Cerebral small vessel disease: A review

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Abstract

Cerebral small vessel disease (CSVD) is the most common, chronic and progressive vascular disease. The changes affect arterioles, capillaries and small veins supplying the white matter and deep structures of the brain. It is the most common incidental finding on brain scans, especially in people over 80 years of age. Magnetic resonance imaging (MRI) plays a key role in the diagnosis of CSVD. The nomenclature and radiological phenotypes of CSVD were published in 2013 based on the unified position of the so-called Centres of Excellence in Neurodegeneration. The disease is characterized by a diverse clinical and radiological picture. It is primarily responsible for stroke incidents, gait disturbances, depression, cognitive impairment, and dementia in the elderly. The CSVD contributes to about 20% of strokes, including 25% of ischemic strokes and 45% of dementias. Common causes of CSVD include arteriosclerosis, cerebral amyloid angiopathy (CAA), genetic small vessel angiopathy, inflammation and immune-mediated small vessel diseases, and venous collagenosis. There is no causal treatment and management is mainly based on combating known risk factors for cardiovascular disease (CVD).

Key words: amyloidosis, cerebral small vessel disease, white matter hyperintensities, lacunar infarcts, microbleeds

Introduction

Cerebral small vessel disease (CSVD) is a chronic, progressive disorder of arterioles, capillaries and small veins supplying the white matter and deep structures of gray matter; it is characterized by a diverse clinical picture and specific changes in neuroimaging and neuropathological investigations of the brain.[1,2] The changes affect small vessels, 50–400 um in diameter, and lead to damage of the white matter in subcortical brain structures. The CSVD is a dynamic disease process not limited to cerebral vessels but affecting the whole body. It is clinically heterogeneous and constitutes the most common cerebrovascular disease (CVD).[1] The CSVD is responsible for about 20% of all strokes, including 25% of ischemic strokes and 45% of vascular dementias.[2,3]

The nomenclature and radiological phenotypes of CSVD were published in 2013 based on the unified position of the so-called Centres of Excellence in Neurodegeneration.[4] The STRIVE protocol (STandards for ReportIng Vascular changes on nEuroimaging) sets diagnostic standards and assesses individual radiological phenotypes of CSVD and their clinical consequences (Table 1).[4] The CSVD is typically recognized on both brain magnetic resonance imaging (MRI) and computed tomography (CT) scans, but MRI has greater sensitivity and specificity. A reliable radiological assessment is only possible with at least 1.5 T MRI including the following sequences: FLAIR (fluid-attenuated inversion recovery), T2* (gradient recalled echo T2*-weighted images) or SWI (susceptibility-weighted imaging), T1, and DWI (diffusion-weighted imaging). Figures 1–5 present MRI findings of CSVD.

Epidemiology

The CSVD occurs 6–10 times more often than stroke.[5] Silent brain infarcts are the most frequently identified incidental findings on brain scans, especially in older people. As many as 25% of people over 80 years of age have had ≥1 silent stroke.[6,7] It has been estimated that for every symptomatic stroke, there are about 10 silent brain changes.[8] The prevalence of CSVD increases with age, with no significant sex differences.[9] Prevalence of white matter
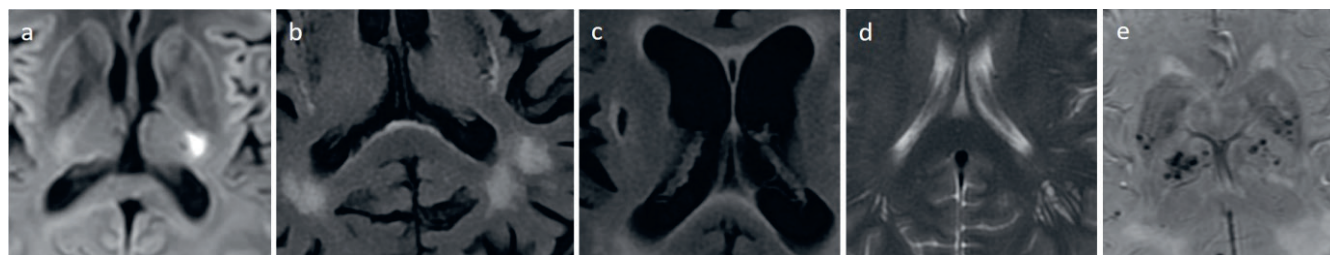

