

# Infective Causes of Stroke in Tropical Regions

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This article has Continuous Medical Education (CME) credit for Iranian physicians and paramedics. They may earn CME credit by reading this article and answering the questions on page 219.

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## Abstract

Vascular diseases of the brain are the second reason of the death and the first cause of morbidity and disability worldwide. In tropical areas stroke has some particular features related to the nature of torrid zones. There are some special causes of the stroke, mainly infectious, although some of them are non-infectious. The most important etiologies are malaria, tuberculosis, cysticercosis, syphilis, and Chagas' disease. The mean age of the patients with stroke in tropical areas seems to be less than that in developed countries, and the disease is more prevalent in younger adults. Prevention and/or treatment of the classic risk factors as well as factors related to tropical zones are the mainstays of controlling the disease. It has to be mentioned that lack of human as well as financial resources makes it difficult to control and treat the disease properly. Herein, the etiologies and risk factors of the cerebrovascular diseases in tropical regions will be reviewed.

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## Introduction

The tropics or torrid zones are the areas between two parallels of latitudes on the earth. The latitudes are located 23° north and south of the equator. This region receives sun light more directly causing higher temperature in this area.<sup>1</sup> Direct sun shine, warm weather, distance from oceans, and different climate characters of those regions cause some special diseases more than other regions. Latin and Central America, sub-Saharan Africa, Middle East, India, and south-eastern countries in Asia are the major countries located in the torrid zones. Non-communicable diseases are an important threat to the health of adults in Africa and other tropical countries. Worldwide, cerebrovascular diseases (CVA) are second to ischemic heart disease as a cause of death leading to 4.4 million death each year with about 3 million death in developing countries.<sup>2</sup> Stroke is a vascular brain injury and a medical emergency caused by sudden interruption of blood flow. The WHO definition of stroke is a syndrome characterized by rapidly developing clinical signs of focal neurologic deficit, lasting 24 hours or longer and/or leading to death with no apparent cause other than of vascular origin.<sup>3</sup> The objective of this study is to review the risk factors of stroke, and highlight some special topics related to stroke in tropical regions and principals of their management.

## Epidemiology

There are several types of CVA, and each type has different causes. The three main types of CVA are cerebral infarction, which consists of more than 85% of stroke cases in developed countries. Ten percent of causes are intracerebral hemorrhage, and the remaining 5% are

subarachnoid hemorrhage.<sup>3</sup> Data on the current epidemiology of stroke in tropical areas are sparse. The prevalence of stroke was not verified in sub-Saharan countries, although the mortality of stroke in adults was reported to be 5.5% of all deaths in Tanzania.<sup>4</sup> The prevalence of stroke survivors in Sub-Saharan Africa was 300/100,000 (95% CI: 250-357) in the population aged over 15 years. This was about half the number that one would expect in a high-income country.<sup>5</sup> In a study in one of the largest cities in Ghana, stroke, heart failure, and renal diseases were accounted for 23% of acute medical admissions and 29% of deaths.<sup>2</sup> In some countries the leading cause of stroke was infective bacterial or tuberculous meningitis.<sup>6,7</sup>

### Risk Factors in Tropical Regions

Stroke is more common in people over 60 years of age, with no major difference between males and females. Mean age of stroke patients in Africa is less than 60 years. Females as many as half of the males are represented in hospital studies in Africa, because women are less interested in admission to the hospitals.<sup>3</sup> In urban Nigeria the crude prevalence rate of stroke was 1.14/1,000 (males: 1.51; females: 0.69). Age adjusted mortality is higher than that in developed countries like Britain, especially in younger patients. Stroke prevalence rates in this study,<sup>3</sup> were lower than those in most developed countries. The lower rates might be related to lower incidence and higher stroke mortality in developing countries.<sup>8</sup>

Hypertension is a major risk factor in developed countries, but it is difficult to confirm it because patients die before admission to the hospital. Abnormal autoregulatory system may induce hypertension in the first post-stroke days.<sup>3</sup> The incidence of stroke is increasing in sub-Saharan Africa, and stroke prevention is an essential way for successful management of stroke. Hypertension was the commonest risk factor in all population groups (55%), but was higher in black patients (59%).<sup>9</sup> It is estimated that if the 10-20 million people who had hypertension in sub-Saharan Africa were treated, about 250,000 deaths would be prevented annually.<sup>2</sup>

