Stroke prevention

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Although there have been considerable improvements in the care of patients following stroke, there are still no drug treatments which have been shown to conclusively improve recovery. Trials still underway are looking at changes in outcome using drugs aimed at limiting the size of the ischaemic penumbra, but there are already a number of proven strategies for prevention of stroke. Programmes to reduce smoking, alcohol intake, and obesity, to increase exercise and to improve glycaemic control in diabetics are no longer controversial, and a decrease in stroke incidence is only one of the expected health benefits of these measures, but the remainder of this article will deal with the options for drug and surgical treatment in the prevention of stroke.

Hypertension

Hypertension has long been recognised as an independent risk factor for stroke, and effective control will reduce the rate of stroke, a finding which has recently been confirmed in three large trials in elderly subjects.¹⁻³ The STOP-Hypertension trial recruited patients aged 70–84 years with systolic pressure of 180–230 mmHg and diastolic pressure of at least 90 mmHg, or diastolic pressure of 105–120 mmHg alone. Significant reductions were achieved in all primary end-points, including fatal and non-fatal stroke, and total mortality. There was a reduction of 14.5 strokes per 1000 patient-years on treatment. The MRC trial studied people aged 65–74 years with mean systolic pressures of 160–209 mmHg and mean diastolic pressures <115 mmHg. Treatment, particularly in the sub group of smokers treated with diuretics, reduced stroke, coronary and all cardiovascular events, reducing the number of strokes by 2.7 per 1000 patient-years of treatment. The SHEP study of isolated systolic hypertension (160–219 mmHg with diastolic pressure <90 mmHg) in subjects over 60 years old showed a reduction in stroke, cardiovascular and coronary morbidity and mortality, and in overall mortality. Six strokes (mainly non-fatal) were prevented per 1000 patient-years of treatment. It appears that isolated systolic hypertension should be treated in the same way as diastolic hypertension, although this has only been demonstrated in the highly selected group of elderly subjects recruited to the SHEP study so far.

Treatment of hypertension in elderly people therefore prevents stroke, but the cost in terms of patient years on treatment may be considerable. This cost may be even greater in younger patients. The MRC trial of treatment of mild hypertension under the age of 65 years required 850 patient years of treatment to prevent one stroke.⁴ This situation might be improved by concentrating treatment on subgroups of hypertensive patients with high risk of stroke, an approach highlighted by follow-up analysis of the MRC trial.⁵ Patients with high blood pressure but no other risk factors may have a low total stroke risk. Treating patients on the basis of overall risk rather than on an arbitrary level of blood pressure is an approach supported by the epidemiological evidence,⁶ and is likely to prove to be a more cost effective approach to stroke prevention. The relationship between rate of cardiovascular complications and level of systolic or diastolic blood pressure is linear, ie, there is no safe upper limit for blood pressure, and patients with a high stroke risk may benefit from having even relatively low blood pressure reduced further.

Primary prevention in patients with atrial fibrillation

Atrial fibrillation complicating rheumatic mitral valve disease has long been recognised as an important cause of embolic stroke, and has been seen as an indication for anticoagulation, although there are no placebo-controlled trials to confirm the effectiveness of this approach. Evidence from the Framingham study has shown that stroke is more common in patients with atrial fibrillation whatever the cause,⁷ and that it is an independent risk factor for stroke.⁸ The risk of ischaemic stroke is five times as great for patients with non-valvular atrial fibrillation compared with the general population,⁹ and is four times as great for

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patients with lone atrial fibrillation, ie, without other evidence of heart disease.¹⁰ However this risk may be much lower for patients with lone atrial fibrillation under the age of 65 years.¹¹ The long held view that patients with paroxysmal atrial fibrillation have a particularly high risk of stroke does not appear to be the case, with a risk of stroke approximately twice that of the general population.¹² However there does appear to be a clustering of embolic episodes in the first months after conversion from paroxysmal to chronic atrial fibrillation.¹²