Fig. 1. A. Acute lacunar infarction on DWI; B. White matter hyperintensities (WMHs) on the FLAIR image; C. Old lacunar infarction seen on the FLAIR image as a dark fluid-filled cavity surrounded by a hyperintense rim; D. Enlarged perivascular spaces on a T2-weighted image; E. Multiple microbleeds bilaterally within basal ganglia and thalami

Table 1. Types of cerebral small vessel disease (CSVD) according to STRIVE after Wardlaw et al.[4]

Type of CSVD	Description
Recent subcortical infarcts	fresh, small (less than 20 mm in axial section) ischemic lesions with respect to perforating arteries, whose radiological features or clinical signs and symptoms indicate their formation in the few weeks before the test; best seen in the DWI sequence; these changes are hypointense in the T1 sequence, hyperintense in the T2 and FLAIR sequences, and isointense in the GRE-T2 sequence
Lacunae of presumed vascular origin	round or oval subcortical lesions 3–15 mm in diameter, filled with fluid, with cerebrospinal fluid-like signal; these lacunae correspond to history of acute cerebral infarction or bleeding from the area of vascularization of the perforating artery; the lesions are characterized by a distinctive image in the FLAIR examination; each lesion is a cavity filled with cerebrospinal fluid and surrounded by a hyperintense rim; they are isointense in the DWI sequence, hypointense in the FLAIR and T1 sequences, and hyperintense in the T2 sequence
White matter hyperintensities	symmetric regardless of size; hyperintense in the T2, FLAIR and GRE-T2 (gradient-echo T2) sequences; isointense in DWI; and hypointense in T1
Widened perivascular spaces (Virchow–Robin perivascular spaces)	mostly seen in basal ganglia <2 mm in size; they usually accompany hyperintense lesions of the white matter and lacunar condition but not brain atrophy; the lesions are hyperintense in T2 sequences, hypointense in FLAIR and T1 sequences, and isointense in the GRE-T2 sequence
Cerebral microbleeds (CMBs)	small, homogeneous lesions <10 mm in diameter, characterized by the 'blooming effect'; the lesions are best seen in the gradient-echo T2 sequence (hypointense lesions); in the T2, T1 and FLAIR sequences, they are isointense; microbleeds correspond to hemosiderin-loaded macrophages that are present in the perivascular space
Brain atrophy	brain atrophy in the context of CSVD is considered only when the patient has not suffered a stroke or head injury

DWI – diffuse-weighted imaging; FLAIR – fluid-attenuated inversion recovery.
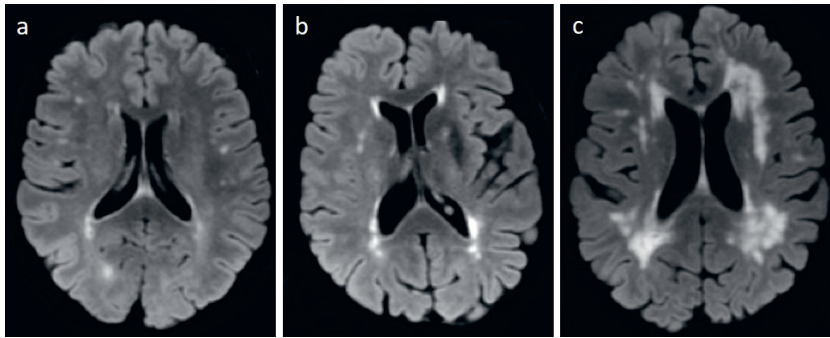
Fig. 2. Grading of white matter hyperintensities (WMHs) on the Fazekas scale

