

The Turning Point in Stroke Investigation for Neurologists

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Abstract: Investigation into stroke was not at all expedient; in fact, stroke was never a field of critical interest for either the Salpêtrière or Pitié Schools, which were attended by Vulpian and Charcot. The results from the few studies on the subject were carried out by sole researchers, including Rostan, Rochoux, Dechambre and Durand-Fardel. Subsequently, interest was first expressed by the leading pathologists, including Rokitansky and Virchow. This came upon the heels of the development of clinical–topographic correlation studies carried out by Déjerine, Marie and Foix, the latter of whom was the father of modern clinical stroke research.

1. The History of Brain Softening and Apoplexia

By comparing clinical features with autopsy, Giovanni Battista Morgagni [1] (1682–1771) laid the foundations of clinical anatomic studies in stroke, utilizing the classification of “sanguineous” (hemorrhagic) vs. “serous” (non-hemorrhagic) apoplexy. He assigned to the latter category cases that probably corresponded to infarction or edema. Subsequently, in 1814, Jean André Rochoux [2] (1787–1852) claimed that apoplexy was always the result of bleeding. Apoplexy described either the lesion (hemorrhage) or the symptoms (loss of movement and sensation). In his monograph, Rochoux also introduced the term “ramollissement” (softening) into the field of stroke care. Later, Léon Rostan (1790–1866) (Figure 1) introduced “spontaneous cerebral softening” as a body separate from encephalitis and apoplexy. However, Rostan did not adopt this. Instead, he regarded it as being similar to hemorrhagic stroke in pathological terms. Specifically, Rostan reported that pathologic and clinical features of brain softening differed from apoplexy in that the former was fatal. The definition of brain softening was harshly contested by Francois Broussais, Lallemand and Calmeil, who claimed that it was due to an “inflammation” and thus should be called encephalitis. Conversely, the ideas of Rostan were embraced by Carswell in England (1835), Abercrombie in Scotland (1836) and Andral in France (1827, 1840). While Rostan had suggested a link between a condition of the arteries (ossification) and parenchymatous lesions in his 1823 “Recherches sur les ramollissements du cerveau”, these lesions were not correlated with vessel stenosis. It was in 1856 when Virchow revisited this hypothesis, [3] and the studies of Adrien Proust (1862), Vincent Laborde (1866) and Jean Louis Prévost and Jules Cotard in France (1865). These observations suggested that arterial occlusions and diminished blood flow to brain regions were the cause of softening, and these lesions were infarctions following Cohnheim’s [4] hypothesis.



Figure 1. Léon Rostan (1790–1866). Source: Reprinted and used with permission from Olivier Walusinski (courtesy).

2. The Coining of Arteriosclerosis, Thrombosis, and Embolism

Rudolf Virchow [3] (1821–1902) was the pioneer in that he was the first to describe arterial thrombosis and embolism. This resulted from an observation he made of the interaction between blood flow and arterial walls. Specifically, he hypothesized that blocking blood flow to any major organ would result in something he later named “ischemia”. At the age of 27, he was able to prove that masses in vessels would provoke something he called a “thrombosis”. To better explain the underlying process leading to a thrombosis, he borrowed the term “arteriosclerosis”, from Lobstein, who coined it in 1829 [5]. Additionally, he is known for the fact that he was able to demonstrate that sections of a thrombosis would often flake off arterial walls and travel throughout the circulation. We know this as an embolism. Furthermore, Virchow [6] was the first to report that a local embolism can be caused by clots of heart origin in patients who had had lower limbs gangrene. He wrote that similar events in the brain may lead to cerebral softening.

Virchow was the mentor of Julius Cohnheim (1839–1884) who was the author of the term “cerebral infarct”, a synonym for stroke. Cohnheim carried out experiments on arterial injection of wax globules, in which he embolized a frog’s tongue. These types of embolization can lead to either no injury, or two kinds of lesions, which for over a century have been defined as “ischemic necrosis” and “hemorrhagic infarct” [4].

Karl von Rokitansky [7] (1804–1878) was responsible for a great scientific feat in the 1840s. He described that some “apoplexies” were primarily due to an enlargement

of the right ventricle, whereas according to Rokitansky, hemorrhage may have been associated with hypertrophy of the left ventricle and, therein, an “impulse”; in that era, the effects of high blood pressure were not fully understood.

3. Atherosclerotic Carotid Disease: Its Evolution

After Virchow, the term carotid disease would be used to describe patients with certain combinations of eyesight loss and focal paralysis. In this regard, in 1872, Adolf Kussmaul [8] (1822–1902) and, in 1881, Franz Penzoldt [9] (1849–1927) both reported on carotid artery thrombosis in the neck region of patients afflicted with ipsilateral eye blindness [8] and contralateral hemiplegia [9].