In Sierra Leone and Mauritania 60% and 56% of the patients were admitted to the hospital due to cerebrovascular accidents had hypertension, respectively.<sup>10,11</sup> In a study from February 2000 over a period of a year in Gambia, hypertension and smoking were the most prevalent risk factors of stroke.<sup>12</sup> Uncontrolled hypertension is one of the major causes of stroke in Latin America, but other risk factors such as heavy alcohol consumption and smoking also play a role.<sup>13</sup>

Diabetes, as a major risk factor of stroke,

has been reported in 2-10% of the population in tropical areas.<sup>14</sup> The prevalence of diabetes in South Africans older than 30 years is 5.5%. Ten percent of stroke patients in adult males and females over 30 years were attributable to diabetes.<sup>15</sup> In one study in sub-Saharan Africa, stroke was accounted for approximately 30% of all diabetic deaths.<sup>16</sup>

The relationship between stroke and high serum levels of low density lipoprotein (LDL) has been shown in several studies. Overall, about 29% of ischemic stroke burden in adult males and females more than 30 years were attributable to hypercholesterolemia with marked variation by population group. High cholesterol was estimated to cause 4.6% of all deaths in South Africa in year 2000.<sup>17</sup> Dyslipidemia was commonest in whites (37%), but least common in blacks (5%).<sup>9</sup> Obesity was present in 44% of stroke patients in Burkina Faso.<sup>18</sup>

Smoking is an increasing problem in the population at risk. It has an additive effect on the other risk factors. The prevalence of current smoking and ever smoking were 3.0% and 15.6%, respectively in Malawi.<sup>19</sup> The prevalence of smoking in 33 countries of Western Pacific and South East Asian regions ranged 28-82% in males and 1-65% in females. The percentage of haemorrhagic stroke attributable to smoking ranged 4-12% in males and 1-9% in females.<sup>20</sup> Risk factors other than smoking increased with age in a study done in Sub-Saharan Africa.<sup>9</sup>

Pregnancy and oral contraceptives (OCP) consumption are important risk factors for venous infarction, especially in early postpartum period.<sup>21,22</sup> There is not any published data about the effect of OCP in Sub-Saharan Africa. Positive past history of stroke, cardiac diseases, obesity, and lack of physical exercises are other important risk factors. Between 4-10% of patients had a positive past history of stroke and up to 11% had a history of transient ischemic attack (TIA). In only 22% of patients an atherosclerotic plaque in major extracranial vessels is shown.<sup>21,22</sup> Cardiac emboli in young adults due to rheumatic heart disease are more prevalent than coronary artery diseases in African patients.<sup>3</sup> It was reported that 22% of strokes were attributed to physical inactivity.<sup>23</sup> Forty-five percent of ischemic strokes were attributed to excess body weight.<sup>24</sup>

The main mechanisms for the cerebrovascular diseases in tropical countries are the same as those in other areas, but it is estimated that between 6 to 12% of the vascular accidents had other unusual etiologies.<sup>1</sup> Those are mainly cerebral malaria, tuberculosis, neurosyphilis, cysticercosis, Chagas' disease, and brucellosis.<sup>1,25</sup> To the best of our knowledge there is a little

reliable information related to the CVDs and tropical infections. Recently, increasing population and travelling from tropical low-income areas to high-income industrialized countries has led to increased presentation of the above mentioned disorders in the developed countries.<sup>26,27</sup>