A. Grade 1, punctate foci; B. Grade 2, early confluent lesions; C. Grade 3, large confluent areas.
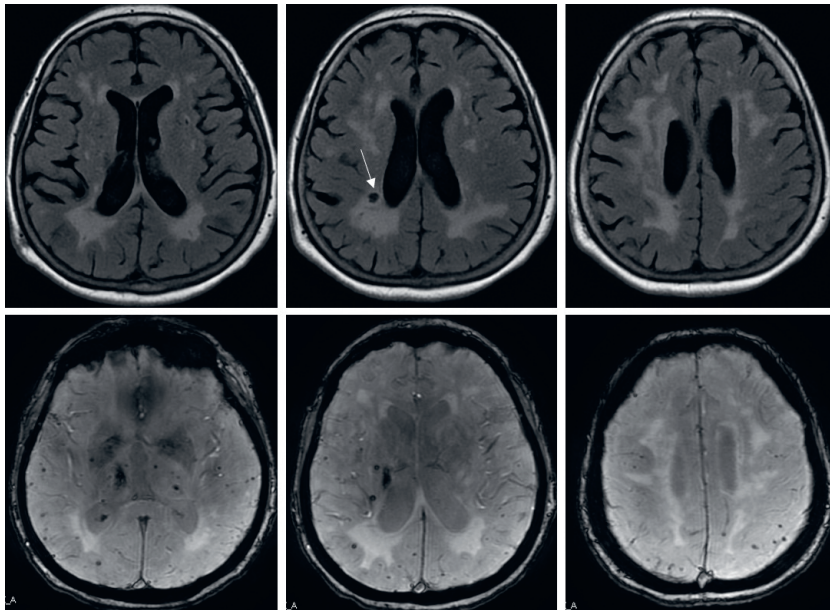

Fig. 3. Hypertensive encephalopathy

FLAIR images (upper row) show diffuse white matter hyperintensities in both hemispheres with old lacunar infarction (arrow). Multiple foci of microbleeds within cortex and deep brain structures on SWI (lower row).
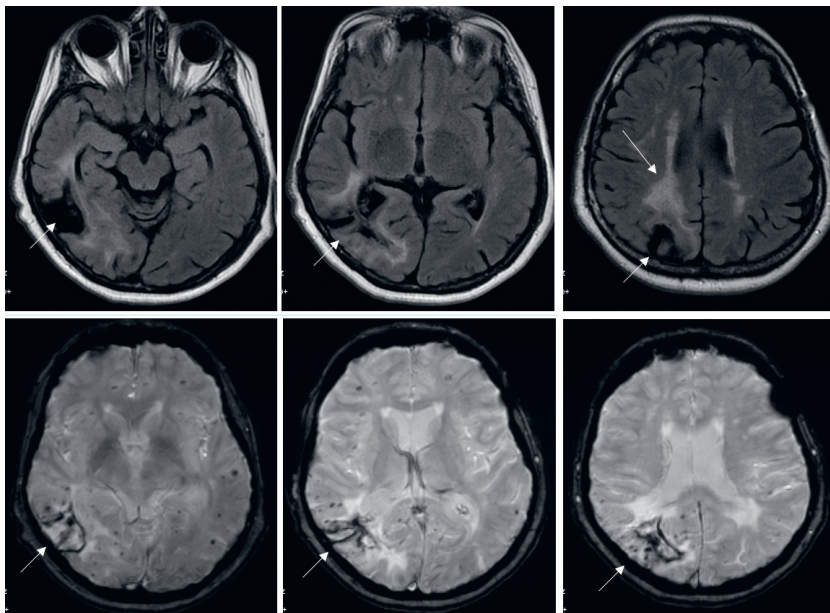
Fig. 4. Cerebral amyloid angiopathy (CAA)

FLAIR images (upper row) show diffuse white matter hyperintensities (long arrow) and focus of brain malacia due to cortical hematoma (short arrows). Multiple foci of microbleeds with cortical distribution and hemosiderin deposits within old cortical hematoma on SWI (lower row, short arrows).

hyperintensities increases from about 5% for people aged 50 years to nearly 100% for people aged 90 years.[10] Also, the prevalence of cerebral microbleeds increases from 6.5% for people aged 45–50 years to about 36% for people aged 80–89 years.[11] There is a noticeable population variability: CSVD lesions are more common in the Chinese population, where lacunar strokes account for 46% of ischemic episodes.[12]

