Pierre Marie's *état vermoulu* to Spatz' cortical granular atrophy and cortical microinfarcts: a scarcely recognised cerebral vascular pathology

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ABSTRACT

Introduction. Pierre Marie's description of *état lacunaire*, the predominantly motor clinical syndrome associated with multiple lacunar infarcts, is well known. However, he also described *état vermoulu*, another vascular pathology characterised by even smaller infarcts limited to the cerebral cortex.

Material and methods. I reviewed original articles and communications by Pierre Marie and his school, and consulted classic neuropathology texts and today's literature to analyse the evolution of the concept of *état vermoulu*.

Results. Pierre Marie associated *état vermoulu* with age and cognitive impairment, and considered it a rare condition. To the contrary, Augusta Dejerine-Klumpke believed that these lesions were frequently identified in studies of serial sections of the brain. Thanks to Hugo Spatz, the concept of *état vermoulu* spread to the scientific literature of other countries under the name cortical granular atrophy. In the following decades, there was little interest in cortical microinfarcts, the underlying pathology in *état vermoulu*, mainly because they cannot be detected in basic neuroimaging studies (CT and MRI up to 3T). As a result, the clinical correlation with the two main syndromes associated with small-vessel disease, cognitive impairment and parkinsonism, led to a (probably biased) focus on subcortical lesions: these were the only lesions visible on basic neuroimaging studies, and the only ones taken into consideration in conventional neuropathology.

Discussion. Seven-Tesla MRI scanners enable us to view the cortical microinfarcts that cause *état vermoulu*, making it possible to estimate the true extent of their contribution to vascular dementia and parkinsonism.

KEYWORDS

Cerebral infarct, arteriolosclerosis, small-vessel disease, lacunar state, granular atrophy, *état vermoulu*, cerebral microinfarcts, Pierre Marie, Dejerine

Introduction

Cerebral vascular pathology encompasses a vast range of lesions, beginning with the basic distinction between ischaemic and haemorrhagic lesions, which frequently co-occur. Ischaemic lesions or infarcts may be classified by their aetiology (atheromatosis, arteriolosclerosis, embolism of other origin, vasculitis, haemodynamic crisis with hypoperfusion, global anoxia, etc). The anatomical characteristics of infarcts are largely determined by aetiology. Atheromatosis and cardioembolism, the most frequent types, occlude large and medium arteries and therefore cause infarcts in specific, extensive anatomical territories. On the other hand, arteriolosclerosis gives rise to small infarcts in the territory of the perforating branches, whose distribution is more random but shows a clear preference for the brainstem and subcortical

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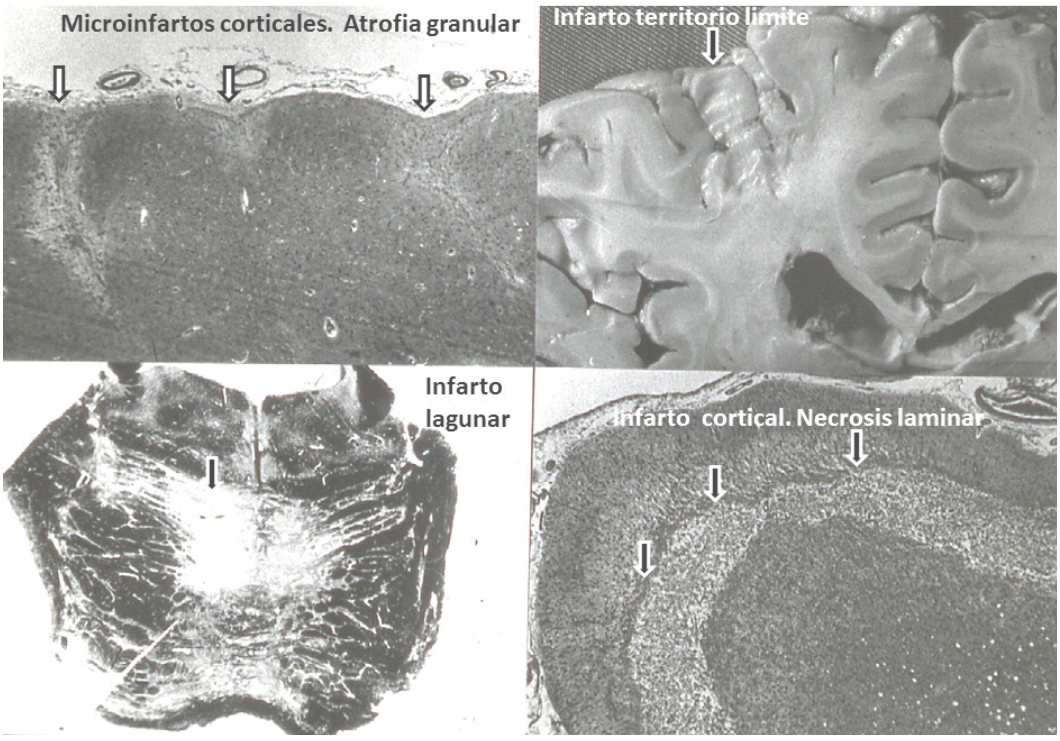


