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Cerebrovascular disease among Chinese populations—recent epidemiological and neuroimaging studies

華人的腦血管疾病—近期流行病學和神經圖像研究

Stroke mortality in individuals of Chinese descent has declined during the past decades, although the absolute number of patients with first-ever stroke is escalating. This review summarises recent epidemiological and imaging studies conducted among Chinese populations. Data indicating differences between Chinese and Caucasian ethnic groups in the pathophysiological mechanisms of stroke are highlighted, and the potential implications of these findings for prevention and management of stroke are discussed.

近十年來，儘管初次中風患者的絕對數不斷增加，華人中風死亡率卻在下降。本文總結了在華人人口中最近進行的流行病學和圖像研究，突出說明在華人和白人族群之間，在中風的病理生理學機製中的不同數據，以及這些發現對於預防和處理中風病的潛在影響。

Key words:
Chinese;
Epidemiology;
Neuroimaging;
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Introduction

Stroke is one of the leading causes of death, disability and dementia throughout the world. The problem of stroke has a particularly strong impact within Asia where more than half of the world's population live, and where stroke is frequently the predominant vascular disease in a given region. The World Health Organisation has estimated a total of 2.7 million stroke deaths in Asia in 2000, including 1.6 million deaths in China alone. The burden of stroke is likely to escalate substantially in the future due to an increasing ageing population.[1]

The epidemiology and pathogenesis of stroke are broad subjects and thus beyond the scope of this article. The focus of the current review and discussion is therefore limited to aspects which are of particular relevance to Chinese populations.

Epidemiology

It is difficult to assess the incidence of stroke in China because of the lack of a surveillance programme. An early door-to-door survey carried out in six cities in 1983, found an annual incidence of 219/100 000 population.[2] Similar results were found in a later study involving seven cities.[3] One of the most striking features of nearly all surveys conducted was the persistent observation of a clear north-south gradient. The highest incidence of 486/100 000 was found in northern China and the lowest of 136/100 000 was found in the southern region. The observed differences

in stroke mortality reflected differences in the prevalence of hypertension.[4]

The latest available data published by the Ministry of Health in Beijing, indicates that the mortality from stroke was 137.72/100 000 in 1999 in mainland China, ranking closely behind malignancy (139.28/100 000) as the second leading cause of death.[5] Mortality is generally higher in metropolitan than in rural regions and among males than females.

In parallel with observations in other countries, stroke mortality has been declining in China, especially for men.[3] Although no single cause was found, the reduction in stroke mortality appeared to be the result of a number of factors, including better surveillance and control of risk factors such as hypertension, lifestyle, and dietary changes, as well as improved medical care for stroke patients.

Similar trends were also found in other Chinese populations. In Singapore, standardised death rates showed a dramatic fall from 99 per 100 000 in 1976 to 59 per 100 000 in 1994.[6] In Hong Kong, a recent study revealed a comparable trend, with stroke mortality in men decreasing from 84/100 000 in 1976 to 41/100 000 in 1995 (a 51% decrease), and in women from 56/100 000 to 35/100 000 (a 38% decrease).[7]

While decreasing stroke mortality is encouraging, the absolute number of patients with first-ever stroke is escalating as the population ages. Statistics from the Hospital Authority in Hong Kong show that the number of annual stroke admissions to public hospitals has surged to more than 20 000 while the total number of stroke deaths has remained stable at about 3000 per year. As a result, the number of stroke survivors in the society continues to grow. Thus, the social and economic burden of stroke in our society cannot be overemphasised and more intensive efforts are required to develop new stroke prevention strategies.

Stroke mechanism

The traditional strategy to prevent stroke highlights the importance of identification and treatment of risk factors. This approach has been very successful to date for common risk factors such as hypertension, and is the reason why stroke mortality has been declining in most developed countries. However, this approach may have reached its limitation as the rate of decline in stroke mortality is slowing.[7] To further reduce the incidence and mortality of stroke in the future, additional tactics may be needed (Fig 1).

