The Plurality of Subcortical Infarction

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I believe that it is time to redefine the lacunar concept more clearly and to attempt to establish a new, more general classification of subcortical infarcts. Clinicians and investigators should make clear what they mean by the terms lacune, lacunar infarct, or lacunar syndrome, and the scientific community should aim at an international consensus definition of these terms. Although involvement of the territory of one single penetrator defines lacunar infarction pathologically, there is no clinical way to confirm this in vivo before the patient’s death. Size of lesion on CT or MRI (classically, <1.5 cm) may be accepted as part of the clinical definition of a lacune, but the fact that it must be caused by single penetrator occlusion may not; it may be compatible with that possibility, but no more.

One should decide whether pathophysiology should be implied in the term lacune. The most restrictive interpretation, which I personally favor, would be to speak of lacunar infarction, presumed or probable, only in the presence of a small (<1.5 cm) infarct limited to the territory of deep perforators and probably caused by in situ small-vessel disease. In the Lausanne Stroke Registry, less than half of the 320 patients with infarct limited to the territory of deep perforators were likely to have so-defined lacunar infarction, whereas a potential cardiac source of embolism, severe stenosis, or occlusion of the ipsilateral internal carotid artery was present in more than one quarter of the cases, in the absence of another potential etiology. One possibility would be to use “infarct limited to the territory of deep perforators” as the generic descriptive term by which lacunar infarcts would correspond to those infarcts limited to the territory of deep perforators likely to be caused by small-vessel disease.

The role of diabetes mellitus as a contributor to small-vessel disease should also be settled. In our experience and in other series, the frequency of diabetes is particularly high in patients with infarct limited to the territory of deep perforators.

The sensitivity and specificity of lacunar syndromes must be reassessed. In a recent review, Fisher reported that over 70 different neurological pictures could be secondary to lacunar infarction. These were as varied as pure motor hemiplegia, isolated internuclear ophthalmoplegia, or acute abulia. The vast majority of these syndromes are not specific at all for lacunar infarction. On the other hand, recent studies have shown that a few of them may still be suggestive of lacunar infarction, the best example being pure motor hemiplegia involving the face, arm, and leg. In 255 patients from the Lausanne Stroke Registry with isolated hemiparesis involving face/arm/leg in any possible combination, we found that proportional face/arm/leg involvement was the only

The designation of the term “subcortical infarction” has often been equated with the diagnosis of lacunar infarction. This identity is incorrect and misleading.

Lacunes were reported by French authors in the 19th and early 20th centuries; they were considered to correspond to small (usually <1 cm diameter) cavities in the deep cerebral hemispheres parenchyma, resulting from three distinct processes: a small area of infarction, a small area of hemorrhage (lacunar hemorrhage), or an increase in perivascular dilatation. In the 1960s, C.M. Fisher described clinicopathological studies on lacunes, which emphasized that lacunar infarcts were usually the consequence of single arteriolar vessel occlusions caused by localized obstruction, described as lipohyalinosis, related to long-standing hypertension. He also suggested that some neurological syndromes (pure motor hemiplegia, pure sensory stroke, ataxic hemiparesis, dysarthria–clumsy hand) were likely to be caused by lacunar infarctions. Based on his clinicopathological studies, Fisher proposed that lacunar infarcts should be separated from other types of cerebral infarction. He emphasized the distinction of superficial infarcts resulting from cortical branch occlusion by embolism versus end-arterial disease.

It became clear that clinical assumptions did not reliably identify the underlying etiology. Moreover, the advent of computerized tomography (CT) and, later, magnetic resonance imaging (MRI) provided the opportunity to increase considerably the possibilities for making the diagnosis of lacunar infarction in vivo, whereas the term “lacune” was in fact neuropathologic. The ultimate point has now been reached as radiologists report lacunes on CT or MRI to describe any kind of small area of hemorrhage (lacunar hemorrhage), or an increase in perivascular dilatation. In the 1960s, C.M. Fisher described clinicopathological studies on lacunes, which emphasized that lacunar infarcts were usually the consequence of single arteriolar vessel occlusions caused by localized obstruction, described as lipohyalinosis, related to long-standing hypertension. He also suggested that some neurological syndromes (pure motor hemiplegia, pure sensory stroke, ataxic hemiparesis, dysarthria–clumsy hand) were likely to be caused by lacunar infarctions. Based on his clinicopathological studies, Fisher proposed that lacunar infarcts should be separated from other types of cerebral infarction. He emphasized the distinction of superficial infarcts resulting from cortical branch occlusion by embolism versus end-arterial disease.

In recent years, papers on lacunes could be classified into two groups: 1) those attempting to show that a) the classic lacunar syndromes are not specific for lacunar infarction; and b) small infarcts in the territory of deep perforators may often not be lacunar, as defined pathologically and etiologically by Fisher; and 2) those trying to validate and defend the “lacunar hypothesis.” This barren dispute was perhaps unavoidable in that the lacunar concept had become rather dogmatic, and dogmas are made to be both destroyed and cherished.