Up until this period, the term cerebral embolism was considered to be a synonym of an embolism originating from the heart. An extracranial artery source was rarely considered up until the early 1960s. In fact, it had been assumed that arterial disease interested intracranial vessels, although Hans Chiari [10] (1851–1916) in 1905 had suggested there might be a link between extracranial carotid disease and stroke. Indeed, he observed a thrombus superimposed on ulcerated carotid plaques in 7 out of 400 autopsies. Four of these seven cases had had cerebral embolisms. This led him to suggest that thrombotic material had broken away from the observed carotid plaques and had traveled to the brain.

In 1914, James Ramsay Hunt [11] (1874–1937) suggested that an obstruction of carotid arteries could determine a “cerebral intermittent claudication”. Moreover, he emphasized “the occurrence of unilateral vascular changes, pallor or atrophy of the optic disk with contralateral hemiplegia (‘optico-cerebral syndrome’) with carotid occlusion”.

4. The Introduction of Lacunar Infarction

Used for the first time in 1838 by Amédé Dechambre [12] (1812–1886), the term lacune described a small cavity that remained after a small stroke. Subsequently, in 1843, Charles Louis Maxime Durand-Fardel [13] (1815–1899) (Figure 2) provided a more detailed explanation by defining a lacune as a small cavity in the brain “without any change in consistency or color from which it was possible to remove a little cellular tissue containing very small vessels with a thin forcep”. For the next five decades, no advances were made in this field. Then, Pierre Marie (1853–1940), a pupil of Charcot, published a paper entitled “Des foyer lacunaires de désintégration et les différents autres états cavitaires du cerveau” in 1901. In this paper, he concluded that lacunes were small softening caused by atherosclerosis. Marie also observed that lacunes tended to be asymptomatic, but “that hemiplegia in old people was more often due to cerebral lacunes than to hemorrhage or softening”. During the early 20th century, all published articles on cerebral lacunes were in agreement with Marie’s definition.



Figure 2. Charles Louis Maxime Durand-Fardel (1815–1899). Source: Reprinted and used with permission from Olivier Walusinski (courtesy).

In the 1960s, Charles Miller Fisher [14] described what he thought to be a more specific pathology of the penetrating arteries, lipohyalinosis or microatheroma, both of which lead to a characteristic of end-artery pattern vascular supply. Additionally, he suggested returning to Durand-Fardel’s original definition of the term lacune, a “small, deep cerebral infarct”.

5. 19th Century Clinical–Anatomic Model

By the mid-19th century, neurology had already been recognized as a medical field. However, Joseph Babinski (1857–1932), one of the most famous neurologists of this period, wrote 288 papers, with only 4 dealing in some way with stroke. Other pathologies interested researchers more. From the 19th century, clinical–anatomic methods had been disseminated throughout Europe, but it was only a bit later that clinicians began investigating an association between arterial vascularization, brain lesions and corresponding clinical features. It was, in fact, Jean-Martin Charcot (1825–1893) who taught anatomic pathology prior to having been appointed to the first chair of neurology in the world. The work of Charcot is widely recognized for its impact on neurology and psychology, but his contribution to vascular neurology remained small.

It was the description of specific brainstem syndromes, including reports by August Millard and Adolph Gubler (1856) [15,16], Achille Foville (1858) [17], Hermann David Weber (1863) [18], Moritz Benedikt (1889) [19], Adolf Wallenberg

(1901) [20], Joseph Babinski and Jean Nageotte (1902) [21] and Henri Claude (1912) [22], that lead to a great awakening. Likewise, Joseph Jules Déjerine [23] (1849–1917) (Figure 3) reported on clinical findings in stroke patients when he described, for the first time, the thalamic syndrome with Gustave Roussy.

The end of the 19th century marked the advent of the first generation of “vascular neurologists”. Among these were Charles Foix [24–27] (1882–1927), a pupil of Marie, who exhibited a particular interest in cerebrovascular events. Foix is considered to be the first vascular neurologist due to his work on the patterns of brain infarction in the middle, anterior and posterior cerebral arteries and the anterior choroidal arteries [24–27]. Foix concentrated on clinical–anatomic studies, with the aim of discovering correlations between any lesion topography and clinical dysfunction. Therein, the interest in stroke gradually—though slowly—increased throughout the 20th century, especially in the 1940s and the 1950s, when the first diagnostic and therapeutic approaches of stroke were introduced. In the 1960s, Fisher described that a thromboembolic mechanism underlies most ischemic strokes and that the source of thrombus might be the heart or a proximal arterial lesion. However, it was only in the 1970s that stroke became a major research field of neurology, and this was due to results from clinical trials on anticoagulant use after ischemic stroke [28] and the first clinical trial on carotid endarterectomy [29,30].



Figure 3. Joseph Jules Déjerine (1849–1917) by E. Gauckler (Masson et Cle, 1922).
Source: Reprinted and used with permission from Olivier Walusinski (courtesy).

In conclusion, without the development of clinical–anatomic correlation studies at the turn of the 19th century, stroke would not have become known as a brain condition worthy of specific research. The priceless accumulation of knowledge over centuries on cerebrovascular events was the result of painstaking and courageous work on the part of single pioneers.

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