Figure 1. Different neuropathological varieties of small-vessel or haemodynamic cerebral infarcts (taken from: Zarranz JJ. Patología vascular cerebral. In: Perianes J. Tratado de medicina interna. Barcelona: Toray; 1978).

regions. Arteriolosclerosis may also cause rarefaction of myelin in the cerebral hemispheres (demyelination without infarct). Haemodynamic crises and anoxia affect the most vulnerable territories, causing such lesions as cortical laminar necrosis (Figure 1) or hippocampal sclerosis. This relationship between specific aetiologies and different types of vascular pathology is oversimplified; in practice, the majority of brains with cerebral vascular pathologies present infarcts of varied morphology.

The two most frequent pathological manifestations of arteriolosclerosis, small infarcts or lacunes and subcortical demyelination, were first described in the 19th century. According to Román,[1] cerebral lacunes were first described by Dechambre in 1838; in 1843, they were classified into different subtypes by Durand-Fardel, who also recognised status cribrosum and subcortical leukoencephalopathy. Alzheimer and Binswanger identified "arteriosclerotic brain atrophy" and "miliary apoplexy" due to multiple lacunes; these authors associated dementia with extensive subcortical demyelination.[1] In turn, Pierre Marie[2] emphasised the clinical manifestation, and particularly motor disorders, in patients with multiple lacunar infarcts, which he termed *état lacunaire*.

Another two of Pierre Marie's contributions (one through his disciple Dougherty)[3,4] are much less well known; these communications describe a different type of cortical infarct, very small in size, which he refers to as *état vermoulu* ("worm-eaten state"; Figure 2) as the surface of the brain appears deformed by craters, as though it had been eaten by moths or worms. This pathology was later recognised by neuropathologists but, as it could not be detected in vivo with modern neuroimaging techniques, whether by computed tomography (CT) or by magnetic resonance imaging (MRI), even with 3T scanners, it was overlooked by clinicians as a cause of the two most relevant syndromes associated with cerebral vascular pathology: dementia

and parkinsonism. Neuropathologists have also placed little emphasis in general on cortical microinfarcts in studies of the clinico-pathological correlation in dementia and vascular parkinsonism.

This study describes the evolution of the concept of *état vermoulu* due to cortical microinfarcts, from its first description to the current recognition of the condition in modern studies with 7T MRI scanners.

Material and methods

I reviewed the articles by Pierre Marie[3] and Dougherty,[4] as well as others listed in the reference section. I also reviewed classical neuropathology textbooks and atlases from my own library.[5-16] The literature search of the PubMed database used the following keywords: "etat vermoulu," "cerebral microinfarcts," "granular atrophy," "vascular parkinsonism," "cerebral small vessel disease," "vascular dementia," and "subcortical vascular dementia."

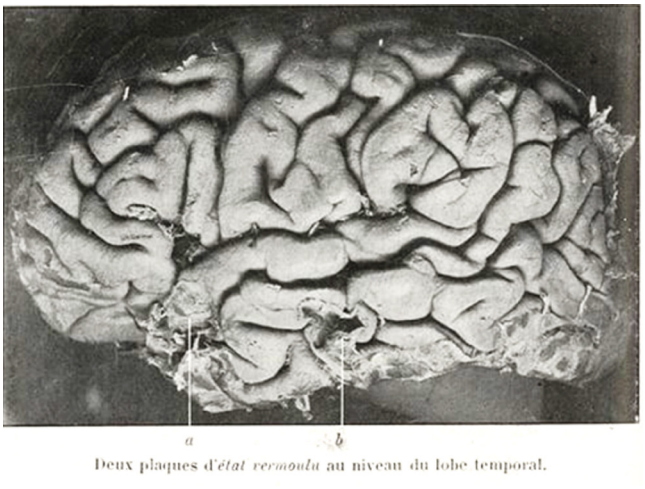


Figure 2. *État vermoulu* (taken from Dougherty[4]). The cortical lesions shown are extensive, larger than true microinfarcts, which are barely visible or invisible to the naked eye.

