Aetiology and pathology of STROKE

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The first part of this month’s special feature examines the prevalence, causes, pathological features and symptoms of stroke, as well as the risk factors predisposing to the syndrome.
Stroke is a disease that many people survive but with persisting impairments. The overall prevalence of stroke in the population is estimated to be 47 per 10,000 and as such is the most common cause of adult physical disability. Cognitive impairment (33 per cent), problems with lower limbs (30 per cent) and speech difficulties (27 per cent) are the most common residual impairments (Table 1, see p34).  

--- Pathology ---

Stroke can be broadly divided into those resulting from infarction of the brain (ischaemic stroke) and those resulting from intracerebral and subarachnoid haemorrhage (haemorrhagic stroke). Approximately 85 per cent of strokes result from infarction, with the remaining 15 per cent being due to haemorrhage. There are many causes of the infarction or haemorrhage, and these are summarised in Panel 1. Where one of the major arteries to the brain is occluded, such as the middle cerebral artery, this is most frequently due to embolism of either a blood clot from the heart, or of atheromatous material and a blood clot from the carotid artery. Occlusion of the smaller perforating arteries resulting in lacunar strokes is most frequently due to local arterial disease resulting from hypertension or diabetes.

Cardiac embolism Atrial fibrillation, which is present in less than 5 per cent of the general population, is found in nearly a

--- Epidemiology ---

It is estimated that there are 5.45 million deaths a year from stroke in the world and over nine million stroke survivors. About two-thirds of these deaths occur in the developing world. Stroke accounts for nearly five million disability-adjusted life years lost all over the world. The pattern of this impact varies, with the highest rates in parts of Europe, South East Asia and the Western Pacific. One in four men and nearly one in five women aged 45 can expect to have a stroke if they live to their 85th year in developed countries.  

There are differences in the standardised mortality ratios (SMRs, ie, mortality rates adjusted for age and sex) for stroke between regions of the world. The highest rates are in Eastern Europe and the former Soviet Union, and the lowest rates are in the United States, Canada, Switzerland and Australia. Most parts of the world have experienced a decline in the mortality rates from stroke over the past 20 years. However, these rates have increased in the countries of the former Soviet Union.

The annual incidence of stroke in developed countries is approximately two per 1,000. However, the exact figure depends on age and the incidence of stroke rises steeply with increasing age. As the number of elderly people is increasing worldwide, the burden of stroke on individual families and on the health services is unlikely to fall rapidly. It has been estimated that between 1983 and 2023, there will be an absolute increase of about 30 per cent in the number of patients experiencing a first stroke.

Men have a 25–30 per cent increased likelihood of suffering a stroke compared with women. In the UK, African-Caribbeans and Africans are twice as likely to suffer a stroke, than the Caucasian population. Furthermore, people in the lowest social class have a 60 per cent increased likelihood of suffering a stroke compared with those in the highest social class. The risk of dying within three months of a stroke is about 30 per cent, but varies according to the subtype of stroke and the initial severity. The cumulative risk of recurrence over five years is high, ranging from 15–42 per cent.

--- Panel 1: Aetiological classification of stroke ---

**Ischaemic**
- Cardioembolic, eg,
  1. Atrial fibrillation
  1. Mural thrombus
  1. Paradoxic embolism through patent foramen ovale
  1. Embolism from infective endocarditis
- Atherothromboembolic, eg,
  1. Carotid atheroma
  1. Vertebrobasilar atheroma
  1. Cerebral artery occlusion
  1. Carotid dissection
- Small vessel disease, eg,
  1. Hypertensive arterial disease
  1. Diabetic vasculopathy
  1. Vasculitis
- Others, eg,
  1. Venous thrombosis
- **Haemorrhagic**
  1. Subarachnoid, eg,
    1. Arteriovenous malformation
    1. Aneurysm
  1. Parenchymal haemorrhage, eg,
    1. Hypertensive arterial disease
    1. Amyloid angiopathy
- **Unknown**

--- Panel 2: Clinical classification of stroke ---

**Ischaemic**
- Total anterior circulation strokes (TACS). All of the following:
  1. Contralateral hemiplegia or hemiparesis
  1. Contralateral hemisensory loss
  1. New disturbance of higher cerebral function, eg, dysphasia, visuo-spatial disturbance

**Partial anterior circulation strokes (PACS). Any of the following:**
- 1. Motor/sensory deficit and hemianopia
- 1. Motor/sensory deficit and new higher cortical dysfunction
- 1. New higher cortical dysfunction and hemianopia
- 1. New higher cortical dysfunction alone
- 1. Pure motor deficit less extensive than for lacunar strokes, eg, monoparesis

**Lacunar strokes (occlusion of single deep perforating artery)**
- 1. Maximum deficit from a single vascular event
- 1. No visual field deficit, no new higher cortical dysfunction, no signs of brain stem disturbance

