# History of "Lacunar Infarction"

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**Abstract:** The concept of lacunar infarction has evolved over the last 200 years, from the first neuropathological observations to the current definition based on neuroimaging. In this chapter, the historical evolution of the definition of lacunar infarcts is reviewed, from the first original description by Amédée Dechambre to the detailed studies by Maxime Durand-Fardel and Virchow. The evolution of the pathogenetic and the etiological considerations from those of Binswanger, Alzheimer, and Pierre Marie to the memorable work of C. Miller Fisher is also revised. The critics of the lacunar hypothesis and the modern neuroimaging aspects are also considered.

## 1. Introduction

The modern concept of lacunar infarction is the result of a long succession of studies over the last 200 years [1]. Nowadays, lacunar infarctions are known to be small cystic cavities in the brain parenchyma caused by an ischemic insult in a territory perfused by a penetrating arteriole originating superficially from the superficial circulation as terminal vessels of medium-sized arteries, or deeper, from the large vessels of the Willis circle, the so-called "arterial perforators". By definition, lacunar infarctions have to be smaller than 15 mm and they represent small holes of encephalomalacia (i.e., lacunes). It is nowadays well known that lacunes can also result from small deep hemorrhages or correlate with isolated dilatation of the perivascular space [2].

## 2. The Historical Evolution of Lacunar Infarcts

### *2.1. Early Concepts*

The first mention of lacunar infarction follows in time the early general descriptions, in 1820, of cerebral infarctions, named at that time "ramollissement du cerveau" or "cerebral softening" [3,4]. Eighteen years later, Amédée Dechambre provided the original description of lacunes, linking them to his name for years. As an intern at the Salpétriere Hospital in Paris, he was the first to study stroke survivors. He performed a brain autopsy, discovering many small lacunes of variable size and form. He identified them as the result of liquefaction and resorption of the infarct (cerebral softening). Maxime Durand-Fardel, the author of one of the first books on ischemic stroke ever published, independently postulated in 1843 the same origin of lacunes of Dechambre, distinguishing them from another type of parenchyma cavitation, the dilatation of the perivascular spaces, referred to as état criblé. Similar conclusions were achieved in the same years by the German pathologist Virchow [5]. In 1866, Laborde hypothesized that a lacune could be also the result of a small brain hemorrhage reabsorption. In 1894, Binswanger and Alzheimer described brains

in which multiple lacunar infarctions were present more or less associated with cognitive decline. At the beginning of the 20th century, Compte observed multiple lacunes in patients with pseudobulbar palsy, and Thurel, in 1929, supposed lacunes as the most frequent etiology of this clinical picture. Independent of the works above described, in 1900, Pierre Marie provided a well-detailed clinical description, under the name of état lacunaire, of a set of recurrent motor deficit episodes, often with a partial resolution, followed by the onset of a clinical picture characterized by small-step gait, urinary incontinence, and pseudobulbar palsy. He also depicted some degree of global intellectual deterioration in these patients. Pierre Marie may be considered the first to have established the lacunar concept by associating the pathological and the clinical pictures. Together with Ferrand, he described a brain pathologic condition characterized by multiple lacunes, very similar to the arteriosclerotic brain atrophy depicted by Alzheimer and Binswanger. Despite what is reported above, in the following years, some confusion arose in the scientific community surrounding the concept of lacunes and their underlying etiology. Depré and Devaux's reported histological observations of lacunes, misinterpreting them as état criblé and therefore assigning them a non-ischemic origin [4]. In his publication in 1842, Durand called état criblé the perivascular spaces dilatation observed around cerebral arterioles in elderly patients, located in the context of white matter, and considered this picture as the result of vascular congestion. In 1920 C. and O. Vogt, even though they were the first to emphasize the "softening hypothesis", called status desintegrationis, as the union of the lacunar lesions in the globus pallidus and the striatum with dilatation of perivascular spaces. The confusion regarding lacunes was so pronounced that, in 1929, Thurel stated that the term état lacunaire should be used for the grey nuclei and that of état criblé for the centrum ovale and myelinated areas.

### *2.2. Lacunar Infarction in the 20th Century*

The issue was solved only many years later by the seminal work of C. Miller Fisher. In 1965, he finally cleared the ambiguity by publishing a memorable paper [6], reporting on an outstanding series of 1042 consecutive brain examinations. A macroscopic search for lacunes, defined as irregular cavities between 0.5 and 15 mm in diameter, was performed through horizontal sections, registering location, size, and appearance. He described a characteristic pathology of vessels supplying the lacunar infarct's territory. The examination of these tiny arteries showed no occlusion at their origin. They had instead focal enlargements of the wall and small transmural hemorrhagic extravasations. He found that the vessel's lumen could also be obliterated by subintimal foam cells and that the walls of these vessels were filled with pink-staining fibrinoid material. Moreover, arteries could be replaced by connective tissue deposition, obliterating the usual vascular layers. He defined, respectively, these processes as segmental arterial disorganization, fibrinoid degeneration, and lipohyalinosis. These changes along the walls of the brain's small

vessels, different from usual atheroma, led to the occlusion of a single penetrating artery, and then to an infarct in the referral vascular territory [7]. Thus, lacunes became the correlate of small deep cerebral infarcts, returning to Durand-Fardel's definition. He also described five classical lacunar syndromes, pure motor, ataxic hemiparesis, dysarthria-clumsy hand, pure sensory, and mixed sensorimotor [8].