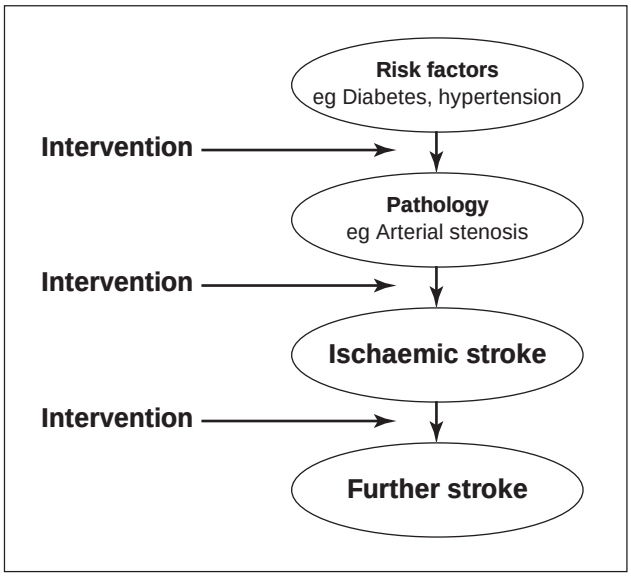

Fig 1. Schematic representation of approaches for stroke prevention

The major deficiency in many current strategies to combat stroke lies in the presumption that stroke is a single disease. According to World Health Organization criteria, stroke is defined as 'rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin.' This definition characterises stroke as a syndrome after exclusion of other causes, rather than as a disease of specific pathology.

Previous approaches to prevention of stroke groups all stroke subtypes together, with the expectation of one panacea for all stroke subtypes. In fact, prevention and treatment of stroke should vary according to various pathophysiology shown. More advanced strategies target a specific pathophysiology and implement precise treatment according to the stroke mechanism. Examples include the use of warfarin to prevent thrombus formation and embolisation to the cerebral circulation, and endarterectomy to remove the source of artery-to-artery embolisation as well as to improve the haemodynamics of cerebral circulation. A pathology-based stroke classification is indispensable for guiding clinicians in instigating the most effective therapy. An example of a simple classification for stroke is outlined in the Table.

Imaging advances

The inability to visualise vascular pathology noninvasively has hindered advances in the understanding of stroke in the past. In the 1980s, the availability of computed tomography (CT) revolutionised stroke management. Over the past decade, advances in

Table. A pathophysiology-based classification of stroke

Ischaemic stroke	Intracerebral haemorrhage
Large artery disease Intracranial (eg internal carotid, middle cerebral, anterior cerebral, posterior cerebral, vertebral, and basilar arteries) Extracranial (eg aorta, subclavian, common carotid, and internal carotid arteries) Small artery disease Lipohyalinosis Microatheroma Leukoaraiosis Cardioembolic Atrial fibrillation Valvular disease Patent foramen ovale/ other structural lesions Venous occlusion Venous sinus thrombosis Hypercoagulability	Hypertension Amyloid angiopathy Antithrombotic-associated (thrombolytic, anticoagulant, and antiplatelet agents) Drug (eg amphetamine, cocaine, and phenylpropanolamine) Haematological (eg thrombocytopenia) Structural lesion (eg tumour, arteritis, and vascular malformation)

technology have greatly assisted the detection of vascular lesions and provided further insights into stroke mechanism. Transoesophageal echocardiography, for example, provides a simple means of diagnosing protruding atheroma in the aorta, clot or spontaneous echo contrast in the left atrium, and patent foramen ovale. Duplex ultrasound with colour flow Doppler allows characterisation of an atherosclerotic plaque, assessment of early atherosclerosis by measuring intima-media thickness, quantification of the degree of stenosis in the carotid artery, and measurement of cerebral blood flow.[8]

Transcranial Doppler ultrasound (TCD) was initially developed to diagnose intracranial large artery stenosis.[9] More advanced applications include detection of an embolic signal and measurement of cerebral reactivity.[10,11] Computed tomography angiography and magnetic resonance angiography (MRA) offer morphological images of luminal stenosis and aneurysm (Fig 2). For the first time, the clinician is able to positively identify the presence of cerebral infarction by diffusion-weighted magnetic resonance imaging (DWI) within hours of onset of symptoms (Fig 3).[12] Using these state-of-the-art neuroimaging techniques, the pathophysiology of stroke in Chinese populations has been elucidated.[13-21]