Results

Brief summary of the biography of Pierre Marie[17-19]

Pierre Marie was born in 1853 in Paris, where he studied first for a degree in law, and subsequently in medicine. In 1878, he began an internship under J.M. Charcot at La Salpêtrière, becoming *médecin des Hôpitaux* in 1888, a tenured professor in 1889, and head of service at the Bicêtre hospital in 1897. In 1907, he was promoted to the position of professor of anatomical pathology at the Faculty of Medicine; Pierre Marie contributed to the development of this discipline together with his disciples and successors Charles Foix and Gustave Roussy. He returned to La Salpêtrière, working in the Jacquart building, in 1912. It was not until the death of Jules Dejerine, with whom he had a very strong personal and professional rivalry,[20] that he was appointed chair of diseases of the nervous system in 1917.

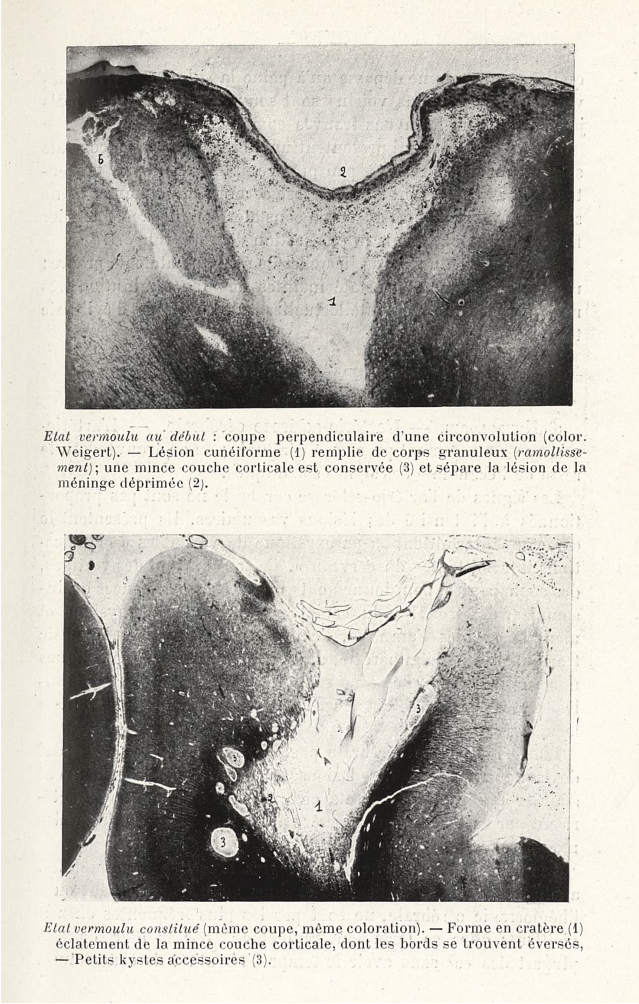
Following the tradition of Charcot, Pierre Marie was an extraordinary visual observer, and contributed to describing and updating a long list of diseases and syndromes: acromegaly, hereditary cleidocranial dysostosis, hypertrophic pulmonary osteoarthropathy, rhizomelic spondylosis (Strümpell ankylosing spondylitis), hereditary motor sensory polyneuropathy (Charcot-Marie-Tooth disease), late-onset cortical cerebellar atrophy, hereditary ataxia with retained reflexes, etc.

In 1923 he edited the two-volume work *Neurologie*. He retired in 1925, at the age of 72 years, and published his two-volume *Travaux et mémoires* in 1926 and 1928. He was the first secretary of the Société Française de Neurologie and, with Édouard Brissaud, founded the journal *Revue Neurologique*. He was also director of *Pratique Neurologique*. He was a member of the Académie Nationale de Médecine and was awarded the title *Commandeur de la Légion d'Honneur.* His latter years were blighted by the deaths of his wife (due to erysipelas), daughter (appendicitis), and son (botulism, contracted at the Institut Pasteur).