All but three of the 114 patients with lacunes included in Fisher's review had hypertension [6]. In many of these patients, brain infarction developed during a period of high blood pressure levels, in an era in which clearly effective antihypertensive medications were not available. Additionally, Prineas and Marshall [9], followed by Cole and Yates [10], confirmed the role of hypertension, respectively in 1966 and 1967. Some years later, in 1982, J.P. Mohr deepened Fisher's pathological concepts [11]. In his work, fibrinoid necrosis affected arterioles and capillaries in a setting of extremely high blood pressure levels. Arterial wall thickness was increased, leading to damage to the autoregulation system of cerebrovascular afferents. According to his hypothesis, high pressure levels increase capillaries' hydrostatic pressure, damaging them irreversibly. Lipohyalinosis, instead, occurs after long exposure to non-malignant high blood pressure. In chronic hypertension, there are also tiny foci of atheromatous deposits, involving the walls of the penetrating arteries [11]. In consideration of that, Fisher and other researchers later postulated also a truly atherosclerotic pathway at the origin of lacunar infarction. It consists of little atherosclerotic plaques inside the small perforators, naming them microatheroma [12]. Hence, the lacunar hypothesis was founded, consisting of two parts. Firstly, symptomatic lacunes present with a limited number of distinct clinical lacunar syndromes. Secondly, lacunes are due to a specific disease of the penetrating arteries. If both conditions are respected, then the stroke has to be classified as caused by a "lacunar infarction" [13].

### *2.3. Lacunar Infarction beyond the Original Concept*

In 1990, Millikan and Futrell [14] formally argued Fisher's lacunar hypothesis. In experimental models, rats with internal carotid photochemically induced damage showed microemboli dissemination to the brain, producing cavitary lesions similar to human lacunes. According to these authors, a lacunar syndrome should instead be considered the clinical result of a small subcortical infarct, and not a particular entity resulting from the combination of hypertension and small vessel disease. A few years later, to ensure the ability of a lacunar syndrome in predicting the radiologic presence of a lacunar infarction on brain imaging, the Northern Manhattan Stroke Study was settled [15]. In this study, a lacunar syndrome had a positive predictive value of 87% in detecting radiologic lacune, and a positive predictive value of 75% in predicting a final diagnosis of lacunar infarction. Notably, 25% of lacunar syndromes that were confirmed radiologically had a non-lacunar (i.e., not caused by small vessel disease) possible mechanism of infarction.

Futrell then developed the microembolic hypothesis. Together with the original observations based on rodent models, it was supposed that small infarcts could be the consequence of embolic occlusion originating from large arteries or from the heart [16]. Evidence supporting this theory was derived from primate models studies [17], but also from observational considerations that emerged from the analysis of data from trials on symptomatic internal carotid stenosis endarterectomies, in which some patients with ischemic lacunar infarction had a reduced stroke risk after vascular surgery of the symptomatic carotid [18].

These observations, therefore, expand the possible etiological mechanisms of lacunar infarction and are coupled with Fisher and Caplan's description of lacunar infarcts associated with atherosclerosis [19,20]. Atherosclerotic plaque lesions of major vessels could occlude the penetrating artery branches' orifices, a condition called intracranial branch atheromatous disease. Thus, also an atheroma originating in the parent artery could occlude the penetrating branches, a condition referred to as junctional atheromatous plaques [21].

## 3. The Current Role of Neuroimaging

The historical evolution of the concept of lacunar infarction has profoundly changed after the introduction of computed tomography (CT) and magnetic resonance imaging (MRI) in recent decades of the 20th century [22]. However, while neuroimaging has made small lesions of the brain visible in vivo, it has also introduced some problems such as the distinction between lacunar infarcts, lacunes due to old hemorrhages, and enlarged perivascular spaces. Historically, the first studies on CT scan detection were conducted in the 1980s [23,24]. When visible, lesions appear as punctuate areas of low density, whereas they transform into hypodense foci, of the same density of the cerebrospinal fluid. Detection rates were variable accordingly to clinical presentation, with global low sensitivity to acute small deep infarcts, especially in the first hours or when located in the posterior fossa [25]. Moreover, the smallest lesions of the posterior fossa were often not considered by researchers because only strokes revealed by classical lacunar syndrome were included, so a higher detection rate of pure motor stroke could be overestimated [26,27]. Indeed, a CT scan does not provide information about the age of lesions detected, unless serially repeated exams are used with evidence of a new lesion not visible in the previous scan [24]. MRI has strongly changed diagnostic capability since its introduction [28]. Even before diffusion imaging's advent, MRI showed higher sensitivity [29]. Among MRI sequences T2 (transverse relaxation time)-weighted appear superior to T1(longitudinal relaxation time)-weighted one [30]. Diffusion weighted imaging (DWI) finally showed the best performance, with hyperintense lesions together with restricted diffusion on apparent diffusion coefficient maps [31]. Notably, MRI acute appearance is strictly dependent on the sequence adopted. A slight hypointensity in T1, and hyperintensity in T2/Fluid-attenuated inversion recovery(FLAIR), with restricted diffusion in DWI

and enhancement in fat suppressed T1-weighted gradient-echo sequence (T1C+) if acute or early subacute. Chronic lesions are isointense to cerebrospinal fluid independently from sequences. There is often a peripheral rim of marginal gliosis, hyperintense in T2/FLAIR sequences.

MRI is also able to distinguish between cavitated lesions due to ischemia, hemorrhage, or enlargement of perivascular spaces. The current history of lacunar infarcts has been characterized by the consensus paper published almost 10 years ago and aimed at defining neuroimaging standards for small vessel disease [32].

## 4. Conclusions

As outlined in this chapter, the definition of lacunar infarctions has evolved for a long time, and it is currently used both for lesions in the acute phase and for those in the chronic stage, according to technical information on the best neuroimaging acquisition techniques available.

**Author Contributions:** G.B., major role in drafting and editing the chapter; L.P. major role in drafting and editing the chapter. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Conflicts of Interest:** The authors declare no conflict of interest.

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