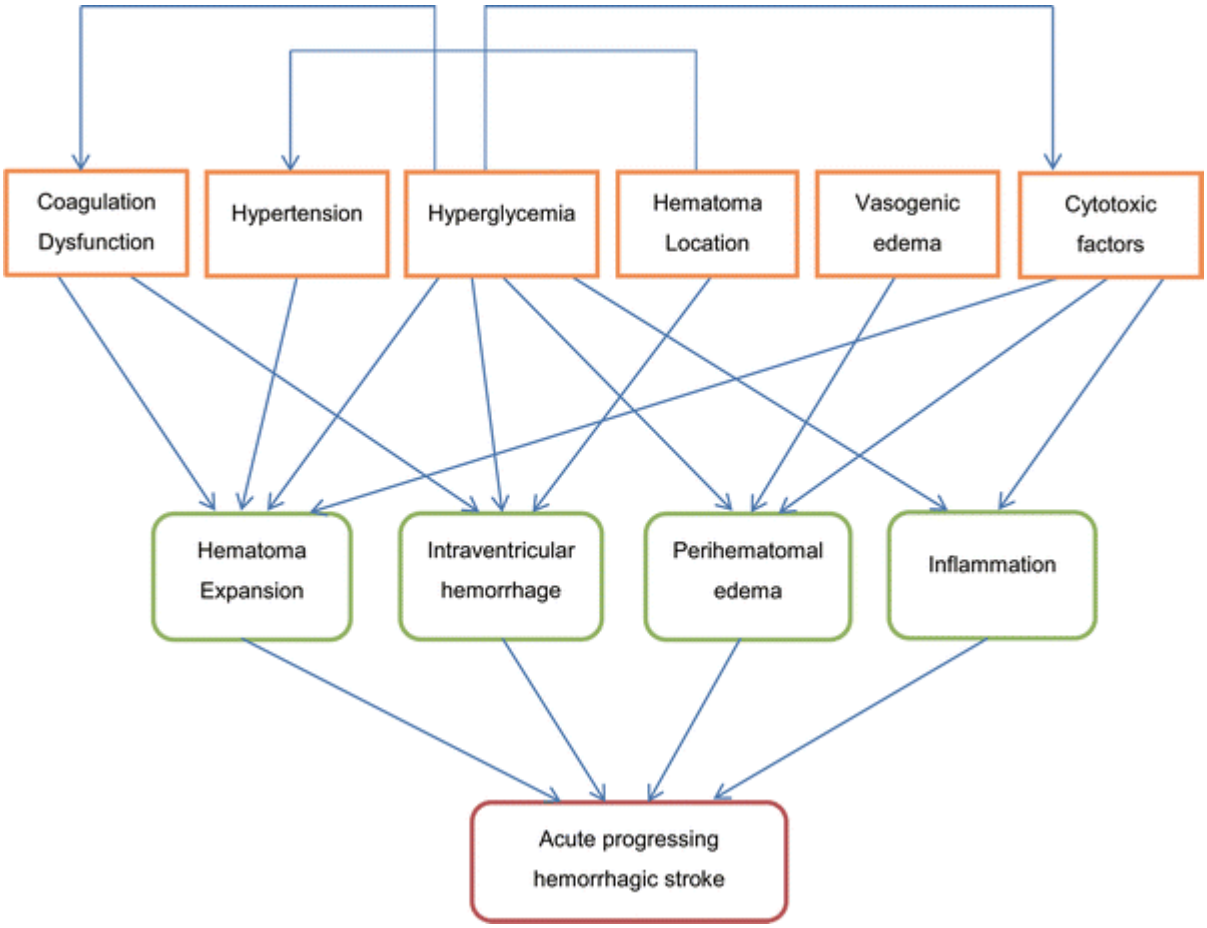
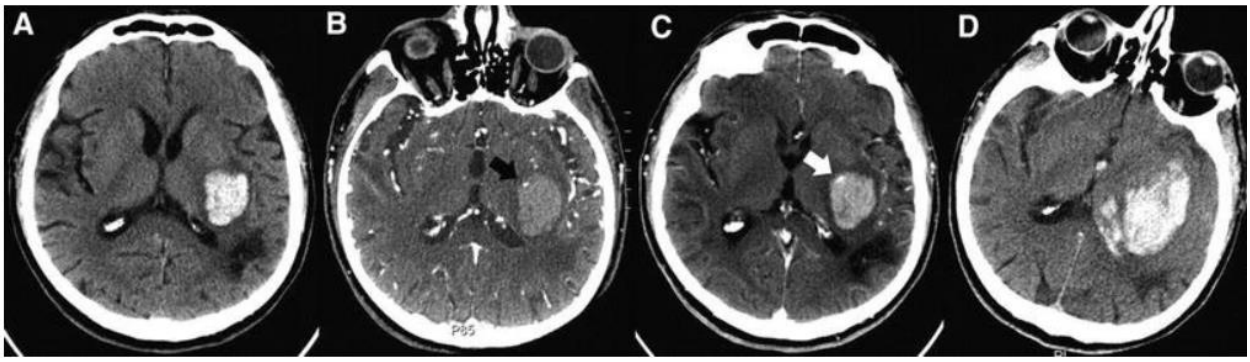