If atrial fibrillation is a risk factor for embolic stroke, the risk of stroke might be expected to be reduced by anticoagulation. This has now been shown to be the case in five multicentre trials of primary prevention with warfarin^{13–17} and in one trial of warfarin as secondary prevention in patients with atrial fibrillation after transient ischaemic attack or non-disabling stroke.¹⁸ The target level of anticoagulation varied between the five trials, but it appears that achieving a prothrombin-time ratio of 1.2 to 1.5 (equivalent to an international normalised ratio (INR) of approximately 1.5 to 3) reduces stroke risk by 69%, equivalent to preventing approximately 30 strokes per 1000 patient years on treatment. The complication rate was low in all the trials, including a rate for intracranial haemorrhage of less than 0.5% per year. These results are probably applicable to elderly patients as the trials included a significant number of patients over 75 years.

The role of aspirin in primary prevention of stroke in patients with atrial fibrillation has also been under recent investigation. Two of the above trials used aspirin or placebo as an alternative to anticoagulation. While one showed a significant reduction in cardio-embolic events using 325 mg of aspirin daily in patients under 75 years,¹⁵ the other showed a non-significant reduction with 75 mg daily.¹³ The second Stroke Prevention in Atrial Fibrillation (SPAF II) trial has recently reported an equal reduction in stroke with 325 mg aspirin when compared with anticoagulation to achieve an INR of 2.0–4.5 in 1100 patients.¹⁹

It would seem reasonable to advise aspirin treatment to those patients in atrial fibrillation who have a low overall risk of stroke (ie, in the absence of hypertension, previous thrombo-embolism or recent heart failure, and with a normal echocardiogram) or in whom anticoagulation is contraindicated, and warfarin for high risk patients. This approach needs to be tested by further trials, however. Age alone should not be used as a contraindication to anticoagulation as although there are good theoretical reasons for expecting a greater risk of haemorrhagic complications with increasing age, the trial evidence is contradictory.^{20–23}

Secondary prevention

Stroke may be preceded by transient ischaemic attacks. The Oxfordshire Community Stroke Project has shown a 13-fold excess risk of stroke in the first year after a transient ischaemic attack and a sevenfold excess risk over the first seven years compared with controls.²⁴ Aspirin treatment is of proven benefit in reducing subsequent stroke after both transient ischaemic attack and non-disabling embolic stroke.²⁵ The dose of aspirin used appears to make little difference to outcome, but 75 mg daily would be expected to have a lower incidence of side effects than higher doses.

Carotid endarterectomy has been used extensively to treat patients with carotid stenosis, especially in the US, in the belief that surgery reduces the risk of stroke. This has now been confirmed for symptomatic patients with severe (>70%) stenosis.^{26,27} The risk of arteriography and surgery outweigh the benefits for mild stenosis (<30%) and the trials are continuing to look at patients with moderate (30–70%) disease. The place of surgery in asymptomatic patients is also awaiting the outcome of trials still in progress.^{28,29} The benefits of surgery must be weighed against the risks which rise with age, and age is bound to be a factor in the decision to offer surgery. The MRC trial had no upper age limit for inclusion, but age would certainly have been a factor affecting referral into the study. The mean age of patients with severe stenosis was 62.2 years. The North American Symptomatic Carotid Endarterectomy Trial had an upper age limit of 80 years with a median age of 65 years for the group undergoing surgery. The mortality and morbidity of endarterectomy would be expected to be low in the highly motivated centres performing many operations per year which take part in multicentre trials. Only if these low levels of risk can be replicated at a local level can surgery be recommended for individual patients. This is a powerful argument for organisation of vascular surgery services into a relatively small number of centres, each performing a large number of operations.

The place of anticoagulation or aspirin in secondary prevention after a transient ischaemic attack or non-disabling stroke in patients with atrial fibrillation has recently been addressed.¹⁸ These patients have a high risk of

Stroke prevention

- strokes are not inevitable, some can be prevented
- results of trials of treatments in acute stroke to reduce cerebral ischaemia will soon be available
- control of hypertension can reduce the incidence of stroke even in the very old
- the use of warfarin should be seriously considered in an older person with atrial fibrillation
- transient ischaemic attacks give warning of a greatly increased risk of stroke
- endarterectomy to prevent stroke should be considered if > 70% of carotid stenosis present

subsequent stroke with an annual rate of 12% which was reduced to 4% by anticoagulation with no episodes of intracranial haemorrhage. Ninety vascular events (mainly strokes) were prevented for every 1000 patient years of anticoagulation. Aspirin in a dose of 300 mg daily had a much smaller beneficial effect, producing a 14% reduction in stroke rate.