Large artery disease

Epidemiological evidence

It has been known for decades that extracranial carotid stenosis is common in Caucasians, while intracranial stenosis predominates in Asians, blacks and Hispanics.[22] The invasiveness of the technique, coupled with the risk of perioperative ischaemic events, prevents investigation of a large cohort of patients by conventional angiography.[23] Thus, the exact prevalence of intracranial stenosis in symptomatic and asymptomatic Chinese patients remains unknown. A study among 114 non-selected autopsy subjects in Hong Kong confirmed that intracranial stenosis is more severe than extracranial stenosis. The results showed that diabetes and hypertension are risk factors for intracranial stenosis, whereas ischaemic heart disease is a risk factor for both extracranial and intracranial stenosis. Furthermore, smoking is associated with extracranial stenosis.[24] A study in Taiwan, using MRA to assess the carotid artery only, confirmed that intracranial disease was more common than extracranial disease in this population, whereas tandem lesions were also very common.[25]

A series of studies have been undertaken by the authors to determine the importance of intracranial stenosis in local populations. Ninety-six patients with transient ischaemic attack (TIA) in Beijing were investigated using TCD. Fifty-one percent of these patients had intracranial stenosis, whereas 19% had extracranial carotid stenosis.[15] A further study of 66 acute stroke patients in Hong Kong showed that 33% had intracranial stenosis and only 6% had extracranial stenosis.[17] Both studies were relatively small and lacked outcome data, however.

A recent large study of 705 consecutive stroke patients in Hong Kong reiterated the predominance of intracranial stenosis previously seen: 37% of patients had intracranial stenosis only, 10% had tandem lesions and 2.3% had extracranial stenosis only.[18] The middle cerebral artery (MCA), vertebrobasilar artery, anterior cerebral artery, and intracranial internal carotid artery were the most common sites for occlusive disease. This study also noted that vascular lesions in this

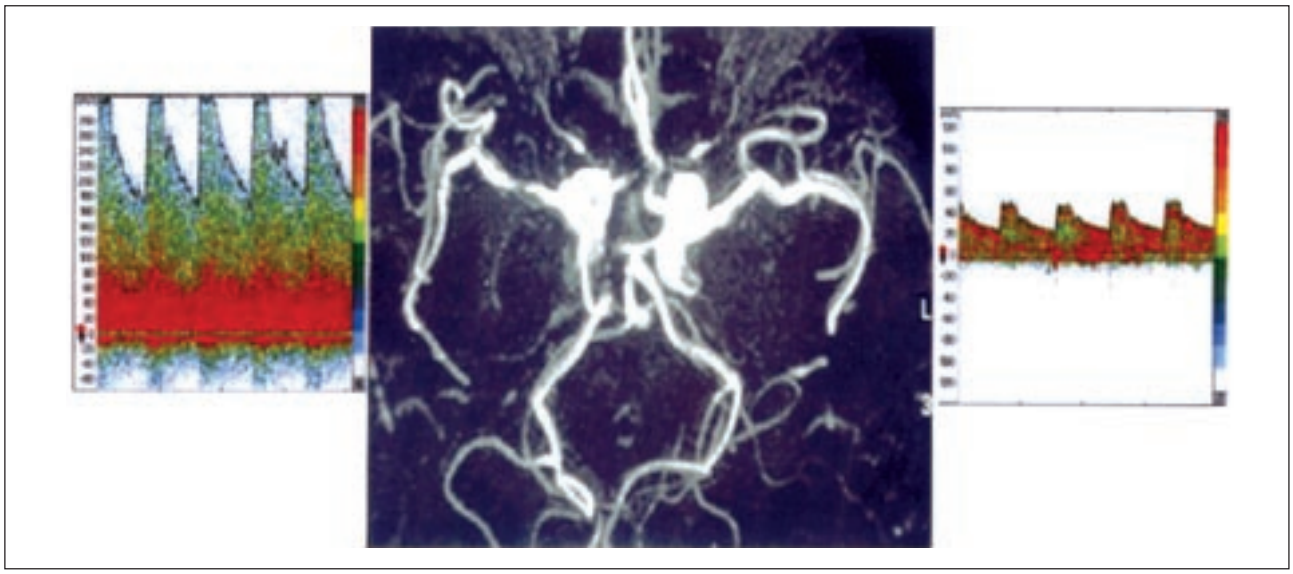

Fig 2. Magnetic resonance angiography and transcranial Doppler ultrasound images of right middle cerebral artery stenosis and normal left middle cerebral artery

