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Characteristics of Cerebral Stroke in the Tibet Autonomous Region of China

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It is well known that cerebrovascular disease has become an important cause of adult death and disability. Strikingly, the Tibet Autonomous Region (TAR) ranks on the top in China for the incidence of stroke.

To help explain this phenomenon, we have searched for and analyzed stroke-related literature for the TAR in the past 2 decades and have referenced reports from other regions at similar altitudes. This article focuses on epidemiology features, risk factors, and pathogenesis of stroke in the TAR in an effort to generate a better understanding of the characteristics of stroke in this region.

The special plateau-related factors such as its high elevation, limited oxygen, the high incidence of hypertension, smoking, and the unique dietary habits of the region are correlated with the high incidence of stroke. In addition to these factors, the pathogenesis of stroke in this high-altitude area is also unique. However, there is no established explanation for the unique occurrence and high incidence of stroke in the TAR.

Our study provides an important rationale not only for the clinic to prevent and treat this disease, but also for the government to develop appropriate health policies for the prevention of stroke in the TAR.

MeSH Keywords: **Altitude Sickness • Hypoxia-Ischemia, Brain • Stroke**

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Background

As the highest place on earth, the Tibet Autonomous Region (TAR) is located on the Tibetan Plateau and is well known as the roof of the world (Figure 1). In general, the altitude of this area is about 3000–5000 meters with an average altitude of roughly 4000 meters, and there are approximately 2.32 million people living within this area [1]. Due to its high altitude, Tibet has formed a unique plateau climate, which is characterized by its thin air (about 60–70% of sea-level air density), low oxygen (35–40% less than the oxygen level at sea level), and low pressure (only half that at sea level). Based on the findings of Chinese stroke-belt study, this unique climate may be associated with the increased incidence of stroke occurring in Tibet to some degree [2].

Stroke is classically defined as an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction (CI), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH). It is a major cause of disability and death worldwide. Such symptoms usually last more than 24 hours and often result in death [3]. According to the World Health Organization (WHO), stroke is the second leading cause of death throughout the world [4]. In less affluent countries, the burden caused by stroke is enormous and can account for more than 85% of the global stroke mortality. In contrast with Western countries, stroke was the top cause of death in China and accounted for approximately 22.5% of all deaths occurring in China in 2005 [2]. Unfortunately, according to a national survey, the incidence of cerebrovascular disease in Tibet is the highest in China [5]. As a representative of the plateau, research on the incidence of stroke in Tibet could contribute to reduce mortality and disability of highland populations around the world. Such research may also provide a reference for local governments to formulate policies in an effort to prevent stroke.

Figure 1. The location of Tibet on the map of China.

Up to now, there have been few epidemiological studies on the population of patients having experienced stroke in Tibet. A recent epidemiological survey in the city of Lhasa on the Tibetan Plateau is one of the few studies having been conducted in this region [6]. Here, we present an epidemiological analysis of stroke in the TAR. In addition, we highlight the possible risk factors and pathogenesis of stroke in the TAR. Overall, this study aims to shed light on the underlying factors influencing the occurrence of stroke in this region, which will serve as an important starting point for the prevention and treatment of this disease in TAR.

The Humanistic Environment in Tibet

Tibet has the fewest number of people in China and the lowest population density. Among the total TAR population, the Tibetans are the main residents of Tibet, accounting for 96.4% of the populace. Therefore, the population experiencing stroke detailed in the literature mainly includes Tibetans who have lived in this area for an extended period of time.

It is well known that the Tibetans on the Tibetan Plateau and the Indians on the Andean Plateau have lived in these areas for about 25 000 and 11 000 years, respectively, and they have evolved and adapted in these long-term hypoxic environments [7–10]. Plateau dwellers are exposed to the opportunity for natural selection by the unavoidable environmental stress of severe lifelong high-altitude hypoxia [11]. This special living environment has attracted wide attention on the investigation of genetic adaptation in Tibetans. Recently, compelling scientific discoveries have disclosed the evolution of genes in Tibetans based on large dataset [12–18]. The majority of these genes such as hypoxia-inducible factor 2 (*EPAS1*) are strongly associated with blood-related phenotypes, such as hemoglobin, homocysteine, and folate in Tibetans [16–18]. Particularly, the single nucleotide polymorphisms (SNPs) in noncoding regions of *EPAS1* show significant differences in frequencies between the Tibetan and Han populations. Importantly, these differences in allele frequencies of *EPAS1* are closely associated with the lower hemoglobin levels in Tibetans [17]. All of these findings provide important insights into understanding the genetic factors of high-altitude adaptation in Tibetans [16–18]. Despite of these genetic evolutions for survival, TAR is considered a high stroke region in China.

