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Neuropathology autopsy practice:

Post-mortem examination in cerebrovascular disease (stroke)

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1 The role of the post-mortem examination

Cerebrovascular diseases can present as acute syndromes (transient ischaemic attack, stroke) or chronic syndromes (vascular cognitive impairment, vascular parkinsonism).

The term ‘stroke’ describes the sudden loss of neurological function that commonly results from blockage or rupture of a blood vessel supplying the brain or spinal cord. There are, however, other pathological causes of sudden loss of neurological function that are not caused by cerebrovascular disease.

Diseases caused by cerebrovascular disorders are common and represent an important health burden, especially in older people. The clinical entities are defined in terms of a combination of clinical features and underlying brain pathology. Clinical diagnosis does not always reliably predict the pathological cause of a cerebrovascular disorder. In many instances, a specific complication of cerebrovascular disease may have a direct bearing on the cause of death. Cerebrovascular disease may also affect young patients, in which case establishing a diagnosis may have a bearing on identifying inherited causes of disease.

In cases of death related to cerebrovascular disease, the post-mortem examination may provide:

- a detailed description of the associated pathology to facilitate accurate classification and diagnosis
- additional information relating to response to treatment or complications in cases where there has been use of a disease-modifying therapy
- audit information related to clinical and imaging diagnoses. Clinical approaches to stroke subtyping are being developed and post-mortem examination may be required to audit performance of such clinically applied schemes. The A-S-C-O scheme assigns a numeric probability to patients against criteria for Atherosclerosis, Small vessel disease, Cardiac source and Other cause[2]
- accurate national statistical information regarding the incidence of the various pathologies seen, including rarer familial syndromes
- support appropriately consented research.

Post-mortem examinations in a patient who has suspected cerebrovascular disease may be performed with consent from the family or may be performed under a legal authority (Coroner or Procurator Fiscal). As such, and in many instances, the brain (and sometimes the spinal cord) will be examined by a general and/or forensic pathologist. However, involving a neuropathologist in the brain examination will maximise information about the nature of the disease processes.

An autopsy in a patient who has suspected cerebrovascular disease may be limited to examination of the central nervous system. This is sometimes the case when a consented examination has been requested. However, since examination of the heart and extracranial vessels provides important information, such examinations may limit interpretation.

2 Brain pathology encountered at post-mortem examination

A range of pathologies may be seen in a patient with cerebrovascular disease.

Atherosclerotic disease typically affecting extracranial vessels is the most common causal pathology and, while it predominantly affects older patients, it may affect younger

patients when there is the possibility of a genetic cause associated with a risk of heritability.

Cardioembolic disease may be linked to disease of valves or myocardium and typically results in ischaemic stroke affecting the territory of supply of the large named cerebral arteries. Other sites for emboli include the large vessels (aorta and carotid). Rarer causes of cerebrovascular embolism are bone marrow embolism (fat embolism) and air embolism. Paradoxical embolism and patent foramen ovale is regarded as being important in some young-onset patients with ischaemic stroke. In some patients, an embolic event may be the result of a therapeutic intervention, where it may lead to medicolegal considerations.

Arteriosclerotic and hypertensive vascular disease leads to damage to small vessels supplying the brain. The development of this type of disease is usually evident by the clinical context of known hypertension or diabetes mellitus. This type of vascular disease leads to multiple small areas of infarction (lacunar infarcts) and can also predispose to deep intracerebral haemorrhages.

Aneurysms and vascular malformations are relatively common, both as a cause of subarachnoid as well as intracerebral bleeding. Spinal vascular malformations also occur and lead to neurological signs linked to spinal cord damage. Rare forms of vascular malformation are familial. In bacterial sepsis, infective arteritis may lead to the formation of cerebral arterial aneurysm (infective aneurysm, mycotic aneurysm).

Amyloid angiopathy: the deposition of amyloid in the wall of small cortical and parenchymal vessels can lead to both ischaemic and haemorrhagic types of pathology. Lobar cerebral haemorrhage is a typical pattern of haemorrhagic stroke linked to amyoid. Rare cases are caused by heritable causes.

Hypoperfusion injury: loss of cerebral perfusion can lead to ischaemic lesions in boundary zone territories. This may also occur in circumstances where raised intracranial pressure impairs cerebral perfusion.

