Clinical and magnetic resonance observations in cerebral small-vessel disease
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Brief historical review
Cerebral small-vessel disease

Hypothesis and controversies

Cerebral small-vessel disease is a term used to denounce specific pathologic alterations of the small perforating arteries in the brain with a diameter of 40-800 μm. These arteries are usually divided into three groups: the anterior perforating arteries, the posterior perforating arteries and the perforating branches of the basilar artery to the brainstem. These vascular changes are thought to cause lacunar infarcts (with specific clinical lacunar syndromes), white matter abnormalities and intracerebral hemorrhages. The pathologic changes are variously called hyalinosis, lipohyalinosis, fibrinoid necrosis and angionecrosis. Some authors stressed the existence of two forms of vessel wall changes: the fibrinoid form of hyalin (fibrinoid necrosis, lipohyalinosis, or segmental disorganization), associated with hypertension and symptomatic disease of the brain, and the collagenous form of hyalin (hyalinosis), a common change in the elderly and usually asymptomatic. In addition, small-vessel disease probably causes the formation of microaneurysms, called Charcot-Bouchard aneurysms, that are associated with intracerebral hemorrhage. Many aspects of the concept of cerebral small-vessel disease are still controversial. The idea that small-vessel disease causes lacunar infarcts with specific lacunar syndromes (the “lacunar hypothesis”, see below) has been subject of vivid discussions. The Charcot-Bouchard aneurysms have been regarded, at least partially, as artifacts of the pathological specimens.

Terminology and confusion

Confusion concerning the terminology starts as soon as pathologists, clinicians and radiologists discuss cerebral small-vessel disease. The pathologist means a structural alteration of the small penetrating arteries and arterioles of the brain in which smooth muscle tissue in the tunica media becomes hypertrophic and is subsequently replaced by extracellular matrix and plasma proteins. It is a normal phenomenon in the elderly, but is believed to be promoted by hypertension and diabetes mellitus. The initial process that eventually causes the structural changes, may be
enhanced small-vessel wall permeability, that can be detected as mural
deposition of serum proteins in the areas of blood-brain barrier break-
down.\textsuperscript{16,18-21}

The clinician uses the term “cerebral small-vessel disease” mainly as a
synonym for lacunar syndromes and cerebral white matter abnormalities
(like Binswangers disease). Clinicians assume, that lacunar syndromes
are mostly caused by lacunar infarcts due to microatheroma at the orifice
of a single perforating artery. Another premise is that white matter lesions
are caused by relative ischemia due to elongation of the small penetrating
arteries and thickening of their walls in the white matter with subsequent
loss of myelin.\textsuperscript{4}

The radiologist concludes to the presence of small-vessel disease as an
explanation of small subcortical lesions of less than 2 cm on CT-scan or
MRI (lacunes) and of hemispheric white matter hypodense lesions (on CT-
scan) or hyperintense lesions (on T2 weighted-MRI). Whether these
specialists all have the same disease concept in mind, is to be questioned.
In this introduction I will review in a historical perspective the most important
aspects of the concept of cerebral small-vessel disease and the controversies
associated with it.
Lacunar infarcts

The lacunar hypothesis consists of two parts. The first part is that distinct clinical syndromes are associated with small deep cerebral infarcts (lacunes). The second part is that these small infarcts are the result of an occlusion of a single perforating artery by characteristic vascular lesions. Initially it was believed to be a hypertensive disease.\textsuperscript{23,24}

History

The first descriptions of lacunes are attributed to French pathologists in the 19th century. Dechambre first coined the term “lacune” in 1838 to define small cavities caused by the resorption of small deep cerebral softenings.\textsuperscript{25,26} Several years earlier, however, Cruveilhier described small brain softenings that he called “petit foyers pisiformes” (small pea-like foci), that can be regarded as lacunes, although he did not use that term.\textsuperscript{26,27} Durand-Fardel was the first who realized that there were several types of lacunes. In his treatise on brain softenings in 1843 he distinguished brain softenings (infarcts) and perivascular dilatation around blood vessels, which he called “l’état criblé”.\textsuperscript{26,28} Proust, in his thesis of 1866, further divided the causes of lacunes as infarcts, hemorrhages, or sometimes just “disorganisation”.\textsuperscript{23,29} Subsequently, other authors recognized lacunes as a result of a type of softening “e causa ignota”, a hemorrhagic lacunar scar, or edema from uremia.\textsuperscript{23}