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Received November 7, 1991; accepted February 3, 1992.
significant predictor of lacunar infarction, whereas other partial combinations, such as face/arm or arm/leg, were not.2 Still, there are studies that continue to consider these partial forms of pure motor hemiparesis as systematically lacunar in their methodological criteria. The point is that pure faciobrachial or brachioocular hemiparesis may well be caused by lacunar infarction but is by no means significantly associated with it, whereas face/arm/leg hemiplegia is. On the other hand, in a patient with hypertension but no heart or carotid disease who develops, for instance, a right faciobrachial sensorimotor stroke with mild speech disturbances, and in whom MRI shows a small left capsulostriate infarct limited to the territory of deep perforators, there is no reason to refute a diagnosis of lacunar infarction solely because he does not have a “classic lacunar syndrome.” In patients with normal imaging, the assumption of a lacunar etiology may rely on the fact that a specific lacunar syndrome (such as pure motor hemiplegia involving face, arm, and leg) is present.

An important point that is commonly overlooked in the endless discussions about the pathophysiology of lacunes is that lacunar infarcts are only one aspect of subcortical infarction. In fact, apart from the deep perforating branches (lenticulostriate arteries) of the middle cerebral artery, there are at least five other arterial networks that supply the subcortical structures.

The deep perforating branches from the anterior cerebral artery include the direct anterior lenticulostriate branches and perforating branches off Heubner’s artery that originates from the A2 segment and also has a superficial-pial territory. The deep perforating branches from the anterior choroidal artery which, like the middle or the anterior cerebral artery, is an artery with a dual blood supply system. The first comes from deep perforating branches and the second from superficial-pial branches that supply part of the medial temporal lobes.

The thalamic arteries come from the P1 and P2 segments of the posterior cerebral artery (paramedian arteries, inferolateral arteries, posterior choroidal arteries) and from the posterior communicating artery (tuberothalamic artery). Although these branches are actually perforators, they may show many reciprocal collaterals and thus cannot be considered terminal arteries. This might be the main difference between thalamic and lenticulostriate arteries and one that may well have significant etiological implications. For instance, paramedian thalamic infarcts are typically embolic, and one of the reasons may be that several embolic occlusions may be necessary to produce infarction, which is less likely to develop when a single penetrating artery is occluded from in situ disease because of the presence of a collateral network. Fisher’s rule that occlusion of a single penetrator will produce a small infarct corresponding to its specific territory may not be applicable to thalamic infarcts because most of thalamic arteries do not appear to be end arteries.

White matter medullary arteries are perforators originating from the superficial (pial) branches of the middle cerebral artery (and, to a lesser degree, the anterior cerebral and posterior cerebral arteries). These branches are 2–5 cm long, with selective territories and without interdigitation. They supply the core of the hemispheric white matter (centrum ovale) and course toward the lateral ventricular wall at the upper level of the lateral ventricles. These “superficial perforators” do not anastomose with the deep perforators (lenticulostriate arteries) but form a border zone at the junction with the deep territory.

Finally, the cortical arteries with subcortical supply include pial branches to the corpus callosum, U fibers, extreme capsule, external capsule, and claustrum.2 The three latter structures in fact have a dual supply that also includes the first short branches of the perforating medullary arteries. Infarction in this territory is not strictly subcortical and will be discussed later.

We thus propose the following CT/MRI-based topographical classification of subcortical supratentorial infarcts: 1) infarcts in the territory of deep perforator(s) from the middle cerebral artery, anterior cerebral artery (including Heubner’s artery), anterior choroidal artery, posterior communicating artery, and posterior cerebral artery; 2) infarcts in the territory of superficial perforator(s) (white matter medullary branches) from the superficial (pial) cerebral arteries; 3) border zone infarcts between types 1 and 2 (in the absence of a collateral network, they are junctional rather than watershed infarcts); and 4) combined infarcts.

The corresponding causes of each of these types of subcortical infarction may be rather stereotyped: small-artery disease is the leading etiology in small (<1.5 cm) type 1 and type 2 infarcts of the perforators territory (i.e., lacunar infarcts, according to the above definition), whereas large-artery disease and cardioembolism are the most common causes of the larger type 1 and type 2 infarcts, which encompass the territory of several perforators;4 in the lenticulostriate territory, such infarcts have been named large striatocapsular infarcts.23,24 Border zone and combined infarcts are usually associated with severe disease of the ipsilateral internal carotid artery.25,26

There is undoubtedly room for improvement of this classification. One project might be to pool prospectively studied patients with pathological data from several centers in a major effort to settle the small-vessel question. Future studies should also aim to refine the possibility of early clinical diagnosis of subcortical infarct subtypes to facilitate subgroup allocations and patient exclusion during therapeutic trials. At the present time, it is all too common to read in trial protocols that lacunar infarction is an exclusion criterion, with no explanation of exactly what is meant by lacunar infarction or with confusion between lacunar and subcortical infarction.

References

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*Stroke*. 1992;23:629-631
doi: 10.1161/01.STR.23.5.629

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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