

Pathology of Intracerebral Haemorrhage

Intracerebral haemorrhage (ICH) is an acute and spontaneous extravasation of blood into the brain parenchyma. Bleeding may also extend into the ventricles or subarachnoid space.¹ ICH is a subtype of stroke with high morbidity and mortality accounting for about 15% of all deaths from stroke.² Depending on the underlying cause of bleeding, ICH is classified as either primary or secondary. Primary ICH, which accounts for 78-88% of cases, originates from the spontaneous rupture of small vessels damaged by chronic hypertension or amyloid angiopathy. Secondary ICH occurs in association with trauma, vascular abnormalities, tumours or impaired coagulation.³ The focus of this article is mainly on the aetiology, pathophysiology and pathology of primary ICH with brief comments on genetics and iatrogenic forms of ICH.

Causes of intracerebral haemorrhage

Table 1 lists the various causes of ICH. Hypertension is still the main cause, being responsible for approximately 55% of cases of ICH.⁴ Cerebral amyloid angiopathy (CAA) is the other major cause of primary ICH/ lobar haemorrhage in the elderly.⁵ Post-traumatic haematomas are usually multiple and about the basal brain surface. Vascular malformations including aneurysms are a common cause of ICH, especially in young normotensive individuals. Coagulopathies may cause multiple or recurrent ICH, sometimes in the presence of systemic bleeding.⁶

Table 1: Causes of ICH

Primary	Secondary
Chronic Hypertension	Trauma
Cerebral Amyloid Angiopathy (CAA)	Ruptured aneurysm
	Vascular malformations
	Tumours (primary and metastatic)
	Coagulopathies
	Drugs or alcohol
	Haemorrhagic conversion of cerebral infarct
	Vasculitis
	Pregnancy (eclampsia, venous thrombosis)
	Others/ unknown

Pathophysiology

ICH was once considered to be a simple, monophasic, rapid bleeding event that stopped quickly as a result of clotting and tamponade.^{1,3} But ICH has now been shown by serial CT scans to be a dynamic and complex process involving several distinct phases. The two most important new concepts are that firstly, many haemorrhages continue to grow and expand over several hours after the onset of symptoms. **Expansion of haematoma:** Most haematomas result from rupture of an artery or arteriole. Their expansion is most likely due to continued bleeding from the primary source and to the mechanical disruption of surrounding vessels. Acute hypertension, a local coagulation deficit, or both may be associated with expansion of the haematoma.^{1,3} Secondly, most of the brain injury and swelling that occurs after ICH is the result of inflammation caused by thrombin and other end products of coagulation.¹ **Secondary brain injury and oedema:** The haematoma initiates oedema and neuronal damage. Oedema typically develops over the first 24-96 hours

and slowly resolves over several weeks. The early oedema is usually secondary to plasma proteins present in the haematoma. Subsequent clotting and complement cascade activation results in disruption of the blood-brain barrier, direct cytotoxicity and more oedema. Lysis of red blood cells with haemoglobin toxicity and formation of free radicals probably accounts for the late onset oedema, which persists for several weeks after the initial haemorrhage.⁷ Neuronal death in the region around the haematoma is predominantly necrotic, with recent evidence suggesting the presence of programmed cell death (apoptosis).³ Unlike primary tissue injury from the haematoma formation, secondary brain injury and oedema are potential therapeutic targets.⁵

Pathology

The most common sites of ICH are cerebral hemispheres, basal ganglia, thalamus, brainstem (predominantly the pons), and cerebellum.³ The gross and microscopic changes in the brain depend on the location of ICH, but the general appearance is similar. In the acute stages, the ICH consists of a liquid or semiliquid mass of blood with surrounding oedema. After a few days, the haematoma changes its consistency and adopts a brown colour, while oedema begins to recede. After several months or years, depending on its size, the haematoma becomes a cavity. Small ICH can be reabsorbed almost completely, leaving behind a small linear scar.⁷

Microscopically, the ICH in its acute stages consists of extravasated well-preserved red blood cells (RBC) without any inflammation. Subsequently, the RBC begins to lyse and neutrophils appear. This is followed by infiltration of macrophages whose main role is to phagocytose blood products and necrotic tissue. The brown discolouration of the slightly older haematomas noted macroscopically is due to the presence of two major haemoglobin-derived pigments, haemosiderin and haematoidin. One of the late events involves proliferation of astrocytes, some containing haemosiderin reflecting their phagocytic activity. The transfer of haemosiderin from macrophages to astrocytes, an event that rarely happens in infants, is common in the adult.⁷ The pathological evolution of ICH is summarised in Table 2 and a knowledge of this temporal sequence helps in estimating the approximate age of a haematoma in the absence of relevant clinical data.⁹

Hypertension

Hypertension-related haemorrhages occur typically in deep areas of the brain such as the basal ganglia and thalamus because vessels in these areas are located close to the high pressure of the circle of Willis.^{9,10} They are less common in the pons, cerebellum or superficial cortex. Pathological studies have shown hyperplasia of the media in artery walls due to proliferation of reactive smooth muscle cells in early hypertension. This has been termed 'hyperplastic arteriosclerosis'. Eventually, the smooth muscle cells die and are replaced by collagen fibres which makes the vessel wall brittle and liable for future leakage.¹⁰ Miliary or microaneurysms, originally described by Charcot and Bouchard, have been recently questioned as the source of haemorrhage, as complex tortuosities of blood vessels affected by hypertensive changes may be misinterpreted as microaneurysms. Fibrinoid necrosis associated with haemorrhage in acute hypertension appears to be haemostatic, whereas in chronic hypertension it has been suggested that fibrinoid necrosis may be a precursor to haemorrhage.⁹



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