Arterial dissection and fibromuscular dysplasia: arterial dissection may be linked to trauma or may be spontaneous. This usually develops in the extracranial arteries and may affect carotid as well as vertebral territories. Dissections in extracranial vessels usually present as ischaemic stroke, but those affecting the intracranial vessels can present as subarachnoid haemorrhage. Fibromuscular dysplasia can present with ischaemic features but can also predispose to arterial dissection.

Vasculitis: In addition to systemic vascultis syndromes affecting the brain, there are well described forms of primary vasculitis limited to the central nervous system, termed 'primary angiitis of the CNS' (PACNS), which usually lead to ischemic stroke. In some patients, an inflammatory vasculitis develops as a response to amyoid angiopathy.

Vascular spasm may lead to cerebral ischaemia. This may be a complication of subarachnoid bleeding as well as drugs (including recreational drugs).

Disorders of coagulation: a range of circumstances may lead to impaired coagulation and predisposition to haemorrhagic stroke; this includes a complication of therapeutic anticoagulation or thrombolysis. Leukaemia or consumption coagulopathy may lead to reduced platelet function. The thrombophilia syndromes may present with predisposition to vascular thrombosis and ischemic stroke, as well as cerebral venous sinus thrombosis.

Rarer causes of cerebrovascular disease: several inherited disorders can present as cerebrovascular disease, for example mitochondrial cytopathy and CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).

3 Clinical information relevant to the post-mortem examination

Most of the information will come from hospital clinical case notes. In some circumstances, this may be supplemented by access to GP records.

As with any post-mortem examination, knowledge of the medical history is important. It is useful to have details in relation to the following.

- Family history: for some less common cerebrovascular diseases there is an emerging recognition of a genetic component to disease. Knowing this will allow planning for archiving of fresh material for genetic analysis, if consented.

- Social, drug and general medical history: systemic vascular diseases may affect the nervous system and lead to presentation as cerebrovascular disease. Recreational drug abuse may be complicated by stroke.

- It is essential to have details of any specific neurological symptoms and signs for planning the examination and determining the need for tissue retention. This is especially important in making decisions about retention of the spinal cord, peripheral nerve and skeletal muscle.

- Planning the examination and subsequent tissue sampling is greatly aided by knowledge of any clinical imaging findings.

- Full details of treatment should be ascertained in cases where a disease-modifying therapy has been used, especially anticoagulation and interventional procedures.

4 Autopsy procedure

A post-mortem examination in a patient with suspected cerebrovascular disease should be performed in the standard way with removal of the brain and spinal cord when indicated.[1,3] After sampling and freezing fresh tissue, if indicated and permitted, the brain should be fixed in formalin for later dissection. If retention of the brain is not authorised, sampling should be considered (see section 6).

External examination of the body

In cerebrovascular disease, there may be non-specific abnormalities that are commonly found. Patients may show muscle wasting linked to loss of motor function. Immobility may have predisposed to pressure sores.

A photograph may be useful for future reference.

Internal examination of the body

In a full post-mortem examination, there should be a standard macroscopic description of each organ system, including measurement of the organ weights. Morbid anatomical causes of death that are visible at the time of post mortem should be sought and, where necessary, supported by histological confirmation. For example, a common mode of death in stroke is the development of a bronchopneumonia.

5 Specific significant organ systems

Head and neck

The scalp and skull should be carefully examined for sign of bruises, which may have been associated with falls. When reflecting the dura, note the presence of any old or recent haematoma. Subdural haematoma in particular may be a cause of focal neurological signs that could be mistaken for other causes of cerebrovascular disease.

Cardiovascular system

Cerebrovascular disease may be associated with cardioembolic pathology and atheromatous disease, especially in the carotid arteries.

The carotid arteries should be examined through their entire length and, when anterior territory ischaemic disease is not otherwise explained, should involve dissection of the carotid siphon.

In cases of posterior territory ischaemic disease, the vertebral arteries should be examined throughout their length.

Respiratory system

Bronchopneumonia is a common cause of death in patients with cerebrovascular disease. Aspiration pneumonia is predisposed in patients with involvement of bulbar motor nuclei (bulbar palsy).

Alimentary system

Patients with swallowing problems may have been treated with a PEG feeding tube.