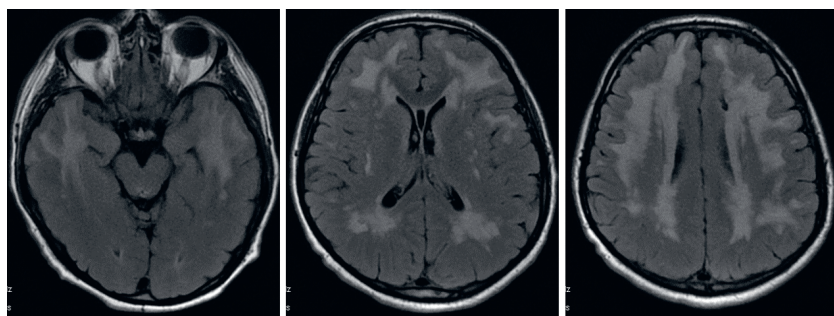Fig. 5. CADASIL. A 38-year-old patient with cognitive impairment. Diffuse white matter hyperintensities in both hemispheres localized typically also within temporal lobes and external capsules

Clinical picture

The CSVD may be asymptomatic for many years, manifesting with accidentally detected changes in radiological examinations.[13–15] In its acute form, CSVD progresses as lacunar stroke or a focus of intracerebral hemorrhage.[16] According to the anatomopathological definition by Donnan, lacunar stroke covers a small area of ischemia formed as a result of microemboli of perforating arterioles in their proximal sections. In most cases, the changes concern lenticulostriate branches extending from the middle and anterior cerebral arteries, thalamoperforating branches extending from the posterior cerebral artery, and paramedian branches extending from the basilar artery and affect the basal ganglia, thalamus, pons, or white matter.[17] According to the classification of the Oxfordshire Community Stroke Project, lacunar stroke proceeds in the form of 1 of 5 syndromes.[18] In most cases (approx. 50–70%), it begins as pure motor stroke (PMS) – isolated, purely motor paresis or paralysis. Other clinical manifestations of this stroke include pure sensory stroke (PSS), sensorimotor stroke (SMS), ataxic hemiparesis (AH), and dysarthria-clumsy hand syndrome (DCHS).[18–20] Cerebral hemorrhage in the course of CSVD is located in deep brain structures and its signs and symptoms depend on the location.

Chronic CSVD is mainly associated with progressive cognitive impairment (from mild cognitive impairment to subcortical dementia).[21–24] Damage to the white matter of the brain leads to extrapyramidal syndrome with dominant posture and gait disorders, early and symmetrical involvement of the lower extremities, slight tremor of the limbs, pseudobulbar syndrome, and sphincter dysfunctions (mainly urgent tenesmus and urinary incontinence), as well as symptoms of depression.[21,25,26] The symptoms progress gradually, leading to loss of independence; the patient withdraws from social life. The risk of death increases, mainly due to falls and accompanying injuries.[27]

Etiology

In most cases, CSVD is sporadic; its occurrence is associated mainly with age and commonly known risk factors for vascular diseases, mainly hypertension and diabetes mellitus.[28] Other risk factors include current and former smoking, obstructive sleep apnea, chronic kidney disease, and branch atheromatous disease.[29]

Cerebral amyloid angiopathy (CAA), a form of CSVD, is the 2nd most common cause of cerebral hemorrhage, after hypertension.[30,31] It is associated with recurrent cerebral hemorrhage, coexisting ischemic strokes and cognitive impairments. The CAA may be sporadic or genetically conditioned; it involves build-up of β-amyloid deposits in the media and adventitia of small- and medium-caliber cerebral arterial vessels and in the venous vessels of the cerebral cortex and pia mater. The familial form of CAA occurs less frequently and involves mutations in different genes on autosomal dominant chromosome 20. The CAA lesions account for about 30% of spontaneous hemorrhages and 5–20% of all hemorrhages in the elderly. The occurrence of CAA type lesions increases with age; they affect 10–40% of older people and 80% of patients with Alzheimer's disease.[32,33] Radiologically, CAA leads to various types of abnormal findings, including microbleed, subarachnoid hemorrhage, superficial siderosis, microinfarction, reversible edema, and irreversible leukoaraiosis (Fig. 4).

In young people, changes in cerebral vessels are determined by genetic factors, with several single-gene disorders causing CSVD. Most often, these are systemic diseases associated with various neurological abnormalities, mainly ischemic or hemorrhagic stroke.[34,35] Uncommon and rare forms of CSVD are presented in Table 2.[2,3]

The most common genetically determined disease characterized by involvement of small vessels is cerebral autosomal-dominant arteriopathy with stroke and ischemic leukoencephalopathy (CADASIL), described for the first time by Van Bogaert in 1955 as a familial form of Binswanger's disease. The CADASIL affects young people and is autosomal dominant due to mutations in the *NOTCH* gene on chromosome 19. It is characterized by systemic signs and symptoms with accompanying neurological abnormalities, most often recurrent ischemic stroke, epilepsy, dementia, and psychiatric disorders.[36–39] Neuroimaging shows 3 types of lesions in patients with CADASIL: white matter hyperintensities; lacunar infarcts in the semioval center, thalamus, basal ganglia, and pons; and cerebral microbleeds (Fig. 5).