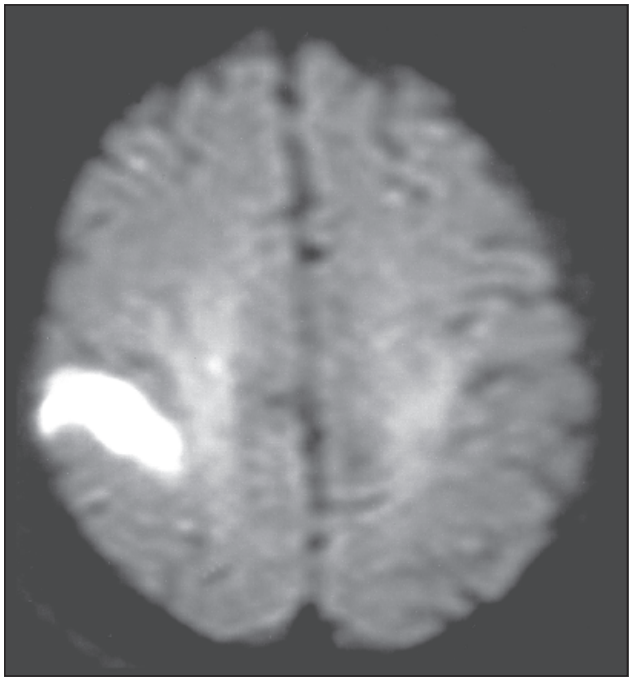

Fig 3. Diffusion-weighted magnetic resonance imaging of an acute cortical cerebral infarct

population tended to be diffuse rather than discrete, as seen in Caucasians. More than half of the patients had two or more (up to nine) lesions. More importantly, the results show that documentation of vascular lesions is no longer an academic curiosity. Instead, detection of the presence and extent of vascular lesions can independently predict the risk of stroke or death at 6-months. Other variables such as hypertension, diabetes, previous stroke and ischaemic heart disease should be seen as confounding factors. The high rate of further vascular events or death in patients with vascular lesions calls for investigation of more aggressive therapy in addition to the current aspirin-only treatment recommended. Given the dismal prognosis of intracranial stenosis after stroke, it would be ideal to treat intracranial stenosis before it produces symptoms.

In 1999, the first population-based study to document the prevalence of intracranial stenosis was conducted in a rural village in China. Transcranial Doppler ultrasound was used to screen 590 subjects and documented a prevalence of 7% for those aged more than 40 years.[26] Risk factors for intracranial stenosis identified included hypertension (odds ratio [OR]=2.53), diabetes (OR=3.00), familial history of stroke (OR=5.20), and history of heart disease (OR= 4.00). The risk rose substantially with an increasing number of coexisting factors. Similar results were subsequently found in a clinic-based study of more than 3000 asymptomatic subjects in Hong Kong. Among subjects with multiple risk factors, the prevalence of intracranial stenosis can be up to 25%. (KS Wong, unpublished data).

The high prevalence of intracranial stenosis among the Chinese populations combined with the safety and feasibility of diagnosis renders the possibility of screening high-risk patients and instigating appropriate therapy at an earlier stage. Following this approach, a multi-centre, randomised, double-blind, placebo-controlled study of the effect of simvastatin on the regression of cerebral artery stenosis is currently underway in Hong Kong.[27]

Pathogenesis

Despite the availability of epidemiological data on large artery disease in Chinese populations, how large artery stenosis causes cerebral infarction remains

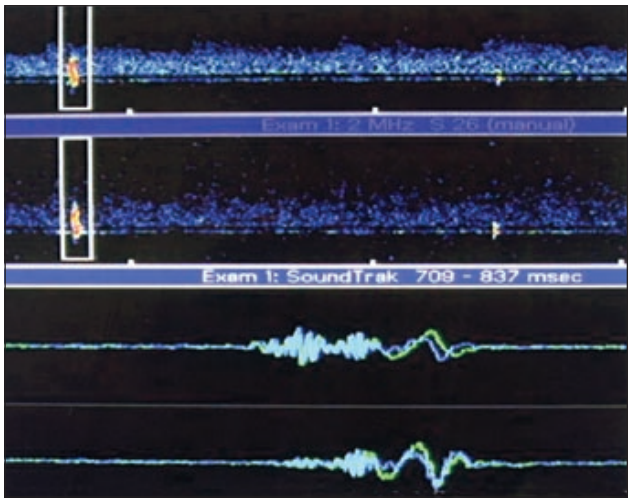

Fig 4. Microembolic signals (inside of the white rectangles, upper two tracings) at 56 cm and 46 cm from transcranial Doppler ultrasound probe. The lower two tracings reveal a time delay between the two signals which represent the time difference for the embolus to travel from the depth of 56 cm to 46 cm

