

RECURRENT STROKE: WHAT HAVE WE LEARNT?

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ABSTRACT

Stroke is the third leading cause of death, a major cause of disability in adults, and is frequently more disabling than fatal. With a decline in mortality from initial cerebral infarction and an increase in the life expectancy of the population, the number of patients with recurrent stroke and ensuing cardiovascular events will become greater. Thus it is important to find out those patients at high risk of stroke recurrence. This case report illustrates the process of recurrent stroke and the resulting disabilities and morbidities in a 42-year-old man. The role of integrated stroke rehabilitation programme is described.

Key words: Stroke, rehabilitation, prevention.

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CASE SUMMARY

History

Mr. BS, a 42-year-old Punjabi man was diagnosed with hypertension for more than thirteen years and diabetes mellitus for more than nine years. He had been under the care of his general practitioner. He presented to a private centre with progressive weakness of the left upper and lower limbs, slurring of speech and left sided facial weakness in the year 2003. His CT brain showed evidence of recent infarction in the right frontal white matter. He was commenced on aspirin, atenolol, enalapril, metformin, gliclazide and lovastatin. He was then discharged and referred to us for intensive physiotherapy of the limbs to ensure good recovery of his motor power. Further history revealed that he had two previous episodes of stroke in the past one month with similar findings although he had fully recovered from these episodes and had no urinary or bowel incontinence.

In the past medical history he had a transient ischaemic attack (TIA) in 1994, when he was first diagnosed to have hypertension. His electrocardiogram, echocardiogram, connective tissue screening, protein C and S, antithrombin III were normal although his lipid profile was deranged. Cerebral angiogram showed a small atherosclerotic plaque in the posterior wall of the right internal carotid artery. He was discharged on aspirin 300 mg daily, nifedipine 10 mg tds and lovastatin 20 mg at night. Subsequently he defaulted follow-up. In 1997 he was diagnosed to have diabetes mellitus. His lifestyle was rather sedentary. His mother was hypertensive and his father had diabetes

mellitus. He was a non-smoker but consumed beer occasionally. He worked as a security guard before the first episode of stroke.

Physical findings

On examination he could walk independently without aid. He was orientated in time, place and person but had slurred speech. His BMI was 30 kg/m², blood pressure was 140/80 mmHg, pulse rate was 74 beats per minute, regular rhythm with good volume. There was no carotid bruit and his cardiovascular, respiratory and abdominal examinations were normal. There was an upper motor neuron lesion of the left 7th cranial nerve. His lower limb reflexes were brisk, foot sensations were intact, motor power was 4/5 in the left upper limb and lower limbs, and his left plantar was up-going. There were no signs of peripheral neuropathy.

Investigations

His laboratory tests are shown in table 1. His CXR and ECG were normal and his magnetic resonance angiography showed right internal carotid stenosis.

Referral

He was referred for physiotherapy, dietitian and eye clinic for assessment of diabetic retinopathy. He was seen by a neurologist and was advised to stop aspirin and started on clopidogrel 75 mg daily in view of recurrent events of stroke.

Table 1. Laboratory results

Investigation	Results
Fasting glucose	6.6 mmol/L
Triglyceride	0.8 mmol/L
Total cholesterol	3.5 mmol/L
HDL- cholesterol	1.28 mmol/L
LDL-cholesterol	1.86 mmol/L
HbA1c	5.6%
Urea	6.2 mmol/L
Creatinine	87 µmol/L
Liver function test	Normal
Chest x-ray	Normal
ECG	Normal
Urinalysis	Protein negative

Progress

Subsequently BS suffered two further episodes of stroke within three months. He didn't make a full recovery and had a neurological sequel. His motor power at the left shoulder joint was 3/5, at elbow and wrist joint was 0/5. In the lower limb, his power was 4/5 at the hip, knee and ankle. He was able to perform activities of daily living and his urination and bowel were normal. However, he was depressed and had poor sleep at night with decreased appetite. He was referred to occupational therapist for assessment of activity of daily living (ADL) and for extensive physiotherapy. He was started on tab citalopram 20 mg nocte, a selective serotonin reuptake inhibitors for depression and was referred to a social worker for financial problems. After a few months, review showed that his depressive symptoms were better but the neurological signs persisted.