Epidemiological Features

Under severe environments, a series of physiological changes have taken place, especially in the central nervous system.

Table 1. Comparison of the risk factors related with stroke between Tibet and Heilongjiang.

	Tibet	Heilongjiang
Location	Southwest of China	Northeast of China
Special environment	High altitude, hypoxia, low pressure, low temperature, physical inactivity	Air pollution, low temperature, physical inactivity
High risk factors	Hypertension, abnormal hemorheology, smoking, drinking	Hypertension, obesity, smoking, drinking
Diets	High fat, protein, and sodium, lack vitamins	High sodium, lack vitamins

The cerebral circulation mechanisms and clinical features of cerebrovascular disease are significantly different from those living in the plains or those who have migrated to the plateaus for a short time [19,20]. Currently, we still lack comprehensive systemic epidemiological surveys that have assessed high-altitude cerebrovascular disease.

Stroke-Belt in TAR

Stroke research at high altitudes in India suggests that long-term residence at high altitude increases the risk of stroke [19]. Also, it has been reported that the risk of stroke in areas above 4500 meters is 10-times that of residents of the plains [20]. Due to the differences in medical conditions, technology levels, and limited epidemiological research, the exact incidence of stroke in the TAR is not clear. According to epidemiological survey regarding the incidence of stroke in workers (81 298) listed in the City Staff Medical Insurance Registry of Lhasa, the capital city of Tibet [21], the annual incidence of stroke occurring is 81.798 per 100 000 per year and the age-standardized annual incidence rate is 88.725 per 100 000 per year. However, a national large-scale population survey of the Chinese stroke-belt demonstrates that Tibet is one of the regions with higher stroke incidence in China [2]. The average incidence of stroke in the stroke belt containing 9 provincial regions is 236.2 per 100 000 population compared with 109.7 per 100 000 population in regions outside of the belt [2]. Specifically, the stroke incidence in Tibet is 450.4 per 100 000 population after age-adjustment, which is only lower than that in Heilongjiang (466.9 per 100 000 population) among Chinese stroke-belt provincial regions [2]. The top 2 stroke regions have distinct geographic environments in China. The common risk factors related with stroke between them are hypertension, salty diets, smoking, and physical inactivity (Table 1) [2]. Importantly, the 33 Communities Chinese Health Studies have demonstrated that long-term exposure to air pollution has close correlation with the hypertension in the Northeast of China [22–24], which may contribute to the high incidence of stroke in Heilongjiang. We will discuss in detail about risk factors in Tibet in the following sections. Additionally, the difference in stroke incidence in Tibet between the 2 surveys may be related with the different populations. The latter covers a wide range of populations in the Tibet region with different economic and educational backgrounds.

Clinical Features of Stroke in TAR

Investigation results of stroke in Lhasa [21] demonstrated that the incidence of stroke in males is much higher than that in females, with an average age of onset of stroke being 60 years old and the age of onset between 26 and 85 years old. However, the seasonal difference in stroke in the TAR is not addressed. Similar to other regions, the incidence rate increases with age. The adjusted annual mortality rate is 25.941 per 100 000. The primary subtype of stroke in Lhasa is cerebral ischemia (CI), which accounts for 59% of stroke. The second subtype is intracerebral hemorrhage (ICH) with 36% incidence among the patients experiencing stroke in the TAR. It should be noted that the proportion of stroke subtypes reported in other studies is not consistent. For instance, Feng et al. reported that ICH accounts for 74.1% of stroke patients in the TAR, which is far higher than the reported ratio for the world of 6.3–41.3% [6]. Additionally, there are three most common hemorrhagic stroke types: aneurysmal subarachnoid hemorrhage (aSAH), spontaneous intracerebral hemorrhage (sICH), and arteriovenous malformation (AVM). Some hospital-based data demonstrated that a high incidence of blood blister-like aneurysm (BLAs) in aSAH subtype occurred in Tibetan hemorrhage stroke [25,26]. Endovascular treatment is the most effective therapy for Tibetan BLAs patients [26]. Furthermore, there is a tendency toward brainstem hemorrhage in sICH subtype and the incidence of infarction and rebleeding in Tibetan patients are significantly higher than that in Han patients in both the surgical and nonsurgical groups, indicating a poorer prognosis of Tibetan patients [25–27].