Table 2. Uncommon and rare forms of cerebral small vessel disease (CSVD)

Genetic conditions causing CSVD: – cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL); – CARASIL: cerebral autosomal recessive arteriopathy subcortical infarcts and leukoencephalopathy (CARASIL); – mitochondrial encephalomyopathy lactic acidosis and stroke-like episodes (MELAS); – Fabry disease; – Type IV collagen mutation-related CSVD (COL4A1/COLA2); – frameshift mutations in *TREX1* gene: retinal vasculopathy with cerebral leukoencephalopathy; – hereditary cerebral hemorrhage with amyloidosis (HCHWA) (Dutch-, Italian-, and Flemish-APP mutations; Icelandic-like mutation of cystatin C).
Immune-mediated CSVD: – primary vasculitis; – secondary central nervous system (CNS) vasculitis; – systemic lupus erythematosus; – Sjögren's syndrome-associated vasculitis; – Behçet's vasculitis.
Infection-mediated CSVD: – meningovascular neurosyphilis; – viral: varicella-zoster virus, cytomegalovirus, hepatitis B and C, human immunodeficiency virus (HIV); – fungi; – schistosomiasis; – cerebral malaria.

A similar condition is cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), more common in Asian regions. It is inherited in an autosomal recessive manner and is associated with mutation in the *HTRA1* gene, located on chromosome 10q26. Abnormalities in the form of recurrent lacunar strokes appear at the age of 20–30 years. In addition, cognitive impairment, gait disturbances, degenerative spinal pain syndrome, and premature baldness are observed.[39]

Changes with respect to *COL4A1* and *COL4A2* genes responsible for the synthesis of type IV collagen alpha chains and associated with microangiopathies may be sporadic or genetically determined.[40] Type IV collagen acts as a scaffold for the cell; it is a component of the basement membrane and extracellular matrix. Abnormal collagen IV structure is associated with fragility of blood vessels and a diverse clinical picture. The spectrum of type IV collagen disorders includes autosomal dominant type I porencephaly; CSVD with hemorrhage; cerebral microangiopathy with Axenfeld–Rieger anomaly; and hereditary angiopathy with nephropathy, aneurysms and muscle cramps (HANAC).[41,42]

Mutations in the *TREX-1* gene may result in Aicardi–Goutières syndrome, systemic and cutaneous lupus erythematosus, and retinal vasculopathy with cerebral leukodystrophy (RVCL). The latter manifests around the age of 40 years and is associated with ischemic strokes, transient cerebral ischemia and psychiatric symptoms. It shows characteristic ocular signs: retinal hemorrhages, macular atrophy and capillary microaneurysms. Additional signs and symptoms may involve other organs (liver, kidneys).[43]

One of the most common mitochondrial diseases – mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS) – is also associated with involvement of small vessels. About 80% of all cases occur in childhood; the clinical picture is dominated by stroke-like signs and symptoms, increasing dementia, migraine headaches, myopathy, and lactic acidosis.[44] In the case of Fabry disease, which is an X-linked inherited disorder of glycosphingolipid metabolism, strokes are observed. The disease is associated with mutation of the *GLA* gene, which is responsible for the activity of lysosomal α-galactosidase A. As a result, trihexosylceramide deposits accumulate in endothelial and smooth muscle cells, ganglion cells, kidneys, eyes, and other tissues. This involves a number of cardiovascular and renal complications at an early age. Patients have symptoms of painful peripheral neuropathy, dysfunction of the autonomic nervous system, and corneal disorders. The disease is associated with frequent strokes and myocardial infarctions. Fabry disease is responsible for 0.5% of vascular events at a young age. Ischemic strokes occur in 76%, transient ischemic attacks in 16% and hemorrhagic strokes in 8% of the cases. Involvement of cerebral small vessels occurs even in asymptomatic individuals; there are characteristic lesions of the pulvinar and frontal and parietal lobes.[45–47]