DISCUSSION

Stroke continues to be an important health issue, and it remains a leading cause of death and disability. Approximately 85% of strokes are ischaemic in nature and the rest is attributable to haemorrhagic causes such as subarachnoid or intracerebral haemorrhage.¹

Why this patient has recurrent episodes of stroke?

In this patient, it is unclear why he had so many episode of recurrent stroke even though he non-smoking, didn't have atrial fibrillation, and his diabetes and dyslipidemia were under control. His BP was higher than the target of 130/80 mmHg (for diabetic with hypertension). His blood pressure was unknown in the past years when was under the care of GP. In the earlier years of his stroke, his compliance to medication could be an issue as had defaulted follow up and treatment until later years. Therefore his blood pressure treatment might not be optimised. Furthermore the delay in initiation of aspirin, hypertensive, diabetic and lipid therapy after the first TIA could have contributed to his

recurrent stroke. Another factor for his recurrent stroke despite taking antiplatelet could be attributed to intracranial carotid artery stenosis; this may need other modes of treatment such as carotid endarterectomy.

Can this patient's recurrent stroke be prevented?
There are few strategies for primary and secondary prevention of stroke.

1. Strategies for primary prevention of stroke

In primary prevention, control of risk factors such as lifestyle modifications (weight loss, alcohol restriction, regular aerobic physical activity, and smoking cessation), measures to control blood pressure, cholesterol levels, diabetes mellitus and atrial fibrillation are important.² In this patient his first cardiovascular event of TIA occurred possibly due to undiagnosed hypertension and dyslipidemia. Therefore early screening and lifestyle modifications play an important role in primary prevention of stroke.

2. Strategies for secondary prevention of stroke

Stroke is a heterogeneous disorder in which multiple disorders can lead to occlusion or rupture of blood vessels supplying the brain.⁴ Modification of stroke risk factors is the principal therapeutic approach. Numerous RCTs have demonstrated that lowering blood pressure in patients with hypertension prevents both haemorrhagic and ischemic strokes. Indeed, systolic BP is a stronger risk factor for stroke than diastolic BP. Regardless of selected drugs treatment, to achieve the target BP of less than 140/90 mmHg is fundamental to stroke prevention.³ A more recent meta-analysis have cast the doubt on the effectiveness of atenolol as a suitable drug for hypertensive patients, notably its use is associated with higher risk of cardiovascular mortality and stroke when compared with non beta-blockers.^{4,5}

There were a few trials that had demonstrated that angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) reduced the risk of stroke by 28-32%.⁶⁻⁸ Summaries of the trials were given in Table 2.

High total cholesterol and LDL-cholesterol levels are associated with an increased risk of ischaemic stroke. Heart Protection Study (HPS),⁹ Scandinavian Simvastatin Survival Study (4S)¹⁰ using statins (HMG Co-A reductase inhibitors) in persons with coronary artery disease or risk factors showed a risk reduction in fatal and nonfatal stroke of 25%. Patients with diabetes are at increased risk for all forms of ischaemic stroke and are more likely to have hypertension and hyperlipidemia.³

Table 2. ACEI AND ARB TRIALS

Clinical trial	Risk reduction
Perindopril Protection Against Recurrent Stroke Study (PROGRESS) ⁶	A randomized, double-blind, placebo-controlled trial that enrolled 6105 men and women, with prior history of stroke or TIA. Active treatment of perindopril 4 mg daily was given for all participants, with the diuretic indapamide 2.5 mg daily in 58% of patients. There was 28% relative risk reduction in stroke.
Losartan intervention for endpoint reduction in hypertension study (LIFE) ⁷	A double blind randomized parallel group study of 1326 patients aged 55-80 years with high blood pressures and they were followed for a mean of 4.7 years. There was 40% relative risk reduction in any stroke, 70% fatal strokes, and 45% atherothrombotic stroke.
Heart Outcomes Prevention Evaluation Trial (HOPE) ⁸	A randomised placebo controlled study of 9297 patients aged >55 years at high risk for cardiovascular events because of evidence of coronary heart disease, stroke, peripheral vascular disease or diabetes plus one other coronary risk factor. They were randomly assigned to receive ramipril (10 mg per day) or placebo for a mean of 5 years. There was 31% and 20% relative risk reduction in stroke and MI respectively.