Bone marrow

In haemorrhagic lesions with no obvious macroscopic explanation, the possibility of a bleeding disorder should be considered and bone marrow sampled to ascertain a disorder.

6 Organ retention

In some situations of cerebrovascular disease, a reliable cause of death can be established by macroscopic examination, supplemented by histology in selected instances where refining a diagnosis is desirable (see below).

In other cases of cerebrovascular disease, it is recommended to retain the brain for prolonged fixation in formalin, prior to examination, to achieve a pathological diagnosis. The person in a qualifying relationship giving consent or the Coroner (or Procurator Fiscal), and through their office the deceased's family, should be informed that a completed neuropathological examination will be provided within a period of three months from the time of death.

The following may be discussed in situations where there is no consent, or Coronial authorisation, for retention of the brain for prolonged fixation.

1. Macroscopic examination only. A macroscopic examination alone may be sufficiently informative to allow a confident statement to be made on the cause of death. When this is not the case, the limitations of macroscopic examination should

be explained to those requesting or authorising the procedure, and should be documented in the final report if they have impacted on interpretation.

2. The brain may be retained in formalin fixation for a period of not more than 24 hours and then sectioned in the standard way. Samples taken for histological analysis can then be selected and placed into cassettes so that they can be fully fixed. This provides sufficient fixation such that sectioning of the brain is significantly easier than in the fresh state. The brain can be photographed, histologically sampled and the remainder returned to the body for burial or cremation. As unexpected findings may be seen in the histology that would suggest further sampling (which would now not be possible), the limitations of the examination should be explained to those requesting or authorising the procedure, and should be documented in the final report if they have impacted on interpretation.

3. Retention of strategic samples of brain in the fresh state may be undertaken. In this scenario, the brain is examined and sectioned in the fresh state. It should be explained to those requesting or authorising the procedure that all tissue retained will be processed for histological examination and that no tissues will be retained outwith paraffin blocks. Limited sampling may not reliably establish underlying pathology and the limitations of the examination should be explained to those requesting or authorising the procedure, and should be documented in the final report if they have impacted on interpretation.

In any method, it is preferable that the brain is photographed. The photographs should be labelled and stored with case file for future reference.

7 Post-mortem examination

The following is suggested as an approach to the investigation of cerebrovascular diseases.

7.1 General histology

Representative histology from main organs and peripheral vessels should be taken as appropriate, as determined by the findings at the post-mortem examination and clinical context. For example, lung may be taken if there has been a suspected bronchopneumonia, heart may be taken in ascertaining a likely cardioembolic cause, and bone marrow in suspected bleeding disorder.

Tissue sampling in special considerations
Skeletal muscle (fresh) for histochemistry and genetic studies in suspected mitochondrial cytopathy
Fresh material for genetic studies in cases of suspected inherited stroke syndrome, e.g. CADASIL, CARASIL
Blood, urine, liver to investigate stroke linked to recreational drug abuse
Blood to investigate thrombophilia syndrome in young onset stroke

7.2 Neuropathology

7.2.1 Stroke

There are two main groups of pathologies linked to the clinical syndrome of stroke: haemorrhagic stroke and ischaemic stroke. The post-mortem examination of the brain

depends on the clinical context and whether an obvious local cause can be seen on initial macroscopic examination.[3]

In all cases of stroke, a full examination of the heart, great vessels and cerebral circulation should be recommended, including examination of the vertebral arteries in ischaemic stroke affecting the posterior territory. If this recommendation is not accepted, the limits of the examination should be discussed with the authority requesting the examination and any limitations documented in the report.

7.2.1.1 Haemorrhagic stroke

Macroscopic findings

Subarachnoid bleeding, intracerebral haematoma (deep or lobar locations), intraventricular bleeding, or mixed pattern. A search for aneurysms on main cerebral vessels should be made in the fresh state. Note any mass effect and consequences of mass effect. Older lesions undergo organisation to leave a cystic gliotic cavity. If the whole brain is to be fixed, evacuate large intracerebral or intraventricular haematomas.

a. Macroscopic examination reveals an identifiable local causative lesion or there is a specific clinical context for the bleed

Aneurysm

Diagnosis: ascertained in the fresh state by careful removal of blood and examination of cerebral arteries.