## Malaria

There are about 400 to 500 million cases of malaria around the world with 30% are located in Asia and the major remainder in Africa.<sup>28</sup> Malaria itself causes 0.5 to 2.5 million deaths each year. Cerebral malaria (CM) which is the most severe complication of malaria is an acute and diffuse encephalopathy associated with *Plasmodium falciparum* infection. Cerebral malaria could be responsible for up to 10% of strokes in endemic regions.<sup>29</sup> Neurological focal signs due to vascular injuries are rare, but may produce severe outcome. Early and adequate treatment is effective way of preventing permanent sequel. The precise mechanism is not known, but the histopathologic hallmark of cerebral malaria is vascular engorgement with infected and non-infected red blood cells with parasites, metabolic disturbances, and host immune responses.<sup>30</sup> Quinine is the mainstay of treatment, and has to be prescribed with adequate loading dose (20 mg/kg of the dihydrochloride salt infused over 4 hours) to ensure that a parasitocidal concentration is reached in the blood.<sup>31</sup> Artemisinin derivatives are also good alternatives. Artemether is used intramuscularly, and artesunate is used intravenously, which may decrease the mortality secondary to CM.<sup>32,33</sup> Fluid, electrolyte balance and acid-base correction are important cornerstones of treatment. Dexamethasone may prolong coma in the survivors and should not be used in CM.<sup>34</sup>

## Tuberculosis

Central nervous system tuberculosis (TB) is a serious type of extra-pulmonary TB, and continues to be an important public health problem in developing countries. World Health Organization estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis* (MTB), with the highest prevalence of tuberculosis in Southeast Asia.<sup>35</sup> Different forms of CNS tuberculosis may cause motor deficit. These are tuberculous myelopathy,<sup>36</sup> intramedullary tuberculoma,<sup>37</sup> syringomyelia,<sup>36</sup> radiculomyelitis,<sup>38</sup> and tuberculous meningitis (TBM),<sup>39</sup> however, the main cause of stroke is TBM. Stroke occurs in 15-75% of patients with TBM occurs, especially in advance stage of the disease with severe illness. The majority of strokes may be asymptomatic, because of being in a silent area or the patient is in deep coma.<sup>40</sup>

In all cases caused by MTB, the bacterium settled in the lungs and disseminated to the nervous system through the hematogenous system. Rupture of rich nodules into the subarachnoid space is the beginning phase of meningitis. It induces lymphocytic infiltration around the meningeal blood vessels, and finally causes arteritis in almost all cases and cerebral infarction.<sup>41</sup> The pathophysiologic mechanism involved consists of chronic basal meningitis followed by tension hydrocephalus and raised intracranial pressure.<sup>42</sup> Neurological involvement accounts for up to 5% of extrapulmonary TB, especially in children and/or immunodeficient patients.<sup>43</sup> There are different reports about the incidence of stroke in neurotuberculosis. Dastur et al.<sup>44</sup> reported cerebral infarction in 41% of 100 autopsied brain. In post-computer tomography era the reported incidence is between 28 to 38% without any prominent sex dominance.<sup>45,46</sup> The highest rate of vascular infarction during TBM, diagnosed by MRI, is reported more than two thirds of the patients.<sup>47</sup> Ninety-two percent of the involved arteries were in the anterior cerebral circulation (carotid system).<sup>43,46</sup> Lenticulostriate arteries of both middle and anterior cerebral arteries are mostly involved. Large infarctions are mainly due to middle cerebral artery involvement, and brainstem infarction is due to occlusion of penetrating branches of basilar artery.<sup>46,48</sup> A recent report showed that the hazard ratio of ischemic stroke for tuberculosis patients (not meningeal or CNS tuberculosis) was 1.52-times (95% CI, 1.21-1.91; P<0.001) higher than that for control group.<sup>49</sup> The current guidelines for treatment are based on the advances of the recent chemotherapeutic achievement of anti-TB drugs,<sup>50</sup> and medical or surgical management for ischemic strokes. Early treatment is mandatory, and delayed treatment is associated with a higher rate of mortality and morbidity. Dexamethasone appears useful as an adjunctive treatment, especially in patients with severe tuberculous meningitis.