BLAs is a special subtype of stroke to which the Tibetan population is more susceptible [25,26]. Although the entire mechanism is not fully understood yet, it is proposed that the high level of hemoglobin, blood viscosity, and tiny thrombi are the basis for the development of BLAs [26]. Specifically, the compensatory

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Table 2. Characteristics of cerebral vascular disease in Tibet Autonomous Region.

	Characteristics	References
Special environment in Tibet	• High altitude • Hypoxia • Low pressure • Low temperature	[1,7–11]
High risk factors	• Hypertension • Abnormal hemorheology • Diets with high-fat, high-protein, high-sodium, and low-potassium • Smoking • Physical in activity and overweight • Alcohol use	[2,6,21,27,28, 33–38,41–45]
Epidemiology features	• High incidence of stroke in TAR • Poorer prognosis of stroke • Special subtype of stroke, such as blood blister-like aneurysm (BLAs)	[2,25–27]
Pathogenesis	• Dysfunction of endothelial cells • Oxidative stress increases the release of ROS from mitochondria • Activation of cytokines, chemokines, HIF1α and inflammatory responses in vascular system • Increased viscosity of blood • Thrombosis formation • Increased leakage of vessel	[39,40,56–65]

high hemoglobin level due to the hypoxic environment in Tibet functions as the initial response and then contributes to an increase in blood viscosity [28]. These facilitate the formation of tiny thrombi in the cerebral circulation system, which ultimately leads to cerebral infarction [26,28]. Although intravenous tissue plasminogen activator (IVtPA) treatment improves the likelihood for good clinical outcome for ischemic stroke [29], there is no conclusive report concerning its therapeutic effects in the TAR region.

High Risk Factors

The INTERSTOKE study [30] was the first standardized case-control study that included analysis of risk factors for stroke in low- and middle-income countries. This study concluded that five risk factors including hypertension, current smoking, abdominal obesity, poor diet, and lack of physical activity, accounted for 80% of the global stroke risk. However, it is unknown if these risk factors are the same as those present in Tibet. To address this question, we have identified possible risk factors for stroke in the TAR and have differentiated the risk factors for stroke in common with those identified in the INTERSTOKE study from those risk factors unique to the TAR region (Table 2). However, it is important to note that cerebral stroke is a complex disease with multiple factors acting together, even some risk factors act independently or synergistically.

Hypertension

Due to its high prevalence and relative risk, hypertension is thought to be the most important risk factor for stroke [31]. A meta-analysis of Chinese stroke populations has shown a significant association between hypertension and stroke [32]. Similarly, accumulating evidence indicates that hypertension is also the most important risk factor in stroke in the TAR [21,33]. The nationwide survey in 1991 reported that the prevalence of hypertension was as high as 19.54% in this area [2]. Another study performed in the town of Yangbajing further demonstrated that blood pressure and prevalence of hypertension are high in Tibetans aged 40 years and older. This study concluded that 56% of people in the group have high blood pressure, with an average blood pressure of 146.6/92.0 mmHg [34]. Additionally, the prevalence of hypertension in patients with ICH in Tibet is as high as 82.55% [6]. The high incidence of hypertension in the TRA may be due to the following reasons: first, residents in the region eat more meat and fatty foods but consume less fresh fruits and vegetables, which is thought to be related to hypertension [34]. Second, the Tibetan plateau is more than 3000 meters above sea level, and residents of Tibet face extreme cold and oxygen deficiency, which restrict their physical activity and lead to obesity. As such, residents tend to consume alcohol to resist the cold. All of these factors are related with hypertension [6]. Finally, the native Tibetans lack a general understanding of hypertension [35,36]. Even if they know that they have high blood pressure, they would rarely take standard medications for hypertension but prefer to take

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Tibetan medicines with unclear efficacy. As such, the control rate of hypertension in this area is very low [34]. There is a need to improve education and primary health care services to this large hypertensive population [34–36].