Pathomechanism

The etiopathogenesis of CSVD takes into account several mechanisms. Pathological processes associated mainly with hypertension in the vascular wall lead to development of lipohyalinosis and fibrohyalinosis; there is a proliferation of connective tissue fibers and dilatation of perivascular space, which causes loss of contractibility and thus vascular sclerosis. In addition, vascular endothelial dysfunction occurs due to blood–brain barrier impairment. The 2nd most common cause of damage to small perforating vessels is CAA. The changes lead to hypoperfusion or vascular flow disorders associated with abnormal self-regulation and impaired vascular wall permeability, and result in multifocal stroke lesions. An important role in the pathogenesis is also played by inflammatory

processes due to the presence of increased inflammatory parameters (interleukin 6, C-reactive protein (CRP)) in cerebrospinal fluid and blood.[2,15]

Prognosis

The CSVD remains clinically silent for a long time and does not affect the condition of the patients. Screening the asymptomatic general population with MRI to detect silent CVD is not recommended. However, changes in the vessels are adverse in long-term evaluation. Asymptomatic, radiologically enhanced small vessel disease diagnosed in the acute period of stroke is associated with a worse prognosis.[48] It was found that the presence of silent cerebral ischemic lesions causes a threefold increase of future stroke, regardless of other risk factors; the risk increases in the case of a larger number of lesions.[49,50] Most incident strokes are ischemic (81–89%), not hemorrhagic (11–19%). In a study by Poggesi et al., CSVD was associated with a worse prognosis. The 12-year prognosis after lacunar stroke is significantly worse than in strokes with different etiologies (7.9 years compared to 4.3 years).[51]

The presence of lesions in the white matter is associated with the risk of stroke, dementia or death, which increased during the five-year follow-up in the Framingham Heart Study. There is a known correlation between the occurrence of clinically silent lesions and cognitive impairment. tHE CSVD on its own or with Alzheimer's disease is the most common cause of cognitive dysfunction and dementia.[52] The risk of dementia increases twofold in patients with silent brain infarction.[49] The patients perform worse in neuropsychological tests if the lesions are located in the thalamus. Lesions outside the thalamus are related to deterioration of psychomotor functions.[22,53] In post-stroke epilepsy, about 11% of patients had lacunar infarcts. Studies suggest involvement of small vessel pathology in epileptogenesis and a higher incidence of temporal lobe epilepsy in the case of comorbid CSVD lesions.[54–56] Intensified retinal vascular remodeling also correlates with a higher incidence of lacunar stroke.[57]

A decrease in the glomerular filtration rate is associated with more frequent presence of silent ischemic lesions regardless of hypertension.[58] At the same time, Oksala et al. showed that a reduction of the estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 is an independent risk factor for increased damage to the white matter of the brain.[59]

Treatment

At the moment, there is no specific treatment available for genetic forms of CSVD. Only for Fabry disease is there a replacement therapy based on intravenously administered α-galactosidase A, which is taken up by cells and tissues by the mannose-6-phosphate receptor pathway and delivered to lysosomes.[3] There are no established therapeutic strategies for either preventing or treating sporadic CSVD. Potential prophylactic and treatment strategies might include those that target brain microvascular endothelium and the blood–brain barrier, microvascular function, and neuroinflammation. Because CSVD and ischemic stroke are presumed to share the same pathology, the diagnostic and therapeutic approaches should be the same. For all patients with CSVD, we should assess common vascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and smoking.[60] The treatment is based primarily on the fight against vascular risk factors and primary and secondary prevention of vascular events. One of the most important modifiable risk factors is hypertension. Non-pharmacological treatment is also important and includes diet, sodium restriction, increased physical activity, and abstaining from smoking. Genetic testing should be considered in young people with extensive CSVD in the absence of sufficient conventional vascular risk factors. A closer understanding of the mechanisms leading to damage of small blood vessels may be associated with new therapeutic approaches.

Conclusions

The CSVD is a very common problem in older people. It is an important clinical problem due to its frequent occurrence and serious clinical consequences. The underlying mechanisms of CSVD are not known in detail. Blood pressure is the most important modifiable risk factor. The presence of genetic CSVD should be considered in young people without typical risk factors for vascular disease.

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