

## PREVALENCE, SYMPTOMS, RISK FACTORS AND MAINTENANCE OF CEREBRAL STROKE: A REVIEW

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### ABSTRACT

Cerebral stroke is a cerebro-vascular disorder and a major cause for morbidity and mortality worldwide. Stroke is the third commonest cause of death worldwide after coronary heart disease and cancer of all types. World Health Organization estimated that over 50 million healthy life, across the globe will be lost by year 2015 as a result of stroke, and 90% of this burden will be borne in low-income and middle-income countries. India is silently witnessing a stroke epidemic. In order to fight stroke with very limited resources it is very important to be aware of different aspects of this medical emergency. This review will provide a brief description, prevalence, symptoms, risk factors and maintenance of stroke.

**Keywords:** cerebral stroke, prevalence, risk factors, stroke maintenance.

### INTRODUCTION

Human brain is the centre of the nervous system and is a highly complex organ. Although the brain comprises only 2% of the total body weight, it receives 15% of the cardiac output, 20% of total body oxygen consumption, and 25% of total body glucose utilization<sup>1</sup>. Under normal physiological condition, glucose is the sole source of ATP in the brain, and since, brain does not store glucose, its deprivation, even for a brief duration, can lead to severe pathological changes such as cerebral stroke and as neurons have a very limited potential to regenerate, the damage caused by ischemia is irreversible. According to the WHO Stroke has been defined as 'rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hr or longer, or leading to death, with no apparent cause other than of vascular origin'. This leads to subsequent breakdown of the metabolic processes in the affected brain territory causing loss of neurological function. Stroke is

divided into two broad categories that define its pathophysiology:

- 1) Ischemic strokes are caused by either cerebral thrombosis or embolism and account for 50%–85% of all strokes worldwide<sup>2</sup>.
  - 2) Haemorrhagic strokes are caused by subarachnoid haemorrhage or intracerebral haemorrhage and account for 1%-7% and 7%-27% respectively of all strokes worldwide<sup>2</sup>.
- In a 2002 study, the majority of strokes (83%) were ischemic in nature; 10% were due to intracerebral hemorrhage, and 7% were due to subarachnoid hemorrhage. In the 2006 update, these numbers had changed; 88% were ischemic, 9% were due to intracerebral hemorrhage, and 3% were due to subarachnoid hemorrhage<sup>3</sup>.

### Sign & Symptoms

Stroke is a medical emergency. Early assessment of stroke is essential in order to start the appropriate therapy and limit any further damage due to stroke, if possible. Symptoms of stroke depend on the type and area of the brain which is affected. Signs of ischemic stroke usually occur suddenly; however, they occur gradually in case of

hemorrhagic stroke. Stroke is characterized by sudden onset of a variety of symptoms. These include- sudden numbness of the face, arms or legs, especially on one side of the body, confusion, difficulty in speaking or understanding speech, trouble seeing in one or both eyes, sudden trouble walking, dizziness, loss of balance or coordination, severe headache with no known cause.

### Prevalence of cerebral stroke

Stroke, the third leading killer of Americans and the leading cause of long-term disability, remains an epidemic. Annually, 15 million people worldwide suffer from stroke. Of these, 5 million die and another 5 million are left permanently disabled, placing a burden on family and community. Stroke burden is projected to rise from around 38 million DALYs (disability adjusted life years) globally in 1990 to 61 million DALYs in 2020 (www.who.int). Stroke is a major health issue as it leaves patients with several residual disabilities like physical dependence, cognitive decline, dementia, depression, and seizures<sup>4</sup>. In an study in United States on around 30,00,000 long-term (>6 months) stroke survivors, 48% had hemi paresis, 22% could not walk, 24% to 53% reported complete or partial dependence on activity of daily living scales, 12% to 18% were aphasic, and 32% were clinically depressed<sup>5</sup>. The average healthcare costs (inpatient and outpatient) for cerebral infarction have been estimated to be between \$8000 and \$16 500; for subarachnoid hemorrhage, between \$27 000 and \$32 911; and for intracerebral hemorrhage, between \$11 100 and \$12 881<sup>6</sup>. Stroke mortality rate in India is 22 times that of malaria and 1.4 times of tuberculosis<sup>7</sup>. Stroke represented 1.2% of total deaths in India<sup>8</sup>. According to the Indian Council for Medical Research, mortality due to strokes has increased by 8% between 1998-2004<sup>9</sup>. Mortality rates due to stroke are the highest in Eastern Europe, north Asia, central Africa, and the south Pacific. In India, the mortality rate was 101-125 persons per 100,000<sup>10</sup>. The American Stroke Association estimates that stroke accounts for 1 of every 15 deaths and occurs once every 45 seconds in the United States, while a death from stroke occurs every 3 minutes. In 2002, about 600,000 people suffered a stroke; about 500,000 of these were first attacks and 100,000 were recurrent attacks. In 2006, this number increased to 700,000, of which 500,000 were first attacks and 200,000 were recurrent attacks<sup>3</sup>. Asians, specifically Chinese and Japanese, have high stroke incidence rates<sup>11</sup>. Stroke incidence and mortality rates in

Japan were very high for most of this century and exceeded those for heart disease. In China 1.5 million people die from stroke each year<sup>12</sup>.