Hemorheology

Abnormal hemorheology is another important risk factor for high altitude cerebrovascular disease, which results in blood circulation disorders and easily leads to acute cerebrovascular disease among residents in the plateau. Hemoglobin has been reported as a critical biomarker altered by the hypoxia [35,36]. People in the TAR live in a low-oxygen environment for an extended time and, as such, demonstrate an increased number of red blood cells, increased platelet aggregation, and elevated hemoglobin in order to adapt to the hypoxic environment [27,28,37,38]. These factors lead to increased blood viscosity and reduced blood flow [20,27,28]. All of these alterations promote thrombosis formation at the damaged blood vessel wall [39]. Furthermore, sticky blood can directly affect the effective amount of cerebral microcirculation and its oxygen transport function, thereby inducing cerebrovascular disorders. Also, elevated blood viscosity caused by polycythemia can damage the vascular endothelium and activate platelets, thereby accelerating the formation of a thrombus and increasing the chance of ischemic stroke [39]. Additionally, increased circulation resistance causes damage to the intima of the vessel wall, which can result in hemorrhagic stroke. Interestingly, residents living in the high-altitude plateau present different cerebral blood flow (CBF) compensation after correction for differences in hematocrit and arterial oxygen saturation [40]. For example, comparative analysis of the CBF of residents living in the Tibetan Plateau and the Andean Plateau demonstrates that the CBF in Himalayans is slightly elevated compared with sea-level residents, and it is 20% higher compared with Andeans [40]. This study suggests that increasing CBF under hypoxic conditions is a compensatory way to increase oxygen supply for the brain tissues. This result also implies that cerebrovascular disease occurs when CBF is not sufficient to compensate for the hypoxia. Currently, there is no systematic study that evaluates the cerebral blood flow using suitable techniques (such as ultrasound detection) among the populace of the TAR. As such, further research is needed to confirm the exact influence of hemorheology on the occurrence of stroke in the TAR.

Diets

Unhealthy diets may increase the risk of ischemic stroke and hemorrhagic stroke. It is inferred that eating fruits and fish helps reduce the risk of stroke. In contrast, the consumption of red meat, organ meat, fried foods, and salty foods increases the risk of stroke [30]. In fact, a unique ethnic food culture has formed in the TAR due to the cold climate of the plateau. Residents here consume more meat, milk, animal fats, and oils, but less vegetables and fruits. Thus, a diet characterized by high-lipids, high-cholesterol, high-salt, and low-vitamins is formed. This local high-salt and high-fat diet increases the risks of hypertension and hyperlipidemia, thereby resulting in cerebral vascular diseases [41–43]. An analysis of lipid profiles of the Highlanders of Lhasa is the first one to address such a diet in this region [44]. In this analysis, they demonstrated that the men have a higher proportion of hypertriglyceridemia while women have a higher proportion of low HDL-C, and both genders have a higher proportion of hypercholesterolemia. Furthermore, diets insufficient in folic acid and vitamins lead to the higher homocysteine levels in residents living in high altitudes [45]. In line with this, Kotwal et al. reported that reduction of cysteine by taking vitamin B12 and folic acid might effectively inhibit the incidence of thrombosis in the plateau [46]. Furthermore, compelling evidence has indicated that increased homocysteine levels is an independent risk factor for coronary and cerebrovascular disease [47–50]. It is also known that homocysteine causes endothelial cell injury, thereby initiating the process of premature atherosclerosis [48,51].

Smoking

It is well known that smoking is a risk factor for ischemic stroke [52,53]. Hansen et al. demonstrated that smoking can cause related small vessel disease and promote ischemic stroke [54]. Also, it can increase blood viscosity, interfere with lipid metabolism, shrink small blood vessels, increase platelet adhesion and accumulation, and promote the formation of atherosclerosis and thrombosis. Moreover, the nicotine in tobacco can act on sympathetic nerves that leads to the release of catecholamines, induces vasoconstriction, increases blood pressure, and causes damage to blood vessel walls in response to long-term smoking. Smoking can also damage vascular endothelial cells and alter blood components to promote atherosclerosis [55]. Most residents in the TAR have a long history of smoking. A stroke survey conducted in Lhasa showed that young patients had a smoking history as high as 30% [21]. Thus, smoking is also an important and prevalent risk factor for stroke in the TRA.

Although many of the possible risk factors for stroke in the TAR have been noted, it is not yet possible to represent all the risk factors such as diabetes, high blood cholesterol, and heart disease for stroke in Tibet due to the lack of sufficient data. Further investigations are still needed to precisely identify the risk factors for high-altitude cerebrovascular disease.

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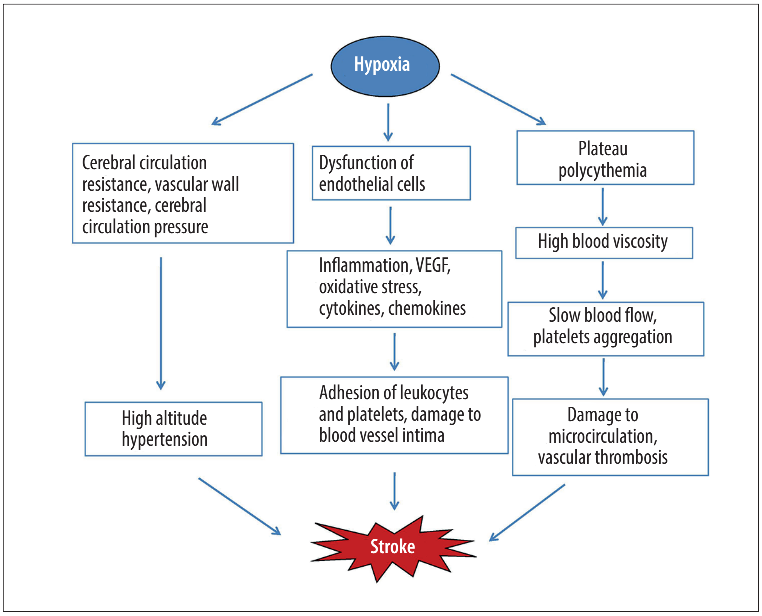