## Syphilis

Syphilis is the great masquerader. Two types of symptomatic neurosyphilis, paraneuritic and meningovascular have been described.<sup>42,51</sup> About 5% of untreated syphilitic patients will develop neurosyphilis,<sup>52</sup> especially in young adults. Two different types of vascular pathology have been described in meningovascular syphilis. Hübner arteritis, which had been described since long times ago, is the most common type and involves the large and medium sized vessels. The other pathology is Nissl's endarteritis characterized by intimal and adventitial proliferation, mainly on small

vessels.<sup>1</sup> Mostly middle cerebral artery is affected.<sup>41</sup> Different types of atherosclerotic plaques have been reported, but it should be defined that the presence of such lesions in neurosyphilitic patients does not imply a cause-and-effect relationship.<sup>53</sup> Neurological manifestations consist of motor and sensory impairment, and relate to the size and location of the lesion. Syphilis can affect any part of the neuraxis. A high index of clinical suspicion requires early diagnosis and treatment of neurosyphilis, particularly in patients with promiscuous sexual activity.<sup>54</sup> However, in HIV positive patients, the diagnosis and treatment of neurosyphilis is challenging.<sup>55</sup>

The guidelines for the treatment of neurosyphilis recommend intravenous penicillin G for 10-14 days or intramuscular benzathine penicillin G plus oral probenecid. The results for the newer drugs such as ceftriaxone or azithromycin have yet to be revealed.<sup>56</sup> All patients should be treated with long-term aspirin or other anti-platelet agents to prevent endothelial proliferation in Nissl's endarteritis.<sup>53</sup>

### Cysticercosis

The association between cerebral cysticercosis and stroke has been widely accepted with an estimated incidence of 10% in endemic areas,<sup>57</sup> and a range of 2 to 12% in different published series.<sup>58</sup> It is the most prevalent infection in the CNS, and is an endemic disease, especially in Latin America and other tropical countries.<sup>1</sup> Neurocysticercosis has been proposed as an independent risk factor for stroke with a high odds ratio of more than 11, especially in young and middle-aged patients.<sup>59</sup> Albendazole and praziquantel are the standard treatment for both paranchymal and meningeal cysticercosis with different protocols.<sup>60,61</sup> Sometimes treatment is risky and will aggravate an intense inflammatory process due to parasite lysis.<sup>1</sup>

### Chagas' Disease

The number of infected people with *Trypanosoma cruzi* was about 16-18 million in 1990s, especially in Latin and Central America.<sup>62</sup> The socioeconomic impact of the disease is more than all the parasitic infections in the above regions.<sup>63</sup> Humid climate and low socioeconomic status are important factors for disease expansion in endemic areas.<sup>64</sup> Embolic infarction is the main mechanism of stroke in Chagas' disease possibly due to left atrial dysfunction in chagas.<sup>65</sup> Chronic cardiomyopathy is established 10-30 years after the initial infection, and affects 30% of patients. The diagnosis of Chagas' disease has been established in more than 40% of stroke patients in endemic region. More than 20% of stroke patients are seropositive for *T. cruzi* in central Brazil.<sup>66</sup> It seems to be that chagasic

cardiomyopathy is independently associated with cerebral infarctions. Apical embolism, thrombus formation, cardiac arrhythmia and wall dysfunction are the major problems inducing emboli to the cerebral vessels.<sup>67</sup> The odds ratio for stroke in chagasic cardiomyopathy is reported 1.09, which is not too high.<sup>68</sup> The main risk factors for stroke secondary to Chagas' disease are a family member with Chagas' disease (OR=10.1) and past history of living in a mud-brick house during childhood (OR=8.9).<sup>69</sup> Trypanocide drugs such as nifurtimox and benznidazole are the drugs of choice. Monitored administration of warfarin in stroke due to chagasic cardiomyopathy is recommended.<sup>66</sup>

### Brucellosis

Brucellosis is a zoonotic disease with different neurological manifestations and still a common health problem in many parts of the world, especially Middle East,<sup>70</sup> Latin America and the Mediterranean Sea.<sup>1</sup> The involvement of CNS occurs in less than 3-5% of patients, mainly in the form of meningitis or meningoencephalitis,<sup>71</sup> and diabetes insipidus,<sup>72</sup> but the other forms such as vasculitis, transient ischemic attacks, ischemic strokes and venous thrombosis occurs rarely.<sup>73,74</sup> Recently, in a local population in Egypt, it was reported that CNS involvement (vascular stroke, meningoencephalitis, and dementia) was recorded in nine patients out of 27 patients (33.3%) with brucellosis.<sup>75</sup> Treatment is a special problem, and there are different protocols. A combination of doxycycline with rifampin and/or co-trimaxazole for six weeks or more has been recommended.<sup>71,73</sup> Other infectious and non-infectious diseases associated with stroke are summarized in table 1.