Pierre Marie described the lacunes more precisely in a monumental work and regarded them as the result of small infarcts, hemorrhages or a destruction of the tissue around a vessel.\textsuperscript{30} In his opinion lacunes were caused by thrombosis or decrease of blood flow due to arteriosclerosis. His influence on the (mostly French) researchers was considerable. Many authors, who studied lacunes in the next years, followed his ideas.\textsuperscript{26,31} The second part of the lacunar hypothesis was born.

The first part of the lacunar hypothesis, that is the association of lacunes with distinct clinical syndromes, was formulated later. This association
was based upon clinico-pathologic correlations. Bourneville reported a patient with hemianesthesia, who had a lacune in the corona radiata. Comte observed that lacunar infarcts often corresponded to a mild hemiplegia. Marie and Ferrand, however, were the first to describe the exact anatomical locations of the lesions and the corresponding clinical syndromes. Foix and Hillemand described specific syndromes due to small pontine infarctions. Although Durand-Fardel initially linked his "état criblé" to dementia, there is still no definite proof of the association of enlarged perivascular spaces with any clinical syndrome. The "état lacunaire" of Marie has been associated with slowly progressive neuro-logical deterioration consisting of dementia, pseudobulbar palsy, in-continence and a gait disorder, like the "marche à petit pas".

In the 1960s a new landmark article appeared. Fisher carefully described lacunes in 114 of 1042 brain autopsies. Of his lacunar cases 111 were hypertensive. Later, he carefully analysed brain autopsies of 4, and subsequently of 10 hypertensive patients by examining 1000-4000 sections from each brain. He found three distinct vascular lesions, which he considered specific for hypertension: micro-atheroma, lipohyalinosis, and micro-aneurysms. Afterwards, in many case reports and series Fisher studied the cerebral small deep infarcts systematically and correlated them with specific lacunar syndromes, which later added up to more than 20.

Controversies and confusion

Since the first descriptions of lacunes a number of controversies emerged, partially because the knowledge of lacunes stems from relatively few autopsied cases. Postmortem examination is rare because of the low case-fatality of these lacunar strokes. Three central issues emerge from the vast literature about lacunes:

1. Are lacunar syndromes always caused by lacunar infarcts?

Fisher reported more than 20 lacunar syndromes, but most of them are uncommon. The four most prevalent syndromes are: pure motor stroke, pure sensory stroke, ataxic hemiparesis (including dysarthria-clumsy hand syndrome and homolateral ataxia with crural paresis) and
pure sensorimotor stroke. Not all patients presenting with these syndromes had a lacunar infarct. Cases have been reported with cortical infarcts, small hemorrhages, subdural hemorrhages, or even tumors.\textsuperscript{35,40} However, it may be assumed, that most lacunar syndromes, if assessed early, are caused by lacunar infarcts.\textsuperscript{41,42}

2. Are there ischemic, hemorrhagic or other causes of lacunes?

Confusion arose about the cause of these small cerebral cavities.\textsuperscript{7,24} An occlusion of a small cerebral artery, remnants of a minor intracerebral hemorrhage, and perivascular dilatation (not associated with infarct), all may result in small subcortical cavities.\textsuperscript{23,30,43} Poirier et al. proposed a classification for the lacunes: type I for areas of cerebral infarcts, type II for cystic scars that are the residuals of small hemorrhages, and type III for areas of perivascular dilatation not associated with infarction.\textsuperscript{31,44} Although this classification seems plausible and sensible, it has not gained wide acceptance in the pathological literature. What Durand-Fardel described as “état criblé” could be called multiple type III lacunes in the classification of Poirier.\textsuperscript{24,28} Many authors postulated a mechanical cause for this finding.\textsuperscript{43,45} In contrast, “l’état lacunaire,” as described by Marie, can be regarded as multiple type I lacunes.\textsuperscript{24,30}

The advent of CT-scan and later of MRI techniques enabled more detailed studies of brain tissue in living individuals, but did not decrease the confusion of what to call lacunar infarcts, old small intracerebral hemorrhages, or widened perivascular spaces. Although the issue can not be resolved definitely without postmortem investigation, new MRI techniques may distinguish hemosiderin deposits or perivascular spaces from infarcts.\textsuperscript{46-49}

3. What is the contribution of vascular risk factors, especially hypertension, to the lacunar lesions and to microangiopathy?