Original communications

Pierre Marie's[3] communication was actually preceded by that of his student Dougherty,[4] with both based on work conducted at his laboratory at Bicêtre. Only a brief summary of Pierre Marie's[3] communication is available today. It appears to have been presented as an oral communication with a presentation of the anatomical pathology specimen. The written summary is as follows:

> I present a new case of the cortical lesion to which I ascribe the term état vermoulu, a lesion that my student Dr Dougherty (of New York) presented earlier this year in a communication to this society. In the present case, we are able to see more clearly



Etat vermoulu au début : coupe perpendiculaire d'une circonvolution (color. Weigert). — Lésion cunéiforme (1) remplie de corps granuleux (*ramollissement*) ; une mince couche corticale est conservée (3) et sépare la lésion de la méninge déprimée (2).

Etat vermoulu constitué (même coupe, même coloration). — Forme en cratère (1) éclatement de la mince couche corticale, dont les bords se trouvent éversés, — Petits kystes accessoires (3).

Figure 3. *État vermoulu* (taken from Léri[22]). Characteristic wedge-shaped cortical microinfarcts that cause a small crater in the surface of the cortex.

> that this is a kind of ulcerative process bringing about destruction of the cortical grey matter, with the underlying white matter remaining intact or barely affected. This is precisely the opposite of what occurs in cortical infarcts (sic), in which the exterior surface of the softened gyri usually displays neither destruction nor ulceration.

It is unclear what Pierre Marie was referring to with the mention of "cortical infarcts without cortical damage," unless this was an error and he meant to say "subcortical." Taking a somewhat cartesian view regarding the pathological classification of cerebral infarcts, we can imagine the idea that may have guided Pierre Marie: I have already made history assigning the name *état lacunaire* to multiple subcortical infarcts, and I now use the term *état vemoulu* to describe purely cortical infarcts.

The complete text and figures from Dougherty's[4] communication are still available, together with the discussion by some attendees of the session. To summarise, he characterises *état vermoulu* as a pathology of the elderly population, present in 2% of the brains examined (the age and number of cases are not stated). The pathology is not "pure" and is associated with lacunar infarcts and "senile" atrophy. Clinical correlation is difficult to establish as all patients presented cognitive impairment. He describes very small focal lesions (the largest measured 2 cm) with tissue softening, with variable distribution across the cortex. Regarding pathogenesis, he attributes the lesions to the obliteration of arterioles and capillaries, followed by the death and disintegration of the corresponding territory. Analysis of the figures reveals a brain with a mixture of genuine small cortical lesions, measuring several millimetres, to which the concept of *état vermoulu* would be applicable, and more extensive lesions that more closely resemble the classical *plaques jaunes* caused by old infarcts (Figure 2). Dougherty's figure 3 shows an infarct affecting an entire cerebellar folium and half of the adjacent one; this lesion is much larger than those that the concept *état vermoulu* apparently seeks to describe. This combination of different types of infarcts in the same brain is very common, and does not invalidate the effort to highlight the individuality of purely cortical microinfarcts.

Two interesting contributions were made to the discussion of Dougherty's case. Firstly, M.E. Dupré noted that he "had had the opportunity to see this type of lesion, which he had been shown by Nissl and Alzheimer at Kraepelin's laboratory. They often coexist with lesions caused by Binswanger chronic subcortical encephalitis, which is observed in patients with dementia due to arteriolosclerosis."

This observation very closely reflects the reality of small-vessel brain disease, highlighting the association between small cortical infarctions and subcortical demyelination and dementia.

The second, more extensive, contribution was from Augusta Dejerine-Klumpke, the wife of Jules Dejerine,

Pierre Marie's great rival in the race for Charcot's chair, occupied at the time by Fulgence Raymond. Mme. Dejerine was herself an extraordinary neurologist and neuropathologist and the author of some excellent anatomical sheets. We may easily imagine that Dougherty would have been very uncomfortable during Mme. Dejerine's emphatic intervention, which contained significant methodological criticism. Her intervention was as follows:

> In the numerous cerebral hemispheres, whether pathological or seemingly normal on first inspection, that M. Dejerine and myself have had the opportunity to study in serial sections at both Bicêtre and at La Salpêtrière, we have often observed the lesions described by M. Dougherty: small superficial foci limited to the grey matter of the gyri, resulting in its complete or near-complete destruction.