**Table 1:** Tropical diseases associated with stroke

Infectious	Non-infectious
Cerebral Malaria	Sickle Cell Disease
Tuberculous Meningitis	Takayasu Disease
Neurosyphilis	Behçet Disease
Cysticercosis	Moyamoya
Chagas' Disease	
Brucellosis	
Viral Hemorrhagic Fever	

### Crimean-Congo Hemorrhagic Fever

Crimean-Congo Hemorrhagic Fever (CCHF) is thought to be an old disease first described in the former Soviet Union. Since 1999 Iranian Ministry of Health reported a cluster of viral hemorrhagic fever in Sistan-Balouchestan, Isfahan and Golestan provinces in Iran. Fever, myalgia, petechia, purpura, bleeding, thrombocytopenia, anemia and

leukopenia are the main signs, symptoms and laboratory findings.<sup>36</sup> Intracerebral hemorrhage due to severe thrombocytopenia may cause hemiparesis or hemiplegia.<sup>36</sup> Hemorrhage in the arm compress median or ulnar nerves, and present itself as motor deficit.<sup>36</sup>

### Management of Stroke

Management consists of drug therapy, physical rehabilitation, control of risk factors and good nursing care. Antiplatelet drugs are the mainstay of drug treatment.<sup>76</sup> They consist of aspirin, dipyridamole, ticlopidine and clopidogrel. The two last drugs are platelet surface glycoprotein inhibitors.<sup>77</sup> For patients with embolic diseases due to cardiac problems or vascular atherothrombotic plaques anticoagulant drugs such as heparin or warfarin could be used. Aspirin is the most frequently used drug in all countries for acute therapy and secondary prevention. Main benefits of aspirin consist of low price and known adverse effects. The most important adverse effect is peptic ulcer and GI bleeding. In those cases ticlopidine and clopidogrel could be useful, but both are expensive. Dipyridamole has an additive pharmacologic effect when used with aspirin. Thrombolysis, carotid endarterectomy and vascular stenting are new procedures which are not available in most countries located in tropical regions. Nursing care include early rehydration, prevention of bedsores, protecting from aspiration pneumonia and rehabilitation. The latter is a combination of physical, occupational and speech therapy. It should be mentioned that in some situations such as intracranial hemorrhage secondary to CCHF or cerebral malaria antiplatelet drugs and heparin are contraindicated. Treatment of the risk factors such as hypertension, diabetes mellitus, and hypercholesterolemia, and smoking cessation are important features of the stroke management. Decreasing salt intake as well as weight and increase in physical activity also are the other important aspects of stroke management.<sup>3,78,79</sup> Effective stroke prevention calls for comprehensive risk reduction including blood pressure control. Population-based health education programs and appropriate public health policy associated with high-risk strategies for hypertensive persons and stroke patients should be developed.<sup>80</sup> The common problems to secondary prevention in Sub-Saharan Africa include high cost of treatment, difficulties in accessing care and lack of blood pressure control in clinics.<sup>5</sup>

### Conclusion

The major mechanisms for CVDs and their risk factors in tropical countries are the same as that

for other areas. A number of vascular accidents had other unusual etiologies. The main problems of stroke in tropical countries are not the same as industrialized countries. The first one is financial limitations, which leads to inappropriate medical care in the hospitals, and the lack of sophisticated imaging facilities that are used for stroke. The other important factor is the lack of secondary prevention success like control of hypertension, hyperlipidemia and tropical infections. The third reason is the lack of human resources experienced in the field of tropical medicine and neurology. The last one which has the equal importance is the lack of definite certificate for death and lack of post-mortem autopsy. The diagnosis is based on clinical, laboratory and radiological findings. It seems that there are many challenges facing physicians and health directors in tropical-low income countries.

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