Aspirin or other antiplatelet agents are highly efficacious for secondary prevention of stroke or TIA, but their effectiveness for primary prevention of stroke is controversial.¹¹ Aspirin reduces the incidence of stroke by about 25%.³ The results of International Stroke Trial (IST) and the Chinese Acute Stroke Trial (CAST) showed that early treatment with aspirin reduces the rate of death or recurrent ischaemic stroke.¹² Ticlopidine is significantly more effective than aspirin for prevention of stroke in patients with TIA or minor ischaemic stroke,¹³ and it reduces the relative risk reduction of stroke by about 25-40%¹⁴ although it was not used in this patient. Clopidogrel, a congener of ticlopidine reduces the relative risk reduction of stroke by about 30%.¹⁴ This drug was used in this patient after several episodes of recurrent stroke because it is much costly than aspirin and ticlopidine and this patient was unable to afford it due to his financial constraint. A recent meta-analysis shows that thienopyridine derivatives (ticlopidine, clopidogrel) are modestly but significantly more effective than aspirin in patients at high risk of stroke.¹⁵

A recent large RCT, European Stroke Prevention Study (ESPS-2) found high dose dipyridamole 200 mg twice daily plus aspirin 25 mg twice daily to be superior to aspirin alone; with a 21% risk reduction relative to aspirin.¹⁶ However it was not used in this patient. Another meta-analysis showed that among patients presented with arterial vascular disease, dipyridamole in the presence or absence of another antiplatelet agent might reduce the risk of further vascular events. However further trials comparing the effects of the combination of dipyridamole with aspirin versus alone are needed.¹⁷

Patients with intracranial atherosclerosis, especially coexisting extracranial carotid disease are at higher risk of suffering death or further vascular events.¹ Perth

Community Stroke Study have shown that approximately 15% of survivors of a first ever stroke experienced a recurrent stroke over the next 5 years of which 25% are fatal within 28 days. The predictors of first recurrent stroke in this study were advanced age, haemorrhagic stroke, and diabetes mellitus. Because the risk of recurrent stroke is highest, 8.8% in the first six months after stroke, strategies for secondary prevention should be initiated as soon as possible after the index event.¹⁸

Carotid endarterectomy reduces the risk of stroke for selected patients with cervical carotid atherosclerosis stenosis. Carotid endarterectomy offers important benefits for patients with high grade (70% or more) cervical carotid stenosis who also have ipsilateral focal ischaemic events i.e. symptomatic carotid artery stenosis.³ A recent meta analysis based on North American Symptomatic Carotid Artery Endarterectomy trial (NASCET) and European Carotid Surgery Trial (ECST) showed that carotid endarterectomy had reduced the risk of disabling stroke or death by 48% in patients with severe stenosis exceeding 70-80%.¹⁹

The efficacy, safety and durability of angioplasty with or without stenting for management of cervical and intracranial carotid artery stenosis are unclear at present.³ Based on recent meta analysis there is insufficient evidence to recommend angioplasty with or without stent placement in routine practice for the prevention of stroke in patients with intracranial artery stenosis.²⁰ No randomised controlled trials were done and evidence from descriptive studies show that the procedure is feasible although it carries a significant morbidity and mortality risk.²⁰

Learning issues

Primary prevention is the most cost effective way in prevention of TIA or stroke. As a primary care physician and front liners we should counsel our patients on lifestyle modifications that include regular exercise, low salt diet and dietary changes, weight reduction, and behavioural modification such as cessation of smoking to prevent cardiovascular and cerebrovascular risk factors. Hypertension is the most prevalent and modifiable risk factor of stroke. Early detection and treatment of hypertension can substantially reduce the risk of stroke. We should carry out opportunistic screening for risk factors, and in the presence of one risk factor, positive family history, and obesity we should screen for other co morbidities. We should perform regular monitoring of these risk factors and optimise the treatment until target levels are achieved.

However once patient had experienced any stroke event, we should prevent further episodes of stroke. In addition to lifestyle modifications, we should optimize the treatment for hypertension, diabetes mellitus and dyslipidemia in order to achieve target levels. In cases of ischaemic stroke patients should be on antiplatelet agents. We should also think of intracranial carotid stenosis in patients with recurrent stroke, and hence timely investigation and early referral to neurologist are paramount.

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