The small infarcts (type I lacunes) may be caused by three conditions, that perhaps are associated with different profiles of risk factors. First, an occlusion near or at the origin of a small cerebral arteriole due to a small (micro)atheroma has been shown to cause a lacunar infarct.\textsuperscript{6} Such
microatheroma consists of lipid containing foam cells, resembling the atherosclerotic plaques in large arteries. Fisher found them in arteries with a diameter of about 400 μm. An occlusion was mostly symptomatic. These microatheromas were usually located at a point of a sharp change in direction of the artery or at the origin of a branch, which suggests an influence of mechanical forces on the deposition of atheroma, as has been observed in large arteries.

Risk factors for these microatheromas are probably similar to those of large-vessel atheroma. Second, Fisher described a focal (up to about 2 mm in length) disorganization of the vessel walls of small arteries (60-200 μm) with widening of the external diameter up to 2 or 3 times the normal values, but with narrowing or occlusion of the lumen, resulting in lacunar infarcts. Several names are used for this phenomenon: fibrinoid necrosis, hyalinosis, and angionecrosis. Fisher later called it “lipohyalinosis”, but others preferred the term “fibrinoid necrosis”. Lipohyalinosis occurs mostly in vessels with a diameter of about 200 μm. An occlusion of the artery is usually asymptomatic. The occlusion in the narrowed vessels is caused by fibrous connective tissue or fibrinoid. The nature of this fibrinoid was not clear. A role for platelets was not found, although Fisher occasionally described “pale pink granular material resembling a mass of platelets”. These lesions were thought to be specifically related to hypertension. Fisher initially stressed the importance of hypertension, since 111 of his 114 initial patients with lacunes had hypertension. However, later studies showed that a substantial part of patients with lacunar infarcts do not have hypertension. Boiten et al. proposed, that patients with only one or few lacunes may have microatheroma and patients with multiple lacunes may have lipohyalinosis. Risk profiles may be different between the two groups, in the sense that patients with single or few lacunes have the usual risk factors for atherosclerosis (smoking, hypercholesterolemia, and hypertension), while patients with multiple lacunes more frequently have only hypertension.

Third, because some of the arteries were normal, Fisher also suggested embolism as a cause of lacunar infarct, but probably an uncommon one. Others corroborated these findings. In a recent autopsy study,
increased vascular permeability was suggested as a cause of part of the lacunes.\textsuperscript{17} The authors found lacunes in patients with normal blood pressure, who all had an extracerebral disease that is associated with increased vessel wall permeability, like liver and kidney diseases. Further studies are needed to confirm these findings.
Chapter I

White matter lesions

History

Binswanger was the first in 1894 to describe a clinico-pathologic relation between dementia and macroscopical cerebral white matter atrophy. This “subcortical arteriosclerotic encephalopathy” was a slowly progressive dementia, usually with intercurrent strokes, beginning in hypertensive patients of about 50 to 70 years. Binswanger did not study the brain microscopically. In 1902 Alzheimer published a microscopic case study of severe demyelination of the cerebral hemispheres in association with lacunar infarcts and arteriolosclerosis. Later, Nissl corroborated these findings. Olszewsky reviewed these cases and added new ones. With his work, the outline of the pathological and clinical entity of Binswanger’s disease began to take shape. Caplan and Schoene gave in 1978 the definite characteristics of the clinical and pathological features of the disease. The role of arteriolosclerosis due to hypertension was considered most important. The incidence was thought to be low, but this may be caused by the scarcity of pathologic examinations. Until 1987 only about 50 cases were described pathologically.

After the advent of the CT-scan, lesions of the cerebral white matter were seen more frequently and interest grew again. In his paper of 1978 Caplan described 3 cases (he later mentioned only 2) of whom a CT-scan was made. However, he did not describe white matter hypodensities, but only hydrocephalus. Rosenberg reported a correlation between the pathologic and the radiologic findings. Goto reported larger series. Hachinski et al. coined the term “leukoaraiosis” to indicate diffuse periventricular hypodense lesions on CT-scan of undetermined origin (the Greek “leuko” means white and “araiosis” rarefaction).