Figure1: Mechanism of acute progressing haemorrhagic stroke

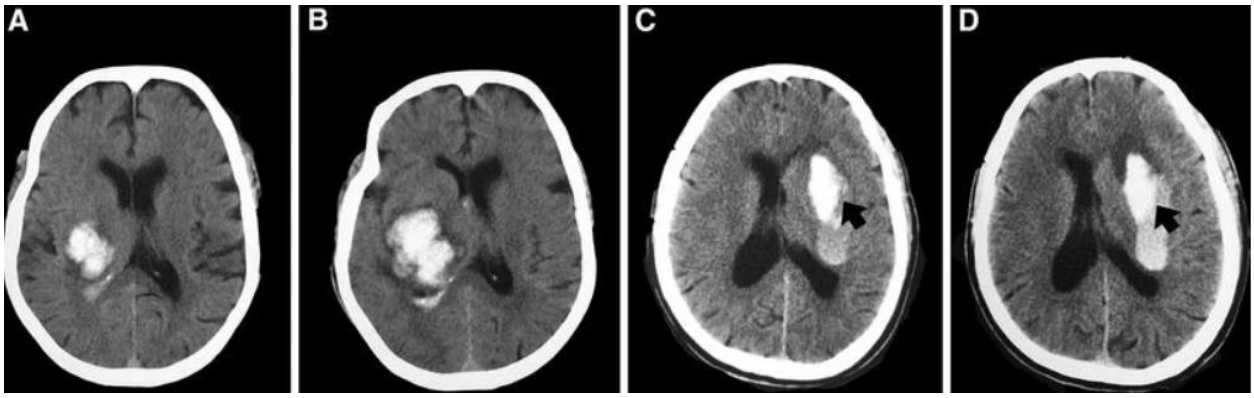
Prediction of Acute Progressing Haemorrhagic Stroke

The predisposing factors described all predict the progression of haemorrhagic stroke. Additionally, researchers have tried to develop more effective ways to predict the progressing haemorrhagic stroke. Because haematoma expansion accounts for the majority of acute progressing, the major explorations on predictions are on haematoma expansion. Several radiological methods have been developed.Haematoma enlargement is less likely to occur in those who have a long interval (>6 h) from onset to first CT [12,]. ICH volume on baseline CT was positively associated with both haematoma expansion and intraventricular haemorrhage occurrence [6]. A meta-analysis concluded that a smaller initial haematoma is less likely to expand [9].A multicentre, prospective, observational study has shown that the 'spot sign' significantly predicted haematoma expansion with a sensitivity of 51 % and specificity of 85 %, and was associated with a worse prognosis and increased mortality [5]. Several researchers have suggested that postcontrast CT extravasation could be an alternate to add the predictive value and sensitivity of spot sign . Furthermore, Almandoz et al. have developed a 'spot sign score' system, involving spot sign numbers, maximal axial dimension and maximal attenuation. The higher scores are associated with higher in-hospital mortality and poor outcome [3, 4]. A clinical trial is being conducted to test its predicting value in early haematoma growth [9] (Fig. 2).



However, although ASA/AHA recommended CTA or contrast CT to identify the patients at risk for haematoma expansion [12], neither of them is a routinely performed examination at the time of hospital admission in many institutions. Haematoma density heterogeneity could be a substitute for the prediction of haematoma expansion. Haematoma heterogeneity refers to the irregularity of shape and density of the initial haematoma on the CT scan, and researchers have found an association between haematoma heterogeneity and haematoma expansion [13]. Takeda et al. concluded that the presence of haematoma volume above 16 mL, haematoma heterogeneity and 1.5 h of a systolic blood pressure above 160 mmHg together increased the likelihood of haematoma expansion to approximately 59 %. Although its definition was traditionally arbitrary, Ji et al. [1] defined the haematoma heterogeneity as a difference of over 20 HU in CT value between two regions exceeding 10 mm^2 in area. Barras et al. used quantitative CT densitometry to measure mean attenuation, square root of variance, coefficient of variation, skewness and kurtosis of the attenuation distribution of the haematoma; they found that the coefficient of variation and the square root of variance, along with the basic haematoma volume, are predictors of greater growth. They suggested that quantitative CT densitometry can be used to identify haematoma heterogeneity [12].

(Fig. 3).



2. Conclusion

Although its definition was traditionally arbitrary,. [1] defined the haematoma heterogeneity as a difference of over 20 HU in CT value between two regions exceeding 10 mm2 in area. Barras et al. used quantitative CT densitometry to measure mean attenuation, square root of variance, coefficient of variation, skewness and kurtosis of the attenuation distribution of the haematoma; they found that

the coefficient of variation and the square root of variance, along with the basic haematoma volume, are predictors of greater growth. They suggested that quantitative CT densitometry can be used to identify haematoma heterogeneity [12].

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