Figure 2. The unique pathogenesis of stroke in Tibet. Hypoxia is a unique risk factor in Tibet to cause stroke [56–65].

Pathogenesis

A variety of pathogenesis of stroke has been reported depending on the etiologies that cause stroke. As for Tibetan stroke, the plateau environment has a very significant impact on the human body; therefore, high altitude cerebrovascular disease has certain characteristics in terms of risk factors, particularly for hypoxia. Regarding the pathogenesis of stroke in the TAR, there is a theory [56] that hypoxia leads to hypoxic damage of the cerebral blood vessel wall. Hypoxia initially causes cerebral vasodilation and increases cerebral blood flow as a compensatory response. As the hypoxic damage continues, it leads to subsequent cerebral circulatory disorders. These include increasing cerebral circulation resistance, vascular wall resistance, and cerebral circulation pressure [56], finally resulting in high altitude hypertension. Additionally, hypoxia increases the blood viscosity due to plateau polycythemia [39]. Subsequently, the blood flow begins to slow down, prompting platelets to adhere to the damaged blood vessel intima [39].

It has been reported that endothelial cells are very sensitive to hypoxia which activates their function rather than induces apoptosis of endothelial cells [57]. This is the primary response to hypoxia and causes dysfunction of endothelial cells [57]. Subsequently, hypoxia induces oxidative stress and releases more reactive oxygen species (ROS) from mitochondria [57–59]. Free radicals activate the expression of cytokines, chemokines, and adhesion molecules [59]. Signaling pathways that are activated by ROS result in the adhesion of leukocytes and platelets, leading to a localized inflammatory state in the vascular system [59]. Furthermore, hypoxia induces the expression of vascular endothelial growth factor (VEGF), causing the occurrence of vascular leakage [60]. In addition to the alterations in the vascular system, cerebral syndromes are closely associated with the hypoxia in high altitudes. Intracranial hypertension and dysfunction in water balance occur in response to hypoxia. Increased pinocytotic vesicles and disassembly of inter endothelial tight junction proteins are observed in endothelial cells [61,62], and capillary permeability may also increase with subsequent swelling of astrocyte end-feet [62]. Moreover, oxidative stress cascades can also provoke membrane destabilization mediated by lipid peroxidation, inflammation, and local hypoxia inducible factor-1α (HIF1α), resulting in blood-brain barrier (BBB) dysfunction [61,62]. In addition to being found in the genetic adaptation in Tibetans [17], transcription factor HIF1α has been implicated in the mediation of inflammatory responses in stroke [63]. This systemic inflammation further contributes to brain injury [64,65]. All together, these findings emphasize that hypoxia is a critical stress to cause multiple vascular alterations in Tibetan stroke (Figure 2). These factors interact with each other and further trigger the release of various coagulation factors, leading to cerebral disease [66,67].

Conclusions

Due to its high altitude, lack of oxygen, strong radiation, and unique diet, the occurrence of stroke in Tibet is very different from other plains areas in terms of epidemiology, risk factors, and pathogenesis (Table 2). As for the pathogenesis, there is no definitive conclusion yet to be drawn from the literature. It is generally accepted that hypoxia damages the function of endothelial cells of the vascular wall, activates inflammatory responses, changes blood flow, and disturbs cerebral circulation. Due to the prevalence of hypertension and overweight (body mass index >25) being greater in the stroke belt than

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in other regions, any improvements in hypertension and obesity diagnosis, treatment, and prevention would be expected to have great impacts on reducing stroke in Tibet. More systematic investigations are needed to explore the risk factors and pathological mechanisms of stroke in the TAR, which will be an effective way to prevent and reduce the incidence of cerebrovascular disease for Tibetans. Additionally, extra investments in public infrastructure for education, prevention, and treatment are required to reduce the stroke burden in Tibet.

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Conflicts of interest

None.

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