Journal of
HYPERTENSION RESEARCH
www.hypertens.org/jhr

Review

J Hypertens Res (2017) 3(4):128–134

Hypertension and cerebral small vessel disease: an intricate relationship

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Received: November 7, 2017, Accepted: December 12, 2017

Abstract

Cerebral small vessel disease represents a common neurological pathology that expresses itself under multiple forms, as acute neurological symptoms in the form of lacunar stroke or as cerebral lesions that can potentially progress and lead to cognitive impairment, depression and gait disturbances. Its pathophysiology is still poorly understood though the considered risk factors are the classical cardiovascular ones, especially hypertension. For the moment, treating blood pressure is regarded to be the most effective on in delaying the progression of the disease. The active therapies to reverse the burden of the disease are yet to be discovered.

Keywords: hypertension, cerebral small vessel disease, stroke, capillary dysfunction

Introduction

Cerebral small vessel disease (SVD) represents a common neurological disease especially in the elderly population. It includes various pathological processes that take place at the level of small arteries, arterioles, capillary bed and the small veins of the brain. SVD is responsible for one in five strokes worldwide, for 25% of ischemic strokes that leave 20% of the patients disabled and accounts for 45% of dementia cases. The clinical manifestations are typical for stroke by lacunar ischemic infarcts, gait disturbances, cognitive decline, depression and even urinary symptoms. Radiologically, on MRI scans, cerebral small vessel disease is associated with small subcortical infarcts, lacunes, white matter hyper-intensities, cerebral micro bleeds especially at the subcortical level, enlarged perivascular spaces (Virchow-Robin) and finally cerebral atrophy.

The pathogenesis of cerebral small vessel disease is poorly understood but in recent years vascular risk factors have been taken into consideration as important contributors to the development of SVD-specific lesions. The major risk factors for the increased severity of SVD markers are advanced age and hypertension. The latter is a particularly major and modifiable risk factor, though the pathological mechanisms linking hy-

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pertension to SVD have not yet been fully understood. Assuming that cardiovascular risk factors are in close connection to SVD, their prevention might reduce the disability and mortality occurring with this disease.

Small vessel disease pathology and pathophysiology and the presumed role of hypertension

The major pathological patterns found in the brain affected by small vessel disease are small, deep, so called 'lacunar infarcts' with size ranging from 1 to 15mm, located in the basal ganglia, pons, thalamus, internal capsule and corona radiata. The degenerative component expressed in the form of leukoaraiosis and leukoencephalopathy areas show myelin degeneration and consequently gliosis. Two vascular pathologies emerge in the brain damage associated with small cerebral vessel disease: hypertrophy of the arterial media and obstruction of the origin of penetrating arteries by intimal cholesterol plaques. The thickening of the media is due to fibrinoid deposition and hypertrophy of smooth muscles, the consequence of hypertension, diabetes, dyslipidemia and probably genetic factors. Further pathologic studies have showed that foam cells localized at subintimal level can obliterate the arterial lumen and that the vascular layers were replaced by abnormal conglomerate of connective tissues known better as lipohyalinosis [1],[2]