uncertain. Possible mechanisms include thrombosis formation leading to complete occlusion or artery-to-artery embolism, haemodynamic compromise, or a combination of both factors. Cerebral embolism was not considered to play an important role in the pathogenesis of cerebral infarction until recently when the means to detect emboli in cerebral arteries became available.[28,29] An example of the microembolic signal detected by TCD monitoring when it passes through different depths is shown in Fig 4. A number of studies have shown that the presence of microembolic signals is associated with an increased risk of stroke.[28]

A pilot study conducted by the authors investigated 20 acute stroke patients with intracranial stenosis and found the presence of a microembolic signal in 15%, however, the microembolic signal was absent in stroke patients without intracranial stenosis. In a recent study, the frequency of microembolic signals was 26% in a further group of 23 patients with acute stroke caused by MCA stenosis, with evidence of cerebral infarction on DWI.[19] More importantly, multiple cerebral infractions on DWI were detected in 44% of patients. The presence of multiple infarctions and microembolic signals suggest an important pathogenic role for artery-to-artery embolism. Furthermore, two common but distinct typographic patterns of infarction on DWI were observed: single lesions in the basal ganglion or single/multiple lesions along the border zone regions (Figs 5 and 6).

On the basis of this data, it appears that intracranial stenosis may cause cerebral infarction by obstructing the orifice of the penetrating artery or sending off

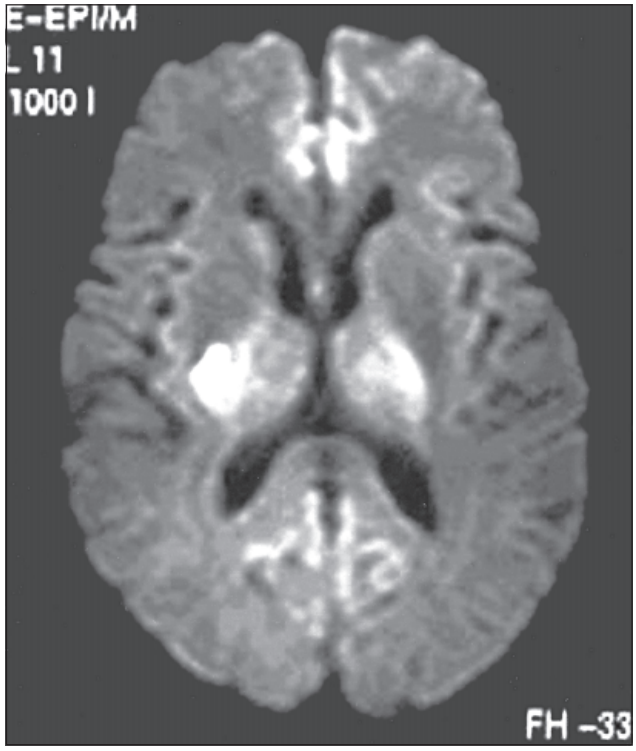

Fig 5. Diffusion-weighted magnetic resonance imaging shows a small subcortical infarct at the right putamen

emboli distally. In regions where perfusion is adequate, these emboli may be cleared. In the border zone area, where perfusion is usually compromised, entrenched emboli may not be cleared as rapidly, and consequently cerebral infarction may occur.[30] The data indicate, therefore, that both artery-to-artery embolism and haemodynamic compromise are important factors in the pathogenesis of cerebral infarction in patients with large artery occlusive disease.

Taken together, these studies suggest that the pathophysiology of cerebrovascular disease in the Chinese populations differs from Caucasians and therefore may demand different treatment and prevention strategies. Data derived from studies on Caucasian stroke patients should not be automatically extrapolated to the Chinese populations given the dissimilarity in stroke mechanism. More clinical trials involving stroke patients in Asia are indicated as a result.

