

Cerebrovascular Disease

Introduction

Cerebrovascular diseases (CVD) are common and serious, ranking worldwide as the third largest cause of morbidity and mortality. The outlook for patients with the recognised clinical presentations of CVD is improving. Clinical trials have delivered effective treatments for patients with acute ischaemic stroke and transient ischaemic attack.¹ Progress in CVD will continue as further research is enhancing our understanding of pathophysiology of carotid atherosclerosis,² lacunar infarction,³ cerebral amyloid related haemorrhage⁴ and the role of cerebrovascular disease in dementia.⁵ Neuropathology is proving central to our understanding of each of these areas. In this article we review the basic pathology of cerebrovascular disease.

Cerebrovascular disease - Overview

Cerebrovascular disease encompasses two main categories; cerebral ischaemia and haemorrhage. Cerebral ischaemic injury results from the occlusion of a major cerebral artery, a small perforating cerebral artery or a venous sinus. Cerebral haemorrhage results from rupture of a cerebral artery, arterial aneurysm, arterio-venous malformation or capillaries. The clinical term 'stroke' refers to the acute clinical manifestation of any one of these processes. However, the full clinical spectrum of CVD is broad including acute behavioural disturbance, progressive cognitive impairment⁶ and parkinsonism.⁷

Cerebral Ischaemia

Cerebral infarction is the endpoint of cerebral ischaemic injury wherever it occurs in the brain. Pathologically this is defined as a region of brain tissue in which all the cellular elements have undergone necrosis i.e. cell death. Infarcts can be divided into acute, subacute (2-4 days) and chronic (days to months). An infarct that has occurred 5-8 hours before death is often characterised by petechial haemorrhages in the grey matter but may be almost undetectable on gross examination in the white matter; microscopic features are usually minimal at this stage. Changes that develop within 12-36 hours include blurring of the grey/white matter interface and slight softening of the brain parenchyma. The chronic infarct shows liquefactive and cystic changes. The histology of infarcts ranges from early eosinophilic neurones (hypoxic neurones - Figure 1a) and a minimal number of neutrophils 6-12 hours after the ischaemic episode to macrophage infiltration in the subacute phase at 5 days leading to liquefactive necrosis and cyst formation with atrophy of surrounding brain in the chronic infarct (Figure 1b). The differential diagnosis for the radiological and macroscopic appearances of cerebral infarction or haemorrhage includes; primary cerebral tumours, metastatic tumours, cerebral abscess and demyelinating

conditions such as acute multiple sclerosis.

It is rational to classify cerebral ischaemic injury into large and small vessel, as they are associated with different clinical syndromes, clinical outcomes and aetiologies.

Large vessel ischaemia

Large vessel infarction results from occlusion of a major cerebral artery within the carotid or vertebrobasilar circulation. They present with severe clinical strokes and are commonly fatal because of extensive brain swelling in days after stroke onset and have a poor long-term outcome.^{2,8} Large vessel occlusive strokes are most commonly a result of thrombo-embolism from extracranial atheroma or cardiac emboli. Other less common large artery conditions that can cause brain infarction are listed in Table 1.

Since the description of the ischaemic penumbra identifying a region of potentially reversible ischaemic tissue within the territory of the occluded large cerebral artery, much of the research in stroke has exploited functional imaging techniques rather than neuropathology. Neuropathological techniques have traditionally been limited in defining the penumbra, however, new pathological techniques are being developed. These techniques entail the use of animal models with a combination of imaging and pathology and they are increasing our understanding of factors involved in the development of infarction.⁹ Although not entirely refined, the concept of the ischaemic penumbra has proved a very powerful stimulus to develop treatment for large vessel ischaemic injury.¹⁰ It has recently been demonstrated that salvaging the ischaemic penumbra is how thrombolytic therapy improves clinical outcomes¹¹ and this should allow the time-window for therapy of strokes to



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Table 1. Less common large artery conditions causing brain infarction