The pathophysiology is centered on capillary dysfunction in conditions that represents risk factors for small vessel disease. In a normal brain and under normal conditions, approximately 30-40% of blood oxygen passes to cerebral parenchyma from the small vessels. The oxygen extraction depends on cerebral blood flow which increases in relation to cerebral activation especially at a cortical level. Capillary dysfunction caused either by changes in its function, permeability or blood flow limits the oxygen extraction to the cells at the microcirculatory level. Several compensatory mechanisms take place. Firstly, in mild capillary dysfunction the cerebral blood flow increases in order to adapt the tissues oxygen extraction. These mechanisms are shown to appear in conditions considered risk factors of small vessel disease, especially hypertension. Consequently, if this phenomenon fails, a paradoxical decrease of the cerebral blood flow takes place in order to limit functional shunting that renders the blood especially to the highly demanding zones when activated-the cortical zones. The measurements taken have shown that the limit of cerebral blood flow in the case of cerebral ischemia and in capillary dysfunction that causes cerebral hypoxia in small vessel disease is the same, approximately 20ml/100ml/min. There are several microvascular phenomena that occurs in various diseases, considered as risk factors for the development of SVD, included in the Pantoni classification (table 1). Extensive research has been made regarding the pericytes, which are the contractile cells in the basement membrane that adapt the capillary lumen. They contract in response to high oxygen concentration and relax when a low pH and lactate is detected due to insufficient oxygen levels. Vasoactive substances like the angiotensin II, the powerful vasoconstrictor endothelin II constrict the pericytes while the adenosine and nitric oxide have a relaxing effect. Hypertension and diabetes, are the main modifiable risk factors that conduct to pericyte loss and the thickening of the basement membrane surrounding the small vessels. [3] A mutation in the NOTCH 3 gene that encodes a receptor protein found at the surface of pericytes is responsible for the neurological condition known as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Another mechanism that disrupts the capillary flow pattern is the lack of integrity of the blood brain barrier due to disruption of endothelial cells, especially under abnormal inflammatory reactions. The glycocalyx dysfunction, the carbohydrate matrix at the endothelial level, when disrupted, can affect the flow regulation as well as the blood hyperviscosity due to diabetes or the rare condition of cryoglobulinemia. All these pathological mechanisms become at some point progressive, leading to a capillary dysfunction that finally results in tissue damage due to lack of nutrition support and hypoxia or exposure to toxins through a disrupted blood brain barrier. [3]. High blood pressure is regarded as the main risk factor for developing small vessel disease in all its forms. Still it is a debated issue if the capillary disruption in response to the effect of angiotensin II that interferes with oxygen extraction precedes the development of systemic high blood pressure. Consequently, hypertension was considered to occur as a systemic response to maintain organ oxygenation by overcoming the increased vascular resistance [4]. However, the patholog-

Table 1. Pantoni classification (the aetiopathogenic classification of cerebral small vessel disease).

Type 1-Arteriosclerosis (due to age or cardiovascular risk factors)	
Risk factor	**Changes at the capillary level**
Age	Pericyte loss and thickening of the basement membrane, capillary deformities.
Hypertension	Pericyte degeneration, thickening of the basement membrane and in vitro studies show abnormal response of the pericytes to angiotensin II and endothelin
Diabetes	Thickeing of the basement membrane, modification of blood rheology due to hyperviscosity. Pericyte apoptosis due to oxidative stress
Type 2- Cerebral amyloid angiopathy	Pericyte degeneration
Type 3- Inherited or genetic disease with small vessel disease component, other than cerebral amyloid angiopathy	
CADASIL/CARASIL	Pericyte loss, thickened basement membrane, deposits of NOTCH 3 extracelluar domains at the level of the capillary wall
MELAS	Aggregates of mitochondria in the endothelial cells
Fabry's disease	Endothelial cells vacuolization, swelling
Hereditary cerebroretinal vasculopathy	Capillary obliterations due to telangiectatic microaneurysms
SVD caused by COL4A1	Abnormal capillary organization
Type 4- Inflammatory and immunologically mediated small vessel disease	
Varicella Zoster	Possible infectious vasculitis
HIV-1	Vasculitic process
Hepatitis C	HCV-cryoglobulinemia associated vasculitis
Treponema pallidum	Lymphoplasmocytic infiltrates and vasculitis
Borrelia burgdorferi	Lymphplasmocytic infiltrates and consequently vasculitis
ANCA associated vasculitis	Fibrinoid necrosis due to toxic protease released by neutrophil adhesion to capillary endothelium
Sneddon's syndrome	Proliferating capillary endothelial cells
Primary angiitis of CNS	Granulomatous form or necrotizing that affects the arteries, arterioles, capillaries and venules
Systemic scleroderma	Lymphocytic infiltrates in the arterial wall
Systemic lupus erythematosus	Capillary abnormalities
Type 5- Venous collagenosis	
Type 6- Other small vessel disease	
Post-radiation angiopathy	Capillary disruption due to tissue hypoxia

ical findings have shown that hypertension disrupts the capillary bed as a primary event, therefore the therapy fighting high blood pressure is to be ensued at this stage in order to prevent the progression of SVD [5].

The clinical expression of small vessel disease and its radiological characteristics

Small vessel disease is expressed in the form of lacunar infarcts or lacunes, white matter hyperintensities, cerebral microbleeds and enlarged perivascular spaces.