### Risk Factors

A risk factor is a variable associated with an increased risk of disease or infection, which is evaluated by comparing the risk of those exposed to the potential risk factor to those not exposed. The overwhelming consequence of stroke is often associated with one or more risk factor. Age, gender, race, ethnicity, and heredity have been identified as markers of risk for stroke. Although these factors cannot be modified, their presence helps identify those at greatest risk, enabling vigorous treatment of those risk factors that can be modified includes Hypertension, Cardiac disease, Diabetic, Smoking, Alcohol, Lipids, Life style, Migraine, Transient Ischemic Attacks etc.

**Age:** Stroke can happen at any age, from newborn (even in a foetus) to seniors. According to the Heart and Stroke Statistical Update for 2002 and 2006 by the American Heart Association, 28% of people who suffered a stroke in a given year were under age 65; for people over age 55, the incidence of stroke more than doubles in each successive decade. **Sex:** Stroke is more common in men than in women but more women than men die of stroke each year because women tend to live longer<sup>3</sup>. The male/female sex ratio for stroke in India is 7:1<sup>13</sup>. This may be due to differences in risk factors such as smoking and drinking which are more prevalent among men in India compared with women<sup>14</sup>. After menopause, the incidence is a little higher in women than in men.

**Race:** The age-adjusted stroke incidence rates (per 1000 person years) are 1.78 for white men, 4.44 for black men, 1.24 for white women, and 3.10 for black women. Blacks have a 38% greater risk of incident (first) strokes than whites<sup>3</sup>. Indians, other than the Parsis, had much lower prevalence of stroke when compared to Caucasians and Chinese. The age adjusted prevalence rate of stroke was between 250-350/100,000. The Parsis originally came from Persia and settled in India during the 7th century. Their religion is Zoroastrianism and they are ethnically distinct from the rest of the Indians<sup>15</sup>.

**Genetic:** An increased incidence of stroke in families has long been noted. Earlier studies suggested an increased risk for men whose mothers died of stroke and women who had a family history of stroke<sup>16</sup>. In the Framingham Study an offspring analysis revealed that both

paternal and maternal histories were associated with an increased risk of stroke<sup>17</sup>. Hypertension: Hypertension is the most consistent and powerful predictor of stroke and is involved in nearly 70% of strokes. Most estimates for hypertension indicate a relative risk of stroke of approximately 4 when hypertension is defined as systolic blood pressure  $\geq 160$  mm Hg and/or diastolic blood pressure  $\geq 95$  mm Hg<sup>18</sup>. Placebo-controlled trials have shown that blood-pressure-lowering treatment reduces the incidence of stroke by 40% in middle-aged or older hypertensive patients with predominantly diastolic hypertension and by 30% in older patients with isolated systolic hypertension<sup>19</sup>. Atrial fibrillation (AF) is the most powerful and treatable cardiac precursor of stroke. The incidence and prevalence of AF increase with age. With each successive decade of life above age 55, incidence of AF doubles. The attributable risk of AF for stroke rose from 1.5% in subjects aged 50 to 59 years to 23.5% in subjects aged 80 to 89 years; i.e. nearly one stroke in four in persons older than 80 was a result of AF. In the Framingham Study, nonvalvular AF was independently associated with a threefold to fivefold increased risk for stroke<sup>20</sup>.

Diabetics have an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension, obesity, and abnormal blood lipids. Among Hawaiian Japanese men in the Honolulu Heart Program, those with diabetes had twice the risk of thromboembolic stroke of persons without diabetes that was independent of other risk factors<sup>21</sup>. Diabetes was found in 27% of their ischemic nonembolic stroke cases.

Lipids are also important modifiable risk factor. Increase in Low Density Lipoproteins (LDL) and decrease High Density Lipoproteins (HDL) are found to be associated with increased occurrence of stroke. Cigarette smoking increases risk of ischemic stroke nearly two times<sup>22</sup> with a clear dose-response relation. Cessation of smoking led to a prompt reduction in stroke risk—major risk was reduced within 2 to 4 years<sup>23</sup>.