<i>Premature atherosclerosis</i>
<i>Dissection (spontaneous or traumatic)</i>
<i>Inherited metabolic diseases (homocystinuria, Fabry's, pseudoxanthoma elasticum, MELAS syndrome)</i>
<i>Fibromuscular dysplasia</i>
<i>Infection (bacterial, fungal, tuberculosis, syphilis, Lyme)</i>
<i>Vasculitis (collagen vascular diseases - systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, polyarteritis nodosa; Takayasu's disease, Wegener's syndrome, cryoglobulinemia, sarcoidosis, inflammatory bowel disease, isolated central nervous system angiitis)</i>
<i>Moyamoya disease</i>
<i>Radiation</i>

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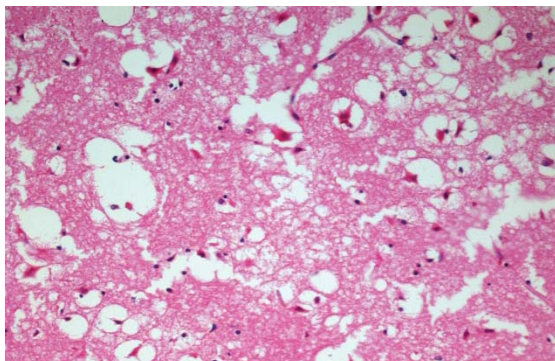


Figure 1a. Histology of an acute cerebral infarct showing neuronal eosinophilia (hypoxic/ischaemic neurones) and vacuolation of the neuropil. (Hematoxylin and eosin x20).

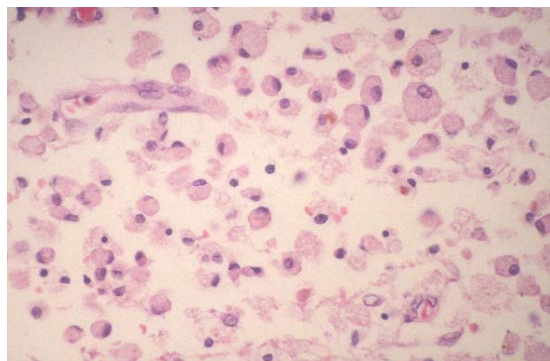


Figure 1b. Histology of a chronic cerebral infarct showing macrophages with foamy or granular cytoplasm. Some of the macrophages contain haemosiderin pigment. (Hematoxylin and eosin x20).

be significantly increased.¹²

Atherosclerosis is the commonest cause of large vessel stroke. It is most severe at the origins of the vertebral arteries and the carotid bifurcation. Pathological study of atherosclerosis has been deemed sufficiently important that an international pathological classification has been devised. This originally comprised six types when presented in 1995. This was modified in 2000 to take in to account further developments in the field (See Table 2). This is another area where imaging and pathology are now being used in tandem to define the actual pathological processes within atheroma in vivo. Figure 2 shows the correlation between MRI finding and intraplaque haemorrhage, a hallmark of clinically symptomatic atheroma (type VI). In addition to atheromatous emboli, infarction can be caused by emboli from cardiac valve vegetations, cardiac thrombi associated with myocardial infarcts, fat, air, malignancies, parasites or material introduced during vascular surgery, interventional procedures or during angiography.

Small vessel ischaemia

The concept of small vessel stroke (lacunar infarction) was proposed by Fisher in 1965.¹³ He described lesions caused by occlusion of perforating cerebral arteries secondary to lipohyalinosis within the artery walls. Research into small vessel ischaemia is undergoing a renaissance. It has recently been shown that the aetiology of clinical syndromes associated with lacunar infarction are not homogeneous and the short or long term prognoses are not benign.¹⁴ A new proposal suggests that in most lacunar strokes, the vascular abnormality is pathologically diffuse, even if the clinical manifestations are focal and

result from small vessel endothelial damage. This in turn leads to a subtle increase in blood-brain barrier permeability, and leakage of substances toxic to the brain into the perivascular tissue.³ Support for this proposal comes from pathological and imaging data. A recently described variant of a small, microvessel-associated basal ganglia lesion with histopathological features distinct from those of classical Types I, II and III lacunes suggests a state of incomplete infarction may exist prior to infarction.¹⁵ This has gained further support from studies using a combination of imaging with computed tomography and magnetic resonance imaging. This has allowed delineation of structures with the density or signal features consistent with an occluded (or at least abnormal) perforating artery associated with the relevant lacunar infarct.¹⁶