**Posterior circulation strokes. Any of the following:**
- 1. Ipsilateral cranial nerve palsy with contralateral long tract signs
- 1. Bilateral motor and/or sensory deficit
- 1. Disorder of conjugate eye movements
- 1. Cerebellar dysfunction
- 1. Isolated hemianopia or cortical blindness
quadrant of patients presenting with stroke. In the majority of cases in people with atrial fibrillation, it is believed that the stroke results from a clot that forms in the left atrium which breaks off and blocks one of the carotid arteries. The other common source of embolism is a clot that forms on the surface of myocardium recently damaged by a heart attack. Clinically, the patient will present 7–10 days after the myocardial infarct with stroke. Infected heart valves can also cause stroke.

**Aortic and carotid atheroma** Atheroma of the aorta and carotid vessels occurs as a result of the same processes that produce atheroma elsewhere in the body. Patients presenting with stroke due to arterial disease are also likely to have evidence of ischaemic heart disease and peripheral vascular disease.

**Small vessel disease** Small vessel disease resulting from occlusion of small arteries and arterioles in the brain, is most frequently associated with hypertension, diabetes and hypercholesterolaemia. Occasionally, it can result from microemboli in the heart or carotid arteries. Often, there are many lesions, and patients may present with multi-infarct dementia rather than a defined area or focal stroke.

**Intracerebral haemorrhage** Damage to the brain results from local pressure exerted by the space-occupying blood clot. Rupture of a large vessel will often be rapidly fatal. However, bleeding from smaller arteries may lead to relatively mild symptoms that may be indistinguishable from a small infarct. Hypertension is the single most important underlying cause of intracerebral haemorrhage. Other risk factors include excessive alcohol consumption, smoking and the use of “social drugs” such as amphetamines.

**Subarachnoid haemorrhage** Subarachnoid haemorrhage most commonly arises as a result of a congenital aneurysm in one of the major arteries. The sudden rupture allows blood into the subarachnoid space and sometimes into the cerebral hemisphere. It is one of the more common causes of stroke in young adults.

**Consequences of a brain infarction** When an artery to the brain becomes blocked, there is likely to be a central area of dead brain tissue surrounded by brain tissue that is ischaemic but not yet dead. The brain becomes less ischaemic as one moves away from the central area. Within the ischaemic brain (ischaemic penumbra), there is evidence of massive release of the neurotransmitter, glutamate, causing a wave of depolarisation that may result in further neuronal damage. Minimising damage in the ischaemic penumbra is the objective of many of the newer treatments in acute stroke. These include thrombolysis, which aims to revascularise the ischaemic area before permanent damage is done, neuro-protectors such as N-methyl-D-aspartate (NMDA) receptor antagonists and drugs to reduce the effects of cerebral oedema. Recovery of neurological function after stroke occurs partly as a result of recovering function in the ischaemic penumbra and partly as a result of neuroplasticity, with the unaffected parts of the brain taking over the function of the damaged brain. It is probable that this is the mechanism through which physiotherapy has its predominant effect.

### Presenting symptoms

Stroke usually occurs without warning. Occasionally, there may be preceding headache, especially with intracerebral or subarachnoid haemorrhage. Neurological symptoms most often develop within a few minutes, although they can develop in an irregular manner over several hours. Classically, haemorrhage develops rapidly and is associated with headache, vomiting and sometimes clouding of consciousness. With the increasing use of brain imaging in the early stages of stroke, it is now recognised that haemorrhage frequently presents in ways that are indistinguishable from infarction.

The symptoms that a patient presents with will depend upon which part of the brain has been damaged. No one patient is likely to be the same as any other, making predictions as to the likely outcome of the stroke almost impossible to make with any degree of certainty. The basic organisation of the brain differs from one person to the next and there are differences in the degree to which certain functions are represented in both cerebral hemispheres. This means that if one hemisphere is affected by the stroke, some people will carry on regardless because the other side of the brain can compensate, although others will be severely affected. There are also differences in the ability of individual brains to compensate for localised damage.

Many conditions can mimic stroke. Space-occupying lesions such as cerebral neoplasm or abscess can present with a more gradual onset, although tumours can remain.

