

Aetiology and pathology of **STROKE**

By ANTHONY RUDD, FRCP, and CHARLES WOLFE, FFPHM, FRCOG

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 should not be regarded as a single disease. Rather, it is the clinical manifestation of a wide range of pathologies, with different aetiologies and prognoses. The World Health Organization's definitions of stroke and transient ischaemic attack (TIA) are based on clinical features and not those seen with imaging. Increasingly, however, it is being recognised that the clinical diagnosis is not in itself sufficient for the adequate management of the patient.

Stroke (or brain attack) is a syndrome characterised by rapidly developing clinical symptoms and/or signs of focal loss of cere-

bral function, in which symptoms last more than 24 hours or lead to death, with no apparent cause other than that it is of vascular origin.

TIA is defined in the same way as stroke but with the symptoms and signs lasting less than 24 hours. The pathogenesis of stroke and TIA are the same and they should be managed with equal vigour. Stroke can be classified according to the underlying cause (Panel 1, p33, adapted from the TOAST classification¹) or the affected territory within the brain (Panel 2², p33).

THE PROBLEM

A general practitioner with an average practice of 2,500 patients will see approximately five new cases of stroke each year. An average district general hospital will be caring for 20 to 30 patients with stroke as

a primary diagnosis, at any one time, or will be admitting 300 to 400 stroke patients a year. Of these, 30 per cent will die within the first three months. Half of the remaining patients will have significant long-term disability. These patients will also need skilled management of their risk factors to prevent recurrences, since over 10 per cent of patients will have a second stroke within a year of the first.

Stroke remains the third largest killer after heart disease and cancer in the developed world, and the commonest cause of adult disability. The public awareness of stroke as a disease, including why it happens, how it should be managed and how it can be prevented is often poor. The medical care available for stroke has failed to keep pace with developments in its treatment. Stroke is still not recognised as a specialty within medicine, and only 50 per cent of hospital

Dr Rudd is consultant physician, stroke unit, Guy's and St Thomas' Hospitals NHS Trust and Dr Wolfe is reader in public health medicine, Guy's, King's and St Thomas' School of Medicine, London

Panel 1: Aetiological classification of stroke

Ischaemic

Cardioembolic, eg,

- 1 Atrial fibrillation
- 1 Mural thrombus
- 1 Paradoxical embolism through patent foramen ovale
- 1 Embolism from infective endocarditis

Atherothromboembolic, eg,

- 1 Carotid atheroma
- 1 Vertebral 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

Unknown

Haemorrhagic

Subarachnoid, eg,

- 1 Arteriovenous malformation
- 1 Aneurysm

Parenchymal haemorrhage, eg,

- 1 Hypertensive arterial disease
- 1 Amyloid angiopathy

trusts employ a physician with special responsibility for stroke. Spending by research funding organisations on stroke is about 1 per cent of that spent on coronary heart disease. One of the reasons for this neglect is probably the perception that there is nothing that can be done for those who have suffered a stroke. This perception is fuelled by the fact that stroke is predominantly a disease of old age, with the average age of stroke victims being 75 years.

There are three facts about stroke that should be widely disseminated:

- 1 Stroke is a largely preventable disease
- 2 Effective treatments are available for stroke
- 3 Age does not significantly influence the outcome of a stroke

EPIDEMIOLOGY

It is estimated that there are 5.45 million deaths a year from stroke in the world and over nine million stroke survivors.³ 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.⁴

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.⁵ 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.⁶ 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.⁶

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.^{5,6}

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).⁷

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).⁸ 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

Panel 2: Clinical classification of stroke

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

quarter 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. Classically, 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

Table 1: Impact of stroke on the population⁷

	Per 100,000 of the population
General — subarachnoid haemorrhage (SAH), TIAs, stroke — diagnosed	
Cases of SAH per year	
New cases TIA per year	14
Carotid territory TIAs	42
First strokes per year	34
All acute strokes per year	200
Stroke survivors alive in community	240
Presenting for diagnosis	600
Impairment or disability—presentation (ie, need acute care), all stroke	Not known
With reduced consciousness	
Severely dependent	84
Incontinent of urine	140
Disoriented/unable to communicate	106
Unable to get out of bed unaided	132
Impairment or disability — at three weeks (ie, need rehabilitation), all stroke	168
Needs help dressing	
Needs help walking	86
Needs help with toilet	67
Communication problems	66
Impairment/disability — at six months (ie, need long-term support)	49
Needs help bathing	
Needs help walking	71
Needs help dressing	22
Difficulty communicating (aphasia)	45
Confused/demented (or severe aphasia)	22
Severely disabled (Barthel disability score <10/20)	39
Services — at six months	13
Needs long-term institutional care	
Possibly needs speech therapy	23
	24

Assumptions:

1. All stroke, first and recurrent (2.4 per 1,000 per year)
2. 30 per cent die by three weeks
3. None die by six months
4. Minimal contribution from SAH to care and rehabilitation needs

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

latent until they become haemorrhagic, thus presenting in an identical way to stroke. Subdural haematoma more commonly presents with clouding of consciousness or confusion and only minor focal signs (ie, signs in a defined area). A history of head injury is only obtained in about 50 per cent of cases of subdural haematoma. Epilepsy can leave a patient with residual focal neurological symptoms and signs for some days after a fit. There may be a history of previous events that will provide a clue. Migraine is itself a cause of stroke, particularly in younger 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 overdiagnosed syndromes, being falsely linked to a wide range of symptoms, including vertigo, confusion, dizzy episodes and loss of consciousness.

RISK FACTORS

In a population of one million, around 1,400 will present each year with a first (1,800) or recurrent (600) stroke and another 500 with transient ischaemic attack.¹⁰ There will be around 1,300 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 sur-

vivors have a 15-fold increased risk of recurrence. This can be reduced by appropriate risk factor management.^{8,9,11,12}

The national clinical guidelines for stroke have been drawn up by a multidisciplinary working party.⁹ 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 5–6mmHg diastolic and 10–12mmHg 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 trial¹⁰ suggests that treatment with perindopril and indapamide produces a mean reduction in systolic blood pressure of 4mmHg diastolic and 9mmHg 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.¹²

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.¹²

Aspirin and other antiplatelet agents The use of aspirin in patients who have had an ischaemic stroke in doses above 75mg daily reduces the risk of stroke by around 13

Panel 3: Guidelines for secondary prevention of stroke (all patients)⁹

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

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

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.¹²

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.¹²

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.¹²

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,¹³ 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.¹⁴ 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.

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Useful links for patients

Hospital pharmacists are well-placed to advise patients and their carers about organisations, both local and national, which give support and information about stroke. Listed below are three organisations which provide useful information:

The Stroke Association

Stroke House
Whitecross Street
London WC1Y 8JJ
Stroke helpline: (local rate) 0845 3033100
Website: www.stroke.org.uk which provides addresses of their regional branches

Chest Heart and Stroke Scotland

65 North Castle Street
Edinburgh EH2 3LT
Stroke helpline: (local rate) 0845 0776000
Website: www.chss.org.uk

Different strokes

This UK-based charity was set up by younger stroke survivors for younger stroke survivors.
Website: www.differentstrokes.co.uk

The National Stroke Association

This American organisation can be accessed at www.stroke.org