Histology: valuable to identify infective causes, minimally helpful in confirming simple Berry aneurysm.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Arteriovenous malformation

Diagnosis: usually ascertained in the fresh state, supplemented by histological examination.

Histology: Not usually adding additional value in most cases.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Hypertensive vascular damage

Diagnosis: suspected from clinical context, supplementary information from the general post mortem and location of bleed (deep hemispheric, pontine or cerebellar).

Histology: histology of deep cerebral vessels can confirm arterial changes of lipohyalinosis and exclude other potential causes.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Amyloid angiopathy

Diagnosis: suspected by the context of the bleed – a common cause of lobar hemorrhage in older patients.

Histology: Confirmed by histology of vessels from the region of the bleed and also exldes other possible causes. Immunostaining can identify the type of amyloid.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Venous sinus or cortical vein thrombosis

Diagnosis: suspected by macroscopic appearances, hemorrhagic infarcts may mimic primary hemorrhage. Ascertained in the fresh state by examination of venous sinuses and noting thrombosis in cortical veins. Local sites of inflammation or infection should be inspected, e.g. middle ear sepsis.

Histology: can confirm thrombosis rather than coagulum.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Iatrogenic haemorrhage

Diagnosis: this is through the context provided by the clinical information. Therapeutic (anticoagulation) and interventional procedures may give rise to haemorrhagic lesions. It is advisable to have the practitioner present to describe any interventional procedure and to highlight relevant imaging features, such that a true explanation of any complication may be determined.

Histology: benefit in excluding other causes and thereby excluding the possibility of a complication of treatment.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Tumour

Diagnosis: may be difficult to delineate from damaged brain at the periphery of a bleed due to other causes.

Histology: Ascertain by histology from the margins of the bleed.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Trauma

Usually evident from the context of the case (see guidance from The Royal College of Pathologists on post-mortem examination in head injury).

b. Macroscopic examination reveals no identifiable local lesion or there is no specific clinical context for the bleed

Associated with impaired coagulation

Histology: check bone marrow for leukemia as well as checking clinical notes for therapeutic anticoagulation. May be a complication of a procedure such as cardiac surgery. Strategic sampling of brain to exclude other causes.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Haemorrhage associated with recreational drug abuse

Diagnosis: clinical suspicion confirmed by performing toxiciology.

Histology: strategic sampling of brain to exclude other causes.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Idiopathic haemorrhage

Diagnosis: process of exclusion, despite investigation as described above. No cause identified despite macroscopic examination, toxicology and histology of brain.

7.2.1.2 Ischaemic stroke

Macroscopic findings

Ischaemic stroke may be caused by thrombosis in a large cerebral vessel, small vessel disease, or be due to cardio embolic phenomena. A small proportion of cases are due to rare conditions.

- *Large vessel disease*: Recent lesions seen as pale, soft areas of brain, often in an anatomic pattern indicating the site of vascular occlusion. Reperfusion may cause haemorrhagic transformation. Note any mass effect and consequences of mass effect. Older lesions undergo organisation to form gliotic cystic regions.

- *Small vessels disease* lacunar infarcts noted in deep grey matter structures, white matter and brain stem. Note distribution.

Atherosclerosis

Diagnosis: ascertained in the fresh state by noting atheromatous vascular disease. Inspection of the carotid bifurcations may reveal complicated atheroma. Thrombosis of cerebral vessels may be seen, and should include examination of the vertebral arteries in the neck when infarction in the posterior territory.

Histology: benefit in excluding other causes and thereby excluding the possibility of a complication of treatment, if in question.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Small vessel disease

Diagnosis: may be suggested by clinical context of known hypertension or diabetes mellitus. Clinically linked to syndromes of lacunar infarction and imaging features (leukoaraiosis and microbleeds). Lacunar infarcts can be identified on slicing the brain in the fresh state.

Histology: Confirm lacunar infarcts. Benefit in excluding other causes and thereby excluding the possibility of a complication of treatment, if in question.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Cardio-embolic causes of ischaemic stroke

Diagnosis: suspected at the time of post-mortem examination by examination of the heart and great vessels, noting a potential site for embolism or primary cardiac disease. In young patients, check for patent foramen ovale and the possibility of paradoxical embolism.

Histology: benefit in excluding other causes and thereby excluding the possibility of a complication of treatment, if in question.