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**Table 1: Impact of stroke on the population**

<table>
<thead>
<tr>
<th>Impact of stroke on the population</th>
<th>Per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>General — subarachnoid haemorrhage (SAH), TIAs, stroke — diagnosed</td>
<td>of the population</td>
</tr>
<tr>
<td>Cases of SAH per year</td>
<td>14</td>
</tr>
<tr>
<td>New cases TIA per year</td>
<td>42</td>
</tr>
<tr>
<td>Carotid territory TIAs</td>
<td>34</td>
</tr>
<tr>
<td>First strokes per year</td>
<td>71</td>
</tr>
<tr>
<td>All acute strokes per year</td>
<td>13</td>
</tr>
<tr>
<td>Stroke survivors alive in community</td>
<td>86</td>
</tr>
<tr>
<td>Presenting for diagnosis</td>
<td>71</td>
</tr>
<tr>
<td>Impairment or disability — presentation (ie, need acute care), all stroke</td>
<td>71</td>
</tr>
<tr>
<td>With reduced consciousness</td>
<td>71</td>
</tr>
<tr>
<td>Severely dependent</td>
<td>22</td>
</tr>
<tr>
<td>Incontinent of urine</td>
<td>22</td>
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<tr>
<td>Disoriented/unable to communicate</td>
<td>22</td>
</tr>
<tr>
<td>Unable to get out of bed unaided</td>
<td>22</td>
</tr>
<tr>
<td>Impairment or disability — at three weeks (ie, need rehabilitation), all stroke</td>
<td>22</td>
</tr>
<tr>
<td>Needs help dressing</td>
<td>22</td>
</tr>
<tr>
<td>Needs help walking</td>
<td>22</td>
</tr>
<tr>
<td>Needs help with toilet</td>
<td>22</td>
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<tr>
<td>Communication problems</td>
<td>22</td>
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<tr>
<td>Impairment or disability — at six months (ie, need long-term support)</td>
<td>22</td>
</tr>
<tr>
<td>Needs help bathing</td>
<td>22</td>
</tr>
<tr>
<td>Needs help walking</td>
<td>22</td>
</tr>
<tr>
<td>Needs help dressing</td>
<td>22</td>
</tr>
<tr>
<td>Difficulty communicating (aphasia)</td>
<td>22</td>
</tr>
<tr>
<td>Confused/demented (or severe aphasia)</td>
<td>22</td>
</tr>
<tr>
<td>Severely disabled (Barthel disability score &lt;10/20)</td>
<td>22</td>
</tr>
<tr>
<td>Services — at six months</td>
<td>22</td>
</tr>
<tr>
<td>Needs long-term institutional care</td>
<td>22</td>
</tr>
<tr>
<td>Possibly needs speech therapy</td>
<td>22</td>
</tr>
<tr>
<td>Assumptions:</td>
<td>22</td>
</tr>
<tr>
<td>1. All stroke, first and recurrent (2.4 per 1,000 per year)</td>
<td>22</td>
</tr>
<tr>
<td>2. 30 per cent die by three weeks</td>
<td>22</td>
</tr>
<tr>
<td>3. None die by six months</td>
<td>22</td>
</tr>
<tr>
<td>4. Minimal contribution from SAH to care and rehabilitation needs</td>
<td>22</td>
</tr>
</tbody>
</table>
consciousness. Fusion, dizzy episodes and loss of range of symptoms, including vertigo, confusion, syndromes, being falsely linked to a wide discrimination from stroke. However cerebellar or brain stem signs sclerosis only rarely presents with hemiparesis. The onset is usually less abrupt than stroke, and a unilateral headache, combined with a history of migraine, will aid in establishing the diagnosis. It is essential that hypoglycaemia is excluded. Multiple patients, but can present with focal neurological symptoms such as hemianopia, dysphasia or hemiparesis. The onset is usually less abrupt than stroke, and a unilateral headache, combined with a history of migraine, will aid in establishing the diagnosis. It is essential that hypoglycaemia is excluded. Multiple sclerosis only rarely presents with hemiparesis. However cerebellar or brain stem signs resulting from demyelination can be difficult to distinguish from stroke.

TIA is one of the most underdiagnosed syndromes, being falsely linked to a wide range of symptoms, including vertigo, confusion, fusion, dizzy episodes and loss of consciousness.

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**Panel 3: Guidelines for secondary prevention of stroke (all patients)**

A

- All patients should have their blood pressure checked, and hypertension persisting for over one month should be treated.
- All patients, not on anticoagulation, should be taking aspirin (50–300 mg) daily, or low dose aspirin and dipyridamole modified release (MR). Where patients are aspirin intolerant clopidogrel 75 mg daily or dipyridamole MR 200 mg twice daily should be used.
- Anticoagulation should be started in every patient with atrial fibrillation unless contraindicated.
- Anticoagulation should not be started until brain imaging has excluded haemorrhage, and 14 days have passed from the onset of an acute ischaemic stroke.
- Anticoagulation should not be used after transient ischaemic attacks or minor strokes unless cardiac embolism is suspected.
- Any patient with a carotid artery stroke, and minor or absent residual disability should be considered for carotid endarterectomy (excision of the lining of the carotid artery).
- Carotid endarterectomy should only be undertaken by a specialist surgeon with a proven low complication rate, and only if the stenosis is measured at greater than 70 per cent.
- Therapy with a statin should be considered for patients with a history of myocardial infarction and a cholesterol above 5 mmol/L following stroke.