Small artery disease

Small subcortical infarcts, so-called lacunar infarcts are common in Chinese populations.[31] Early pathological study of these 'lacunar' infarcts in the era of uncontrolled hypertension suggested lipohylinosis or microatheroma of a small artery as the underlying cause. Thus, if a small subcortical infarct is seen on a CT scan of the brain, many clinicians may infer that small artery disease is the primary source of infarction.

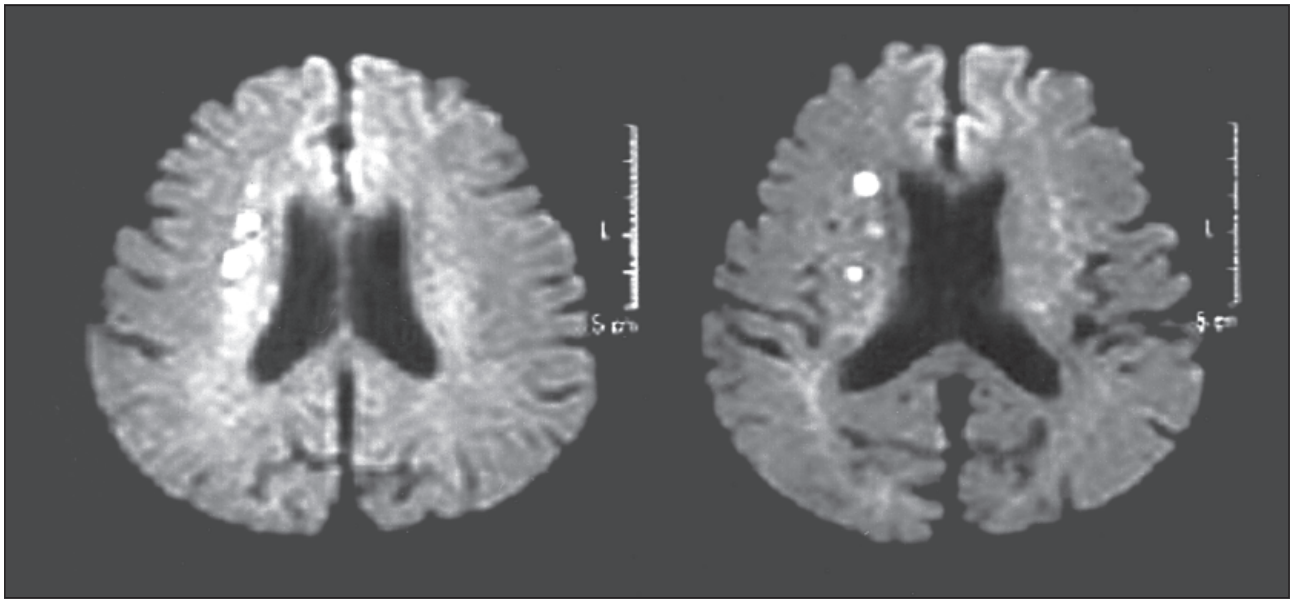

Fig 6. Diffusion-weighted magnetic resonance imaging shows multiple acute infarcts in chain form along the internal border zone region

This assumption, although widely accepted overseas, may not be applicable in Chinese patients. In recent years, a few studies have reported that lacunar stroke may be associated with intracranial large artery stenosis. Lyrer et al[32] reported that 22 (45%) patients with isolated MCA stenosis presented clinically with a lacunar syndrome. In a study of Chinese stroke patients with intracranial large artery occlusive disease documented by TCD, 59% of the patients presented with a lacunar syndrome.[17] Data presented from a study of Japanese stroke patients, indicated that 54 (65%) had significant large artery stenosis of a total of 83 patients who had a lacunar syndrome clinically.[33] The site of the occlusion of the penetrating artery is commonly located at the orifice of the artery (branch occlusive disease).[34] The presence of a small subcortical infarct on neuroimaging, therefore, does not preclude further investigation of the vasculature.