The lacunar infarct represents a small zone of ischemia, ranging from 1 to 15 mm, induced by occlusion of a small perforating artery in the white matter at the level of basal ganglia, pons and brainstem. It manifests clinically in the form of brutal neurological symptoms known as lacunar syndrome. There are five classic syndromes, detailed as follows. Pure motor hemiparesis, the most common of the five; the lesion occurs in the posterior limb of the internal capsule or at the level of basal pons. Clinically a contralateral equally distributed motor deficit occurs with all the pyramidal pattern characteristics. The second lacunar syndrome is represented by ataxic hemiparesis, a combination of motor weakness associated to ipsilateral cerebellar ataxia. The stroke is localized also in the posterior limb of internal capsule, corona radiata or infratentorial at the level of pontine pyramids. Thirdly a stroke at the level of genu of the internal capsule can express itself in the form of an ataxic hemiparesis associated to dysarthria. A syndrome in the form of sole sensory deficit occurs when there is a lesion in the ventral postero-lateral nucleus of the thalamus. The clinical deficit is represented by contralateral numbness in possibly all sensory modalities. The last lacunar syndrome is a combination of motor and sensory contralateral deficit when the lesion touches the thalamus and the posterior limb of internal capsule in the same time. Radiologically, an acute lacunar infarct is hyperintense on diffusion-weighed imaging, hypointense on an apparent diffusion coefficient map, hyperintense on T2 and fluid-attenuated inversion recovery (FLAIR) sequence, hypointense on T1 and hypodense on CT scan [6], [7]. Risk factors for lacunar syndromes are high blood pressure (both systolic and diastolic), diabetes, smoking, age, male sex, internal carotid artery stenosis.

The clinically silent SVD involves the white matter hyperintensities (WMH), the lacunes, the cerebral microbleeds (CMB) and the enlarged perivascular spaces. The white matter hyperintensities of supposedly vascular origin are a common finding in older subjects. The related symptoms develop slowly in the form of vascular associated cognitive impairment, urinary and gait disturbances. It has been shown that WMH triples the risk of stroke, doubles that of dementia and finally increases the mortality due to cerebrovascular events. It is thought that apart from age, WMH are strongly associated with high blood pressure especially correlated with a high diastolic one. Paradoxically some studies have shown that low blood pressure can impair the autoregulation of cerebral blood flow and consequently results in cerebral ischemia of hemodynamic cause thus increasing the risk of developing white matter lesions [8]. Some limited pathological studies mention areas of demyelination and oligodendrocytes loss and in the more severe cases edema due to disruption of the blood brain barrier. The mechanisms are probably diffuse atheroma that leads to partial but chronic ischemia [9], venous collagenosis [10] or hypotensive situations. The RSS study (Rotterdam Scan Study) showed that a high homocysteine level could be linked to the developing of WMH, due to endothelial dysfunction [11]. Diabetes and cholesterol levels failed to make a connection to development of WMH. The diagnosis of WMH is made on MRI scans where the lesions are most often symmetric, bilaterally distributed in the subcortical white matter and in the pons. They are hyperintense on T2 and FLAIR sequences. Risk factors associated with WMH are hypertension, increasing long term blood pressure fluctuations, age.

The lacunes are small chronic cavities presumed the consequence of a healed lacunar infarct ischemic or hemorrhagic at its origin, filled with CSF. The most often, they are asymptomatic and are a common finding in the elderly. It was hypothesized that isolated lacunes with no association to WMH are connected to hypercholesterolemia and diabetes due to widespread microatheroma. In other cases, WMH is caused by fibrinoid necrosis due to hypertension and age [12]. On MRI examination, the lacune is hypointense on FLAIR sequences associated to a hyperintense rim.

The cerebral microbleeds are usually small, rounded, homogenous perivascular lesions. The major component are hemosiderin-laden macrophages. The

main pathologies associated to CMB are hypertension and amyloid angiopathy. The RSS found that hypertension was related to subcortical CMB whereas amyloid angiopathy with cortical CMB. The presence of CMB is increasing the risk of intracerebral hemorrhage and are also associated to the risk of developing cognitive impairment. In patients suffering from ischemic stroke or intracerebral hemorrhage of non-traumatic origin the CMB can be found in 33.5 to 67.5% of subjects [13]. Radiologically they can be recognized as homogenous hypointensities on T2-weighted (gradient-echo) and susceptibility-weighted imaging (SWI) sequences on MRI. The most consistent risk factors associated with CMB are hypertension, diabetes, smoking, low total serum cholesterol levels and low triglycerides.