Various lifestyle factors such as obesity, physical inactivity, diet, and acute triggers as emotional stress have been associated with increased stroke risk. Obesity has been associated with higher levels of blood pressure, blood glucose, and atherogenic serum lipids according to Honolulu Heart Study it was identified as an independent factor related to stroke incidence. In recent years evidence supports a protective effect of

moderate physical activity on stroke incidence in men and women by reducing blood pressure, weight, and pulse rate; raising HDL cholesterol and lowering LDL cholesterol; decreasing platelet aggregability; increasing insulin sensitivity and improving glucose tolerance; and promoting a lifestyle conducive to changing diet and promoting cessation of cigarette smoking<sup>24</sup>. Increased consumption of fish, green tea, and milk were protective of stroke, while diets high in fat and cholesterol could be deleterious<sup>25</sup>.

### Management of stroke

In stroke, the onset of injury and symptomatology typically coincides. Moreover, there is a distinct and relatively brief temporal pattern of injury which makes stroke as a devastating and debilitating event – one associated with high mortality and a high emotional cost and financial burden to patients, families and society. So Cerebral stroke has been considered as a major health problem world over and is increasingly recognized as a medical emergency and treatment of the patient begins even before a diagnosis can be reached but prompt differentiation of stroke as ischemic or hemorrhagic is vital to determining appropriate management. The most likely reasons for early deterioration and death of the stroke patient are complications involving other systems: for example, aspiration pneumonia, septicemia, arrhythmias, myocardial ischemia, hypertension-associated pulmonary oedema or renal failure, or pulmonary embolism. Therefore, the most important management of ischemic stroke actually resides with the prevention, identification, and prompt treatment of these critical comorbidities.

### Prevention of stroke

There is very compelling evidence from clinical trials of cholesterol lowering for ischemic heart disease indicating that risk for the first stroke is markedly diminished with pharmacological lowering of low-density lipoprotein (LDL) and total cholesterol<sup>26</sup>. Statin therapy reduces LDL cholesterol level, with each 10% reduction in LDL cholesterol estimated to decrease the risk for stroke by 15%. For patients with established coronary artery disease, there is now compelling evidence that statins reduces the risk for stroke compared with placebo<sup>27</sup>. In this study of 2,838 Diabetic patients, there was a dramatic 48% reduction in the relative risk for stroke for those on the statin compared with placebo. The benefit of statins for stroke prevention in patients with diabetes is very clear. The American Heart Association

recommended that adults with diabetes, particularly those with other atherosclerosis risk factor, be treated with statins<sup>28</sup>.

The potential role of LDL lowering with statin therapy for secondary prevention after a stroke, the SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study was undertaken. In this study, 4,731 patients with prior strokes were randomized to placebo or atorvastatin 80 mg/ day. During the median follow-up period of nearly 5 years, there was a 16% risk reduction with atorvastatin treatment for fatal or nonfatal stroke ( $p > 0.03$ )<sup>29</sup>.

It has been seen that for symptomatic patients with a >5-year life expectancy and 50% to 99% stenoses, CEA should be considered and for asymptomatic patients with a >5-year life expectancy and 60% to 99% stenosis, it is reasonable to consider Carotid endarterectomy<sup>30</sup>. The SPAF (Stroke Prevention in Atrial Fibrillation) study and additional landmark studies have clearly established the roles of warfarin and aspirin for stroke prevention. In hypertensive patients, numerous classes of antihypertensive medications, including thiazide diuretic agents, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and calcium channel blockers, have all been shown to decrease the risk for cardiovascular events including stroke<sup>31</sup>.

Effect of diet and life style was studied over 114,000 men and women based on the factors as body mass index <25 kg/m<sup>2</sup>, >30 min/day of moderate activity, not smoking, modest alcohol intake, and scoring in the top 40% on a healthy diet score. For women, 54% of ischemic stroke risk is attributable to lack of adherence to low-risk lifestyle. For men, 52% of ischemic strokes may have been prevented. Thus, for both men and women, a healthy lifestyle has an immense impact on stroke risk. It clearly must be the cornerstone of all physician recommendations for stroke prevention<sup>32</sup>.