Cerebral haemorrhage

Intraparenchymal cerebral haemorrhage is less common than cerebral ischaemia, but has a worse prognosis. Specific treatments are still lacking for this condition although it is hoped that this will change now cerebral haemorrhage is being systemically investigated.¹⁷ Intraparenchymal haemorrhage can be classified into subcortical and lobar haemorrhage. In many cases the underlying pathological conditions that lead to both types of haemorrhage are the same and there is significant overlap with the causes of cerebral ischaemia i.e. arteriolosclerosis and lipohyalinosis in many cases. Anticoagulation, trauma and underlying vascular abnormalities are more specific aetiological factors of cerebral haemorrhage. In young patients cerebral haemorrhage can be associated with the use of recreational drugs such as cocaine and amphetamines.

Cerebral amyloid angiopathy related haemorrhage (CAA-H) is another area where new pathological insights are emerging. CAA-H is characterised by extracellular deposition of amyloid in cortical and leptomeningeal vessels (Figure 3). It is the most common cause of lobar haemorrhage particularly in elderly normotensive individuals. Risk factors for CAA include mutations of the amyloid precursor protein (APP) gene and possession of the epsilon 4 allele of apolipoprotein E. The deposition of amyloid in blood vessel walls results in rigid and fragile blood vessels that are prone to haemorrhage. Pathological studies have highlighted an additional factor. In some patients the clinical expression of the disease relates to an associated vasculitic

reaction.⁴ Pathological studies also suggest that CAA may have a relevance that extends beyond cerebral haemorrhage as it may be central to how CVD and Alzheimer's pathology interact to produce dementia.⁵

Summary

The sheer size and spectrum of the clinical burden of CVD continues to evolve. This is stimulating research and clinical services for patients with CVD. Neuropathology remains central to this effort.

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Table 2: Stary classification of Atherosclerosis

Type I	Isolated macrophage foam cells
Type II	Multiple foam cells layers formed
Type III	Isolated extracellular lipid pools added
Type IV	Confluent extracellular lipid core formed
Type V	Fibromuscular tissue layers produced
Type VI	Surface defect, haematoma, thrombosis
Type VII	Calcification predominates
Type VIII	Fibrous tissue predominates

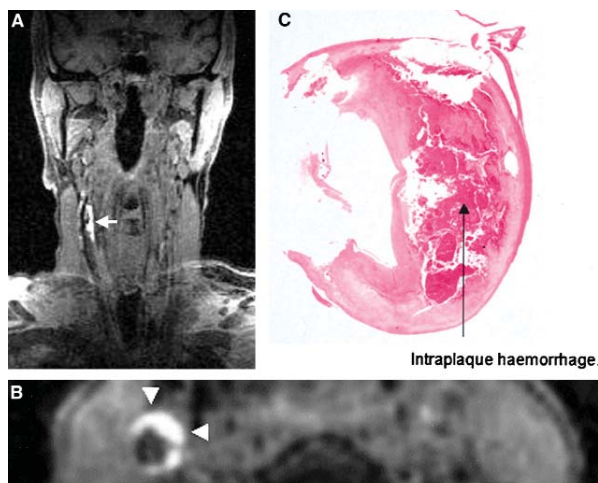


Figure 2. A and B, Extensive area of intraplaque haemorrhage is demonstrated on coronal (arrow) and axial (arrowheads) views. C, Intraplaque haemorrhage is seen on histological specimen (arrow). Moody et al - publisher LWV.

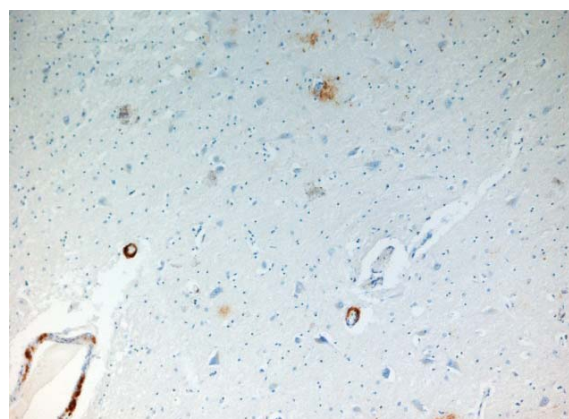


Figure 3: CAA demonstrated using an anti-A β antibody. Note the amyloid deposited in blood vessel walls.