The enlarged perivascular spaces(PVS) are another expression though controversial of SVD. They represent an extension of subarachnoid spaces filled with CSF. Usually they are smaller than 3mm, the criterion that can help to distinguish them from lacunes. Although when a few are present they are not considered of pathological origin, with ageing more PVS can increase the risk of developing a cognitive impairment [14]. The pathological mechanism might be related to a dysfunction of the blood brain barrier [15]. On MRI sequences PVS are hyperintense on T2 as are the lacunes. The difference lies in the localization, the PVS have a perivascular distribution. On FLAIR sequences the hypointense lacunes are surrounded by a hyperintense rim [7]. On CT scan the PVS are non-detectable.

Treatment and management of cerebral small vessel disease

The acute management in the case of lacunar stroke consists in administering intravenous thrombolysis using the tissue plasminogen activator (r-PA) even if thrombus formation is not the leading pathological mechanism causing the stroke. The NINDS study showed that treatment with intravenous thrombolysis was not inferior in the case of lacunar stroke compared to non-lacunar strokes. Another questionable issue in using thrombolysis in lacunar stroke refers to the frequent association with other entities of SVD, mainly the cerebral microbleeds and the white matter hyperintensities. The possibility of increased hemorrhagic transformation associated to thrombolysis in these patients was studied in 2007 [17]. From a total of 242 patients that received r-PA, 5.8% developed a symptomatic cerebral hemorrhage in the presence of cerebral microbleeds, while in those without CMB 2.7% had a bleeding. Another meta-analysis on 790 subjects revealed the same results [18]. In conclusion clinical data suggests that benefits of r-PA administration exceed the risks even if used in patients that can possibly develop hemorrhagic complications. However, it should be cautiously used in patients with multiples CMB. The patients having more than 5 CMB have a 30% risk of hemorrhagic complication post r-PA compared those without or only with one CMB [19].

The other part of the small vessel disease management includes the control of the risk factors. Among them hypertension bears a striking importance. Is has been shown that a consistent and long course treatment of hypertension reduces the stroke risk by 28% [20]. The Secondary Prevention of Small Subcortical Stroke trial (SPS3) tested two groups one with a target blood pressure of 130-149mmHg and the other one <130mmHg. There was no significant reduction in recurrent lacunar stroke in the two groups. However, in the latter one the risk of developing a primary intracerebral hemorrhage was significantly reduced (63%) during a mean follow-up of 3.7 years. The PROGRESS-Perindopril Protection Against Recurrent Stroke Study [20] showed that an intensive lowering regime of hypertension can delay the progression of white matter hyperintensities associated to cognitive decline. However, this will not reverse de cognitive impairment in patients already symptomatic. So the key message is to target systolic blood pressure to <130mmHg; there are no data regarding the preferred antihypertensive treatment.

Other recommendations regarding modifiable risk factors refer to the lowering of the levels of LDL cholesterol. The SPARLC trial (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) has shown that atorvastatin had a similar efficacy in the lacunar stroke group compared to the large artery atherosclerosis group, even if there was a mild but still significant augmentation of cerebral bleeding [22]. The use of antiplatelets are considered beneficial in lacunar infarction as in non-lacunar infarction that are not of cardioembolic origin. Currently the use of

single regime antiplatelet is advised (aspirin or clopidogrel), the combination therapy is strongly opposed to as it increases significantly the risk of bleeding and death (2.1 risk of bleeding complications in the dual group compared to 1.1% in the aspirin only group, P<0.0010 SPS3 trial) [21]. In the VITATOPS MRI study, the high level of homocysteine lowered by treatment with B complex vitamins are thought to reduce the volume of WMH. Vitamin E administration is also thought to be beneficial in the attenuation of WMH, all that in subject that are not cognitively impaired [23].

Conclusion

Life expectancy continues to gradually increase along with health care improvement. However, this leads to a growing proportion of older adults with relative high incidence cerebrovascular diseases and the associated cognitive impairment. Therefore, the life quality decreases and there is an increasingly heavy burden on society for medical care. Cerebral small vessel disease should be regarded as a "whole -brain disease". Prevention and treatment of the modifiable risk factors should be the first step in the management of the disease. Small cerebral vessel disease is part of the cerebrovascular diseases and with its diverse expression at clinical and subclinical level it has drawn attention, knowing that its mechanisms are still largely unknown. In this way the target therapies are yet to be used and the current guidelines offer only advice on how to manage the known cardiovascular risk factors.

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