### Treatment of stroke

In case of stroke immediate medical attention is critical for better recovery. The type of treatment depends on the diagnosis of stroke. As seen by cerebral angiography, around 80% of cases of cerebral stroke are because of thromboembolic occlusion, so thrombolytic therapy is indicated for ischemic stroke but it is likely to aggravate damage if administered to a hemorrhagic case. The practical benefit of thrombolysis with tissue plasminogen activator (tPA) in acute ischemic stroke has been tested in several large randomised-controlled trials,

the most notable of which are the American-based trials NINDS<sup>33</sup> and ATLANTIS<sup>34</sup> and the European-based trials ECASS-I<sup>35</sup> and ECASS-II<sup>36</sup>. From these and other studies, a general consensus has emerged that tPA may result in a long-term improvement in functional outcome. Tissue plasminogen activator (t-PA) is the only FDA approved drug used to treat ischemic stroke has to be administered intravenously within three hours of the onset of stroke. Several trials on streptokinase found it to be less successful than tPA that might be because of adverse pharmacological properties - as an anticoagulant and hypotensive<sup>37,38,39</sup>. A novel thrombolytic - desmoteplase, derived from the vampire bat - is currently undergoing trial as an alternative to tPA that may be given as a single bolus, up to 9 hr post stroke<sup>40</sup>.

Antiplatelet agents such as aspirin, clopidogrel bisulfate, and aspirin with dipyridamole may be prescribed to reduce the risk of recurrent stroke. Acute treatment of stroke with aspirin reduces death and dependency, but the size of this effect is small: ~80 patients need to be treated to prevent 1 event, or a relative risk reduction of 3%<sup>41</sup>. This result was based upon 2 trials involving ~40,000 patients in total, prescribed aspirin within 48 hr of stroke onset<sup>42,43</sup>. Similarly, secondary prevention with daily aspirin reduces further major vascular events by about 15%, equivalent to a NNT (number-needed-to-treat) of 100<sup>10</sup>. The addition of dipyridamole to aspirin<sup>44</sup> or substituting clopidogrel for aspirin<sup>45</sup> provide significantly better protection against future strokes than aspirin alone, with NNTs of ~50 and 60, respectively, compared with 80 for aspirin<sup>46</sup>. A head-to-head comparison of aspirin with dipyridamole found reductions in cardiovascular events with both drugs, but the combination of the two, in the same trial, was found to double the beneficial effect of each individually<sup>47</sup>.

Antihypertensive agents such as labetalol and enalapril are also used to reduce blood pressure in case of hypertension, with or without diuretics. The ideal anti-hypertensives in acute stroke are intravenous  $\alpha$  and/or  $\beta$  blockers (mainly labetalol and also nitrates), providing that the blood pressure can be monitored every 5–15 min to allow for gradual titration of dose. In chronic stroke situations the initiation of anti-hypertensives provides the most effective means of secondary prevention over all ischemic strokes<sup>46</sup>. A logical strategy to BP reduction is one that combines inhibition of the renin-angiotension-aldosterone system, using either an ACE inhibitor (or angiotensin-II type 1 receptor blocker) or beta-blocker, with

vasodilation, via either calcium antagonists or diuretics<sup>48</sup> for example a combination of perindopril with indapamide.

Recent study has suggested that those prostaglandins that act as ligands onto cAMP-coupled receptors, for example, PGE2 on EP2, or PGI2 on IP, may confer neuroprotective effects, independent of their vasodilatory functions<sup>49</sup>. In a recent randomised controlled trial involving 20,000 arteriopathies (predominantly previous ischemic stroke or coronary disease), secondary prevention with simvastatin 40 mg daily was associated with a 25% reduction in ischemic stroke, and a similar reduction in any major cardiovascular event, by 2 years<sup>50</sup>. In case of seizures accompanying stroke, anticonvulsants such as diazepam and lorazepam may be administered. Another possible target Piracetam, a g-amino butyric acid (GABA) derivative that has been shown to be neuroprotective in pilot studies has been tried<sup>51</sup>. Clomethiazole, a direct GABA agonist, seems to have a marginal benefit in patients with large strokes<sup>52</sup>. Sodium channel blockers, such as phenytoin, lifarizine and lamotrigine, are also under study, which act by inhibiting electrical depolarization in penumbral regions and thereby reducing postischemic glutamate release<sup>53</sup>.

## CONCLUSION

It is increasingly important for all physicians to be able to identify symptoms of cerebral ischemia. Neurons have a very limited tolerance for ischemia, making the rapid evaluation and diagnosis of stroke critical. Normally, thrombolytic therapy is indicated for ischemic stroke but it is likely to aggravate damage if administered to a hemorrhagic case. Hence care must be given to identify the type of stroke before appropriate treatment. Today the only treatment approved is rt-PA given intravenously within 3 hours of symptom onset but unfortunately only 5–15% (at most) of patients arrives at the hospital with in this time window. Hence preference should be given to primary and secondary risk factors to prevent the stroke possibility and above all modifiable risk factors specially adjusted life style can play prominent role in prevention of stroke for ex. the average consumption of salt in India is 15-16 grams per person per day. If we are able to reduce the salt intake by 2-3 grams per person per day, it would be a great achievement.

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