She later stressed once more that serial sections are essential for detecting lesions deeper in the sulci, and not only those affecting the gyri, which are more accessible on initial inspection. Contradicting Dougherty's assertions, she believed that these lesions were able to cause descending secondary degeneration. She also recommended that normal anatomy not be studied by analysing the brains of elderly patients, who frequently present these cortical lesions. She concluded, perhaps with the irony or smugness of addressing somebody who had reinvented the wheel, that "the finding reported by M. Dougherty, while not uncommon, is nonetheless important knowledge for one who conducts research on the brain."

Therefore, while Pierre Marie, through Dougherty, presented his *état vermoulu* as a rare or novel pathology, Dupré indicated that it was a frequent finding and was known by Alzheimer and Nissl, and Mme. Dejerine also noted (besides her other comments) that it was often observed in studies of the complete brain. Essentially, these opinions, which depend at least partly on the method of observation, have been transmitted to the present day.

Two years later, Ficaï[21] (another disciple of Pierre Marie) presented four brains displaying *état vermoulu* from Bicêtre; these were probably the same specimens described in previous studies. At the time, it was common to report the same cases repeatedly, first individually and later in the context of doctoral theses or compilations and reviews. This seems also to have been the case for the reference that Léri (another student of Pierre Marie) makes to *état vermoulu* in his *Titres et travaux scientifiques*.[22] He presents the macroscopic image of the same brain as that included in Dougherty's[4] communication. Léri also contributes two histological images (Figure 3) that are highly representative of small cortical infarcts, with the characteristic craters observed in *état vermoulu*.

État vermoulu in other countries: Hugo Spatz' granular atrophy of the cortex

The concept of *état vermoulu* quickly reached the United States, according to an item discussing a publication with this title in *Revue Neurologique*.[23] It also reached Germany, with some works using the same name for the pathology.[24,25]

However, Spatz[26-29] dedicated several articles to the subject, using for the first time the term granular atrophy of the cortex. In the first of these texts, he attributed the lesions to a haemodynamic mechanism, as he found no vascular, parenchymal, or meningeal lesions adjacent to the microinfarcts. This haemodynamic pathogenesis contradicts Pierre Marie's hypothesis that the lesions were caused by occlusion of arterioles and capillaries. However, in subsequent articles, Spatz[27-29] highlights the possibility that the underlying pathology may be thromboangiitis obliterans. Thanks to the work of such an influential author as Spatz, the association between granular atrophy of the cortex and Buerger disease became a classic concept, especially in the German literature (von Winiwarter-Buerger disease), but also among English-speaking authors.[8] On the other hand, other authors stressed that the most important factors in the pathogenesis of granular atrophy of the cortex were such haemodynamic mechanisms as spasm, sudden drops in arteriolar and capillary blood pressure, low blood debit, cardiac insufficiency, and hypoxia.[30] The pathogenic dichotomy between microvascular occlusion and haemodynamic ischaemia had now taken root.

Some of the subsequent studies addressing this pathology in the United States also used the term granular atrophy.[31] However, in the classic neuropathology textbook by Weil,[5] the chapter on cerebral vascular pathology draws a clear distinction between status cribrosum and lacunar state, and once more uses the term *état vermoulu*: "the cortex may show formation of holes, imitating a worm-eaten state ('état vermoulu')" (Figure 4).

The scars forming after cortical softening produce many bizarre pictures. The cortex may show formation of holes, imitating a worm-eaten state (état vermoulu), or there may be deep fissures (fig. 92).

TEXTBOOK
OF
NEUROPATHOLOGY

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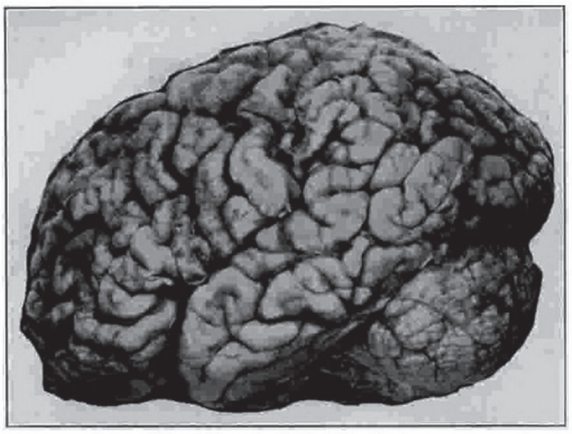


Fig. 92. Arteriosclerosis of Brain
Cortical changes: verrucose appearance of middle frontal and anterior central gyrus with operculum; état vermoulu in upper part of supramarginal gyrus

Figure 4. *État vermoulu* (taken from Weil[31]).