The next important advance was the introduction of the MRI, which shows white matter lesions even more frequently. Diffuse periventricular rims, caps around the horns of the lateral ventricles, focal regular or irregular periventricular lesions extending into the white matter, and focal lesions in the corona radiata, centrum semiovale and subcortical...
white matter apart from the periventricular lesions, were described.\textsuperscript{62} It was clear that many lesions were not associated with symptoms. Periventricular hyperintensities on T2-weighted MRI limited to small caps and pencil-thin linings were found to be asymptomatic.\textsuperscript{70,71} Periventricular lesions extending to the adjacent white matter and focal white matter lesions were considered signs of Binswanger’s disease.\textsuperscript{62} These lesions are thought to be associated with cognitive decline and disequilibrium.\textsuperscript{72-74} However, many other conditions may have a similar appearance on MRI, i.e. white matter edema, multiple sclerosis, gliomatosis cerebri, progressive multifocal leukoencephalopathy, subcortical infarcts, radiation-related white matter damage, various toxic and metabolic disorders, and leukodystrophies.\textsuperscript{62} In recent years other vascular disorders associated with small-artery lesions were identified as causes of white matter lesions. Cerebral amyloid angiopathy leads to intracerebral hemorrhages, small cortical infarcts and white matter lesions.\textsuperscript{75,76} The cerebral small arteries are widespread infiltrated with amyloid, usually limited to the cortex, pia, and subcortical areas adjacent to the cortex.\textsuperscript{62,75} “Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy” (CADASIL) is an autosomal dominant disorder with a defective Notch3 gene located at chromosome 19, characterized by extensive white matter disease, subcortical infarcts, migraine-like headaches and dementia.\textsuperscript{77-80} Pathologically, small arteries in the brain, skin and peripheral nerves show granular eosinophilic deposits in the media with narrowing of the lumen.\textsuperscript{81} Less common diseases are also reported to cause white matter changes, like pseudoxanthoma elasticum,\textsuperscript{82} the antiphospholipid antibody syndrome,\textsuperscript{62} and Fabry’s disease.\textsuperscript{83-85}

Controversies and confusion

Postmortem examination is also rare in patients with white matter lesions, because of the low case-fatality. As mentioned above these lesions are frequently found on CT-scans and MRI. Most authors use the term “leukoaraiosis” for periventricular abnormalities on both CT and MRI techniques, but some prefer to reserve leukoaraiosis only for CT scans findings.\textsuperscript{86} In this thesis we use the more descriptive term “white matter lesions” (WML) for white matter abnormalities seen on both CT-scan and MRI.
1. Does Binswanger’s disease exist?

Binswanger himself unintentionally caused the controversy that would surround his name during decades. His report was extensive, but imprecise. In addition, despite of his promise to do so, he never reported on the microscopical findings in his patients. Much debate arose whether this disorder is appropriately attributed to and named after Binswanger. Nevertheless, he was the first to separate the arteriosclerotic vascular dementias from the infectious dementias caused by syphilis. Nowadays, some experts do not consider Binswanger’s disease as a specific disease entity. The condition described by Binswanger was probably a chronic ischemic disorder which can have many causes. Instead of this eponym more descriptive terms would be preferable. Unfortunately, the alternative terms that have been proposed (leukoaraiosis, subcortical/periventricular leukoencephalopathy, white matter lesions/changes/disease), have in turn led to new confusion of tongues.