B

- All patients should be assessed for other vascular risk factors and be treated or advised appropriately.

C

- Anticoagulation should be considered for all patients who have ischaemic stroke associated with mitral valve disease, prosthetic heart valves, or within three months of myocardial infarction.
- Carotid ultrasound should be performed on all patients who would be considered for carotid endarterectomy.
- All patients should be given appropriate advice on lifestyle factors.

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**Key:***

- **A** = Meta-analysis or randomised controlled trial evidence
- **B** = At least one well-designed, controlled, quasi-experimental or descriptive study
- **C** = Expert committee report or respected authority report

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**Risk factors**

In a population of one million, around 400 will present each year with a first (1,800) or recurrent (600) stroke and another 500 with transient ischaemic attack. There will be around 1300 deaths or dependent survivors who may benefit from appropriate secondary prevention. The causes of the first stroke are the same as those that result in a subsequent stroke. Stroke survivors have a 15-fold increased risk of recurrence. This can be reduced by appropriate risk factor management.

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The national clinical guidelines for stroke have been drawn up by a multidisciplinary working party. The advice for secondary prevention is given in Panel 3.

**Hypertension**

The major risk factor for stroke is hypertension and current trial data, although limited, suggest that lowering blood pressure by 5–6 mmHg diastolic and 10–12 mmHg systolic for two to three years should reduce annual risk of stroke from 7 per cent to 4.8 per cent with 45 patients needing to be treated to avoid one stroke per year. The PROGRESS trial suggests that treatment with perindopril and indapamide produces a mean reduction in systolic blood pressure of 4 mmHg diastolic and 9 mmHg systolic, reducing the risk of recurrence by 14 per cent in both hypertensive and normotensive patients.

**Smoking**

Smoking increases the risk of stroke by around 50 per cent and reduction by the use of nicotine replacement patches, behavioural modification, advice and social skills training, as well as encouragement and brief advice given by well-trained GPs or other health professionals during routine consultations, are all effective. The number needed to quit smoking is 43 to avoid one stroke per year.

**Cholesterol reduction**

The association between raised cholesterol and stroke subtype is not clear-cut. There have been no formal trials of cholesterol-lowering in TIA or stroke, but there is indirect evidence that cholesterol reduction using statins reduces the risk of stroke risk by around 24 per cent. Subgroup analysis suggests that the number needed to treat (NNT) for statin therapy would be 59 to avoid one stroke per year.

**Aspirin and other antiplatelet agents**

The use of aspirin in patients who have had an ischaemic stroke in doses above 75 mg daily reduces the risk of stroke by around 13
per cent and the NNT is 100. Aspirin is appropriate for around three-quarters of stroke patients and is cheap. Clopidogrel is more effective than aspirin with an NNT of 62. The combination of dipyridamole and aspirin is again more effective (NNT = 53) than aspirin. The other, much more expensive, antiplatelet agents should only be considered where aspirin is contraindicated.12

Anticoagulation As life expectancy continues to rise, the prevalence of atrial fibrillation is set to increase dramatically and management with aspirin or warfarin is effective at reducing recurrence. Warfarin is more effective (NNT = 12). Unfortunately, management is often difficult with this drug and side effects are considerable. Aspirin should be considered if treatment with warfarin is not possible. Warfarin has been shown to be superior to aspirin in mild to moderate strokes.13

Carotid endarterectomy Carotid endarterectomy is the excision of the lining of the carotid artery. The trial evidence would suggest an NNT of 26 for severe stenosis but this surgical procedure is an expensive one.14 Other behavioural risk factors Excessive weight, a sedentary lifestyle, excessive alcohol intake and a poor diet all contribute to cardiovascular risk. Although the evidence base for interventions here is poor, it is likely that correcting such behaviour will be beneficial, if not for reducing stroke, for other co-morbidities.15

STROKE SERVICES

It is estimated that stroke services accounted for at least 4–6 per cent of the NHS budget in the UK but these figures do not take into account social service and carer costs. In an audit of stroke care in the UK in 1999, only 25 per cent of patients spent over half their hospital stay in a stroke unit,15 which is the single most effective intervention that is currently known for stroke, both in reducing mortality and disability. The quality of assessment, rehabilitation, discharge planning and secondary prevention were inadequate in many parts of the country. The Government has made stroke one of its priorities in recent years and the core standards for stroke care to be achieved by 2004 were identified in chapter 5 of the National Service Framework for Older People.16 If these standards are met, it will represent a revolution in the approach to stroke care in England.

CONCLUSION

Stroke is one of the major public health problems in developed countries. Major advances have been made in understanding the aetiology, pathology and management of the disease. However considerable progress is still needed both in research and implementation of research findings to reduce the burden of stroke to society.

REFERENCES