Brain retention: indicated if there is consent for teaching/training, if there are unusual clinical features that warrant wider sampling, or if there are medicolegal considerations.

Rare causes of ischaemic stroke

Diagnosis: Ascertained by clinical context supplemented by histology and other investigations.

Histology and investigation: Unusual causes of ischaemic stroke may only be identified with histology of cerebral vessels and brain such as cerebral vasculitis, arterial dissection and fibromuscular dysplasia (particularly affects vertebral arteries). Check bone marrow for haematological causation. Consider taking blood for serology to look for a thrombophilia syndrome. A small proportion of patients presenting with stroke have an inherited cause, the risk being highest with young-onset disease, consider preserving fresh frozen material for genetic studies, with consent.

Brain retention: recommend retaining the brain in young-onset stroke to facilitate wide sampling by histology, if there are unusual clinical features, or if there are medicolegal considerations.

7.2.2. Regional sampling

The following block set is recommended as part of the assessment of cerebrovascular disease. The blocks should represent both normal and abnormal regions (see Appendix 1). Multiple small blocks may be taken or alternatively a smaller number of large blocks may incorporate several specified regions.

a) Block 1 Middle frontal gyrus to look at perfusion boundary zone.

b) Block 2 Putamen and globus pallidus to look at deep small vessels and lacunar infarcts.

c) Block 3 Hippocampus and parahippocampal gyrus to look at an area vulnerable to hypoxia/ischemia.

d) Block 4 Occipital cortex to look at perfusion boundary zone.

e) Block 5 Midbrain to look at changes due to mass effect (if present).

f) Block 6 Pons to look at changes due to mass effect (if present), as well as deep small vessels and lacunar infarcts.

g) Block 7 Medulla oblongata to look at changes due to mass effect (if present).

h) Block 8 Cerebellar hemisphere to look at perfusion boundary zone.

i) Block 9 Samples of periphery of a haematoma to look for a cause for the bleed or samples of infarcted area and adjacent brain to confirm infarction and possible cause.

j) Block_10 Local vessels supplying pathological area to assess cause of disease.

7.2.3 Spinal cord

The spinal cord is examined in suspected vascular conditions affecting the spinal cord, as determined by clinical information.

7.3 Staining

7.3.1. General stains

The blocks should be stained with H&E, and a myelin stain for general morphological assessment. Vascular structure can be demonstrated with an elastic Van Gieson stain.

7.3.2 Specific stains

Immunohistochemistry can be used to determine type of amyloid deposition in cases of amyloid angiopathy.

8 Other samples required

Fresh tissue should be preserved in the context of consent to perform genetic testing where an inherited cause of cerebrovascular disease is suspected.

Samples should be taken for toxicology where stroke linked to recreational drug abuse is suspected.

9 The clinicopathological summary

The clinicopathological summary needs to be clear and concise. Statements of fact should be provided. The pathologist should clearly outline the macroscopic and microscopic observations. This should be considered in light of the clinical history provided. An overall summary should be made to correlate the pathological findings with the clinical history provided and, in particular, to highlight any consistencies or inconsistencies between the two.

Summary of post-mortem examination in case of cerebrovascular disease

Macroscopic brain examination

1) Subarachnoid blood:
   - distribution (diffuse or localised).

2) Haematoma:
   - site: deep or lobar, temporal, frontal, other site
   - measurement.

3) Brain herniation (↑ ICP):
   - uncal herniation (remove brainstem and cerebellum for better assessment), bilateral or unilateral
   - tonsillar herniation, usually associated with haemorrhage and necrosis rather than only bulging
   - supracallosal (or sub-falcine) herniation
   - mid-line brain shift – corpus callosum and lateral ventricle.

4) Brain swelling – flattening of gyri, bilateral or one cerebral hemisphere.

5) Infarction and ischaemia:
   - site
   - size
   - arterial territory.

6) White matter and cortical softening or gliosis:
   - site
   - size
   - arterial territory.

7) Cerebral vessels:

- anatomy
- atheroma – specify degree of occlusion
- thrombosis.

Microscopic brain examination

The pathological diagnosis of cerebrovascular disease should be applied according to published references.[1-5]

Further reading and references

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Appendix 1 Recommended blocks to assess cerebrovascular disease

Include appropriate images

Seek permission to use some of the images from Love 2011