A chronic form of small artery disease, known variously as leukoaraiosis, Binswanger's disease, or subcortical arteriosclerotic encephalopathy, is a common radiological finding on magnetic resonance imaging (MRI) and CT scans. It is characterised by hypodensity on CT and increased density on T2 image in MRI in the periventricular and subcortical regions. The pathology, risk factors, aetiology, and clinical significance of this condition remain controversial except that advancing age and hypertension are the two most recognised risk factors. The clinical picture is quite variable although it is typically associated with cognitive impairment and/or gait disturbance. There is no established treatment.

Intracerebral haemorrhage

In the decades before the advent of non-invasive neuroimaging, spontaneous intracerebral haemorrhage (ICH) was thought to be the predominant type of stroke in Chinese populations. Although ICH is relatively more common than in whites, many studies in the era of CT scan have shown that ICH accounts for only 20% to 30% of all stroke in Chinese populations.[31,35,36] Hypertension remains the principal cause of spontaneous ICH. Thus, the importance of active surveillance and treatment of hypertension at the community level cannot be overemphasised. Weakening of the vessel wall of the penetrating artery in the basal ganglion as a result of chronic hypertension, so called Charcot-Bouchard aneurysm, is regarded as a potential source of ICH. Pathological examination usually reveals the presence of lipohyalinosis in addition to microaneurysm, suggesting co-existence of small artery disease.

Traditionally, cerebral amyloid angiopathy (CAA) was regarded as a rare cause of ICH. Abnormal deposition of amyloid in the vessel wall of small arteries and arterioles causes affected vessels to bleed easily. Cerebral amyloid angiopathy mainly affects elderly persons aged 65 years or older. Other characteristic features include a lobar distribution, multiple foci, and a tendency for recurrent bleeding. Recent studies have suggested that CAA plays an important role in the pathogenesis of ICH among patients treated with warfarin and thrombolytic therapy.[37] Amyloid angiopathy may also be the cause of many cases of aspirin-associated ICH.[38]

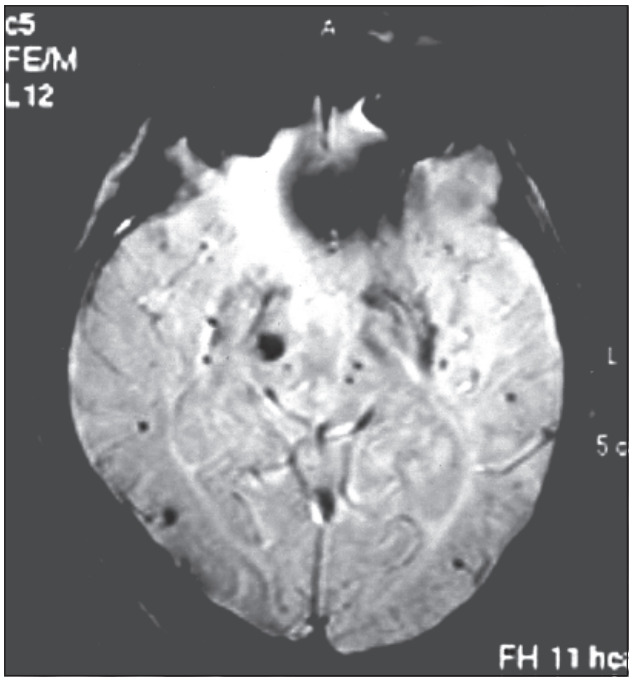

Fig 7. Scattered multiple haemosiderin deposits (hypodense lesions) represent past asymptomatic small intracerebral haemorrhages

Histological examination was the only method used to diagnose this condition until the availability of gradient-echo MRI. Because of the tendency of CAA to cause recurrent haemorrhages in the lobar region, the presence of multiple asymptomatic microhaemorrhages, which are shown on MRI as haemosiderin deposits, is regarded as evidence of CAA (Fig 7).[39] This non-invasive means of identifying previous microhaemorrhages may have the potential to help clinicians identify patients at high risk of ICH among those patients who need long-term antithrombotic therapy. A small case-control study in Hong Kong recently suggested that ICH is uncommon among patients with few (less than two) or no microhaemorrhages on MRI.[20] Obviously, more research into this rapidly evolving field is needed to confirm this hypothesis.

Conclusion

With modern neuroimaging techniques, clinicians are now able to accurately assess the risk of ischaemic and haemorrhagic stroke in individual patients. It is envisaged that in the near future, stroke prevention and treatment strategies will be similarly individualised and tailored according to the underlying stroke mechanism.

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