Vascular dementia

Multi-infarct dementia and small vessel disease are increasingly being recognised as common causes of dementia and are important as they are potentially preventable. Dementia is a serious and often overlooked cause of morbidity from stroke disease. All the measures discussed above would also be expected to decrease the rates of vascular dementia, but there is little trial evidence to support this at present as none of the stroke prevention trials have used dementia as an end point. However, the importance of risk factors such as smoking³⁰ and atrial fibrillation³¹ are well recognised and at least one small trial of aspirin in patients with multi-infarct dementia has shown some benefits.³²

Conclusion

Reducing the effects of vascular disease remains one of the greatest challenges facing medicine in the West. Resulting stroke and dementia are common and are serious causes of morbidity and mortality. Risk factors are now well defined making effective prevention strategies a real possibility, and many of these strategies have now been shown to be effective in large trials. It now remains to be shown that these methods are generally applicable in practice and that already stretched services can cope with the increased workload and expense. An all encompassing stroke prevention programme would now involve health education for the whole population, government measures especially aimed at reducing smoking, and changes in medical treatment, both at an individual level and in reorganising services. Such a complex package requires central organisation, and the role of government is pivotal. The undertaking by the government in the UK to reduce stroke as set out in *The Health of the Nation* is therefore to be welcomed.³³

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Parkinson's disease

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Fifteen years ago the pathology of Parkinson's disease was thought to be neatly parcelled in the substantia nigra with deficiencies of the dopaminergic system in the nitro-striatal pathways. The elegant pathological simplicity previously envisioned is now known to be much more complex.

Pathology

The hallmark of Parkinson's disease was said to be the total or subtotal loss of nigral cells in the substantia nigra but this is also seen in normal ageing and is most marked in the dorsal part of the pars compacta while in idiopathic Parkinson's disease it is seen in the ventral part. Lewy bodies are seen in the brains of patients with idiopathic Parkinson's disease but their precise role is not clear.¹ They are also seen in the brains of 10% of elderly controls without Parkinson's disease but are more frequent in those with the disease.^{1,2} Whether they are a cause or a marker of disease is not yet clear.

The previous supposition that only dopaminergic pathways are involved is known to be wrong. Abnormalities in adrenergic, cholinergic, and serotonergic pathways have all been noted.³ The dopamine receptor has been analysed and subdivided and there are currently at least five dopamine receptor subtypes (D₁ to D₅) classified. Pharmacological agents with differing affinities for these receptors have been and are being developed.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is known to produce a clinical syndrome very similar to Parkinson's disease.^{4–6} MPTP is converted by monoamine oxidase-B to the toxic metabolite MPP⁺ which inactivates mitochondrial complex I. Mitochondrial complex I is one of four complexes that convert pyruvate to adenosine triphosphate in the mitochondria. MPTP accumulates in the mitochondria of dopaminergic neurons and eventually kills them. In idiopathic Parkinson's disease levels of complex I are known to be depressed and mitochondrial defects have been reported in the brains,^{7,8} platelets⁹ and muscles¹⁰ of patients with Parkinson's disease. No MPTP-like substance has yet been identified in the environment but this pathological model involving an environmental cause as a potent factor is a tempting one.

Clinical features

Other features known to be of significance in addition to the classic triad of tremor, bradykinesia, and rigidity are impaired postural reflexes, shuffling gait, progression of physical signs, asymmetry at onset and response to dopaminergic agents. Dysarthria is common and dysphagia is increasingly recognised as a problem. Many methods are currently used to evaluate the degree of disability and severity of Parkinson's disease.^{11–14}

Other conditions may share features with idiopathic Parkinson's disease and need to be excluded. These include progressive supranuclear palsies, multi-system atrophy, exposure to toxins, Wilson's disease and Alzheimer's disease with extrapyramidal symptoms.

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