2. Are WML due to ischemia?

The special anatomy of the blood supply of the cerebral white matter is assumed to be the reason for specific vulnerability of these areas to (chronic) ischemia. From the brain surface, long penetrating arteries originating from the pial network run perpendicularly to the cortex down along the course of the myelinated fibers. They are usually 20-50 mm long and have a diameter of 100-200 μm. These arteries do not arborate, but give off short perpendicular branches, that each provide a small cylindrically shaped brain area of blood. From the walls of the lateral ventricles, ventriculofugal vessels arise from the chorioidal arteries or the rami striati. They are 15 mm long and run upwards to the penetrating arteries. No (or only very few) anastomoses are made with the pial system. This pattern gives rise to an arterial borderzone, that is susceptible to decreases in cerebral blood flow from many causes. Small artery changes due to hypertension (hyalinosis) or other causes of small artery disease lead to thickening of the walls, elongation and tortuosity of the penetrating vessels, resulting in hypoperfusion and ischemic rarefaction of the white matter.
fibres are spared, which can be explained by the abovementioned anatomy. Hypoperfusion in these areas is confirmed in blood flow studies in hypertensive patients using SPECT and PET techniques. Experimental work in animals also supports this hypothesis.

3. Is hypertension the main cause of WML?
In the first descriptions of WML almost all patients had hypertension, which suggests a causal relationship. Later epidemiological studies found that age is the most important risk factor, but hypertension is still the most frequently reported treatable risk factor. Diabetes mellitus and cardiac disease have been reported as additional risk factors. However, some patients have WML without hypertension and many elderly patients do not have WML, so there must be other factors that predispose to these lesions. Several authors reported fluctuations in diurnal blood pressure to be responsible for WML. Others found genetic factors as apolipoprotein E polymorphism in association with WML. Nevertheless, hypertension remains the main risk factor that is treatable.
Chapter I

Intracerebral hemorrhage

History

Hippocrates (460 - 370 BC) was probably the first who described a patient with an intracerebral hemorrhage, when he narrated of a woman in the third month of pregnancy, who developed headache, right arm weakness and an inability to articulate. \(^{109}\) Other writers after him put their interest in the prognosis of the disease, and not in its cause, since it was in those days the mark of a wise physician to be able to give an accurate prediction of the patients fate. Much later in 1658 Wepfer recognized the possible role of “hardening of the pulse” with which he meant hypertension, well before blood pressure could be measured for the first time by the method of Riva-Rocci in 1896.\(^{110,111}\) Charcot and his protegé Bouchard were the first in 1868 to link intracerebral hemorrhage (ICH) with a disease of the small vessels. They described small saccular or fusiform dilatations of arteries with a diameter of 250-400 \(\mu\)m everywhere in the brain in 3 of 48 patients who died of a stroke.\(^{10}\) These lesions were later called the “Charcot-Bouchard aneurysms” or miliary aneurysms. They observed degenerative changes in the adventitia and believed that the aneurysms were caused by periarteritis and were not related to atheroma. Later, other authors confirmed their findings, but some doubted the existence of the miliary aneurysms.\(^{110-112}\) Among the believers discussion arose about the etiology: medial degeneration, arteritis or atheroma were all invoked as possible causes of the aneurysms.\(^{111}\) Duret studied the distribution of ICHs and recognized the frequent localization in the area of the deep branches of the cerebral arteries in the basal ganglia, thalamus and brainstem. He called the lenticulostriate arteries “the arteries of the cerebral hemorrhage”.\(^{109}\) Ross Russel rediscovered the miliary aneurysms in 1963, when he demonstrated many saccular dilatations of the small intracerebral arteries in 54 post-mortal brains with X-ray micro-angiography, after injection of barium sulphate into the cerebral arteries. He was the first who also found them in elderly, normotensive patients.\(^{111}\) Cole and Yates corroborated these findings and confirmed that hypertension was an important risk factor for the development of miliary aneurysms.\(^{113}\) Fisher found in a painstaking study that miliary aneurysms were associated with severe
lipohyalinosis. In the periphery of a hematoma he also noted small globoid caps ("fibrin globes"), that in his opinion were small bleeding capillaries due to pressure of the expanding hematoma. He stressed that in patients with fresh or old ICH, small hemorrhages of less than 0.5 cm could be found and that ICHs were not always lethal, in contrast to the ideas of poor prognosis of ICH that dominated at that time. Rosenblum also found an association between lipohyalinosis (or, as he called it, fibrinoid necrosis) and miliary aneurysms. Wakai et al. corroborated these findings in surgical specimens of patients with ICH. None of the aforementioned authors found direct evidence that ICH arose from a miliary aneurysm. In an electron microscopic study Takebayashi studied the parent arteries from which an ICH emerged and found differences in wall changes between these arteries and arteries that were connected to miliary aneurysms (see below). He and his group thought that miliary aneurysms were remnants of a small hemorrhage after a minor rupture of a small artery.