An extensive article on granular atrophy was published in Switzerland.[32] Following the ideas of other authors,[29,33] Wildi[32] proposed two types of lesions. One type were larger, irregularly distributed, multifocal lesions, with a very similar appearance to that described in the original communication by Pierre Marie. According to Wildi, this variety was rarer and was associated with arteriolar pathology, particularly secondary to hypertension; the author questioned the role of inflammatory vasculitis. He also proposed a more frequent, "systematised" variety. Regarding the latter form (Figure 5), he reproduced Morel's description[33]:

> Granular atrophy extends in a band, 1-2 fingers wide, from the frontal pole to the area of the temporal pole, describing a wide curve: it continues over its length from F2 to its foot, continues […] and flexes downward […] in a sickle shape […]; it is situated over the area where the territory of the Sylvian artery meets that of the anterior cerebral artery on the one hand and the posterior cerebral artery on the other […]. Furthermore, it is symmetrical.

The author concludes that: *1)* granular atrophy lesions are not exceptional, appearing in 4.7% of all autopsies if the brain is studied macroscopically after removal of the meninges, but have received little attention; and *2)* the bilateral, symmetrical pathological topography of the systematised variety represents a strong argument in favour of haemodynamic pathogenesis, with ischaemia in anastomotic or watershed territories, to the point that he added the concept "cardiopathy" to that of granular atrophy. However, he also described how the pathogenic mechanisms, like the lesions, may overlap, and that granular atrophy often co-presents with other types of infarct, subcortical leukoencephalopathy, or hippocampal sclerosis.

Recent neuropathological textbooks and atlases show little interest in granular atrophy

Of the neuropathological textbooks and atlases from recent decades that I have consulted, few comment on granular atrophy as a particular variety of cerebral vascular pathology.[5-16] It is specifically mentioned and

illustrated in the works by Weil,[5] mentioned previously, and Greenfield[8] and Escourolle and Poirier,[11] and is essentially discussed in relation to arteriolosclerosis and factors related to haemodynamic failure. The atlas by Malamud and Hirano[12] expands the causes of granular atrophy, including a case secondary to lupus erythematosus; following the classic approach of Spatz, the authors associated it with vasculitis, such as Buerger thromboangiitis. Ferrer and Vidal[34] only dedicate a brief paragraph to the condition in their review of the neuropathology of cerebrovascular disease. They refer to it as "an old term that designates local atrophy and gliosis producing a granular appearance on the surface of the cerebral cortex at the sites that usually correspond to the borders of the major territories of the cerebral arteries."

Cortical microinfarcts may go undetected in ordinary brain autopsy studies

As noted by Augusta Dejerine-Klumpke[4] and Wildi,[32] cortical microinfarcts may go undetected both if macroscopic inspection is rushed and the meninges are not removed (Figure 6), and if microscopic or macroscopic studies do not include rigorous processing with serial sections. This methodology based on the study of the brain in large blocks, after embedding in celloidin or paraffin or freezing, is very costly and is beyond the means, or at least rarely performed, at most neuropathology laboratories. When microinfarcts are diffuse and extensive (Figure 7), the difficulty lies not in detecting them but in quantifying them. However, when microinfarcts are restricted to a small number of gyri, extensive study is needed to detect them (Figure 8A-C). Sampling based on small blocks can easily fail to detect cortical microinfarcts. Attempts have been made to mitigate this limitation by using larger samples. The study by Westover et al.[35] included samples of up to 23 brain areas, obtaining more than 90 histological preparations; despite this, the samples constituted less than 1 cm^3 of brain tissue, according to the authors' calculations. In the analysis of their results, the authors conclude that if one or two microinfarcts are detected in routine processing of the brain, then the whole brain will probably present hundreds or even thousands of lesions. In a review of 32 articles addressing the neuropathology of cortical microinfarcts, Brundel et al.[36] conclude that these lesions are common in the brains of elderly individuals, especially those with cognitive impairment, but that as sampling was not complete or systematic, it is impossible to ascertain their true density and contribution to symptoms. The conclusion that cortical microinfarcts are frequent is consistent with the arguments of the classical authors Augusta Dejerine-Klumpke and Alzheimer, and more recently Wildi,[32] and raises the question of their true significance in the pathogenesis of the two most relevant ischaemic neurological syndromes, cognitive impairment/dementia and parkinsonism.