The advent of the CT-scan marked a new era for the diagnosis of hematomas and permitted confirmation of ICH during life. One could speak of BCT (before CT) and ACT (after CT) eras. It soon became clear that many patients survived small and moderate sized hematomas, and that earlier clinico-pathological series were biased towards larger ICH that were fatal. Recently, MRI allowed detection of old hemorrhages in the form of hemosiderin containing lesions in the brain. Offenbacher confirmed the pathologic findings of Fisher by showing remnants of small old hemorrhages in patients presenting with ICH on MRI.

Controversies and confusion

Three questions about ICH had kept the minds of researchers busy during the decades.

1. Is hypertension the main risk factor for ICH?

As a reflex clinicians and laymen associate the word "brain hemorrhage" with hypertension. Indeed the first authors describing ICH already recognised the relation with hypertension. But later hospital-based
epidemiological studies found patients with ICH who never had hypertension. In the Harvard Stroke Registry 41% of patients with ICH had no history of hypertension. Brott et al. found that among patients with spontaneous ICH, only 45% had hypertension. Foulkes et al. noted that no more than 65% of patients with ICH had hypertension. Caplan proposed the hypothesis that in some cases acute elevations of blood pressure or blood flow may lead to rupture of arterioles and capillaries of persons without hypertension. He considered arterial walls of normotensive patients more vulnerable to acute elevations of blood pressure than arterial walls of hypertensive patients, since the latter are thickened and relatively protected against high pressures.

Other factors like bleeding disorders, anticoagulant therapy and drug abuse, or congenital anomalies like vascular malformations are associated with ICH. Specific diseases like amyloid angiopathy, and perhaps CADASIL, are also associated with ICH. Hemorrhage into intracranial tumors are less common causes of ICH.

2. Are miliary aneurysms the source of ICH?

Charcot and Bouchard’s hypothesis that the miliary aneurysms are the cause of ICH was attractive and gained widely acceptance for a while. But some authors doubted the existence of the aneurysms. Challa et al. stained the alkaline phosphatase in the endothelial cells with a special technique and found a much lower frequency of these lesions. They pleaded that part of the miliary aneurysms that were studied with intra-arterial injections (like in the work of Ross Russell) were artifacts due to the pressure exerted by intra-arterial injections of contrast medium. Nobody ever found direct evidence that a miliary aneurysm was the source of an ICH. Ross Russell had the strongest, but still indirect, evidence by showing a rupture of one of the miliary aneurysms at its thinnest site in the wall, due to the injection of the contrast medium.

In an electron microscopic study Takebayashi et al. found differences
in changes in the walls of ruptured arteries at the bleeding site and those of the parent arteries of miliary aneurysms. The ruptured arteries showed disruption of the lamina elastica and medial degeneration with atrophy and segmentation of medial smooth muscle cells, and cell debris. The walls of the arteries connected to miliary aneurysms showed severe degeneration of smooth muscle cells and subendothelial deposition of fibrin and plasma materials. The walls of the aneurysm itself contained no vascular elements, except for endothelial cells, that have the property to regenerate easily. In addition, they found that ruptured arteries usually have a diameter of 200-700 μm, while arteries with miliary aneurysms have a diameter of less than 200 μm. These findings suggest that miliary aneurysms are merely reabsorbed old microhemorrhages and that they probably do not enlarge to cause symptoms. In contrast, ICH is in their view the result of complete rupture of somewhat larger arteries.

3. What are the causes of miliary aneurysms?
Charcot and Bouchard thought that miliary aneurysms were the result of periarteritis and that they were not related to atheroma. Their work soon gave rise to discussions whether medial degeneration, arteritis, dissection, or atheroma leads to these lesions. The common coexistence with lipohyalinosis and the similar preference for the small penetrating arteries were suggestive of a causative relation.
Takebayashi et al. showed that the walls of the aneurysms did not contain vascular elements. They proposed that they are remnants of small hemorrhages, due to minor rupture of very small arteries. Lipohyalinosis may have caused these small ruptures.
References


Brief historical review


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Chapter I


Brief historical review