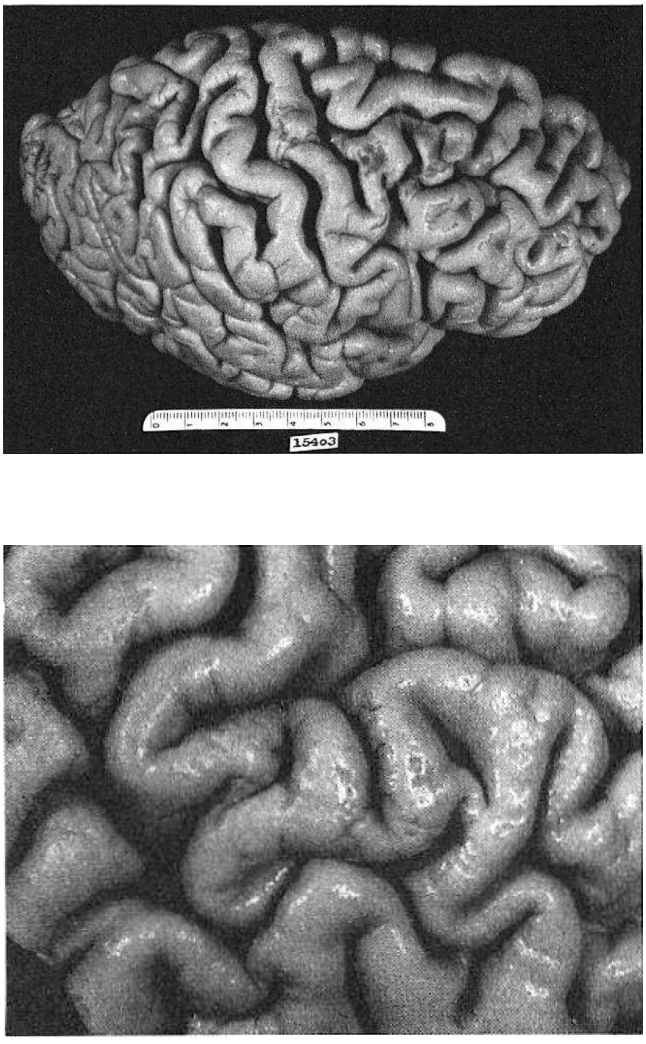


Figure 5. Granular atrophy (taken from Wildi[32]). A) Spatz-Lindenberg disease type I. Lesions present as relatively large cortical ulceration of irregular distribution. B) Type II or "systematised" disease. Lesions are very small and are distributed in a band, in the F2 region in this image, which is stereotyped and symmetrical in both hemispheres, in all cases.

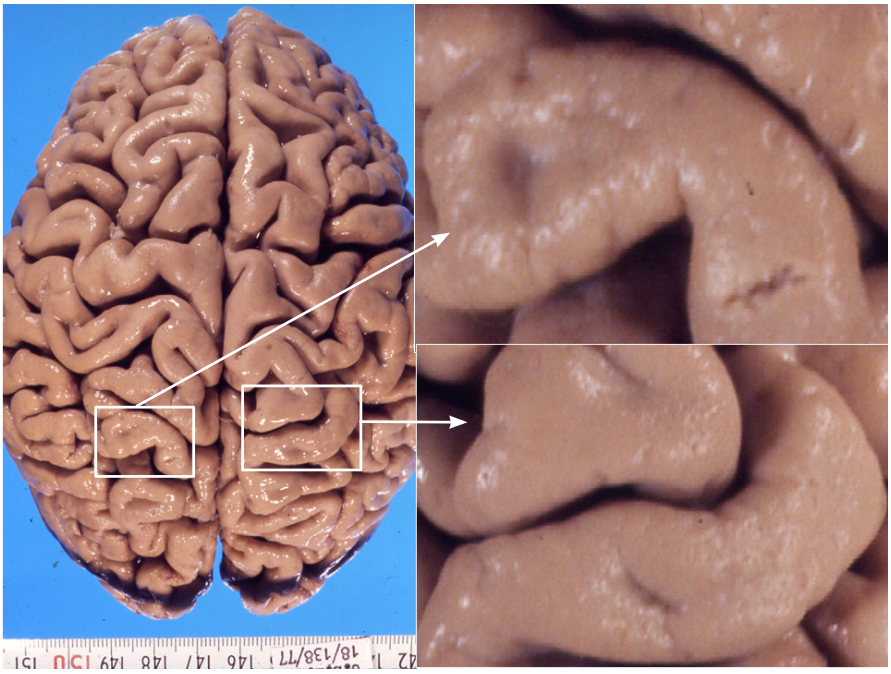


Figure 6. The small cortical craters observed in *état vermoulu* or granular atrophy are more easily identified in fixed brain tissue after removal of the leptomeninges.

Cortical microinfarcts are not detected in basic neuroimaging studies

The incorporation of CT studies, and later MRI, with scanners of up to 1.5 T, as routine diagnostic techniques has enabled in vivo study of four characteristic lesions caused by arteriolosclerosis: altered white matter density or signal, lacunar infarcts, status cribrosum of the basal ganglia, and hippocampal sclerosis. However, it is not possible to detect cortical microinfarcts, which are difficult to identify even with 3T MRI studies.[37] This shortcoming reinforced the idea, dominant since the 1990s, that both cognitive impairment[38-46] and parkinsonism[47-50] secondary to ischaemia are fundamentally caused by subcortical lesions; this hypothesis was considered in the creation of criteria for the clinical and pathological diagnosis of both entities. As recently as 2013, recommendations for standard neuroimaging studies of small vessel disease did not include cortical microinfarcts.[51]

Detection of cortical microinfarcts with seven-Tesla magnetic resonance imaging

Brundel et al.[36] demonstrated for the first time that cortical microinfarcts observed in autopsy studies could be detected in ex vivo MRI studies at 7 T. More recent studies with 7T MRI demonstrate that cortical microinfarcts can also be detected in vivo.[36,37,52-62] They are common in elderly individuals (24%) and patients with cognitive impairment (62% if aetiology is vascular and 43% in Alzheimer disease). Their distribution is not random, and they appear to be concentrated in "bands" in the cortical areas where classical texts report predominance of granular atrophy. Dysautonomia and haemodynamic crises probably increase the frequency of cortical microinfarctions.[63]

The dilemma of the clinical correlation with neuropathological or neuroimaging findings of microinfarcts

The gold standard for confirming clinical diagnosis of many neurological entities that cause dementia or

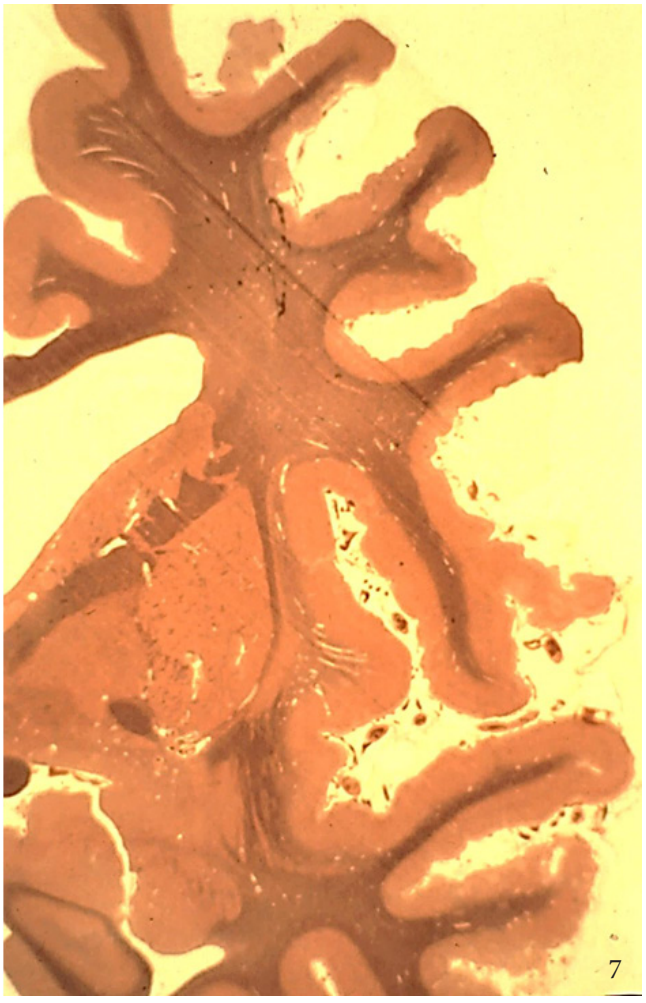
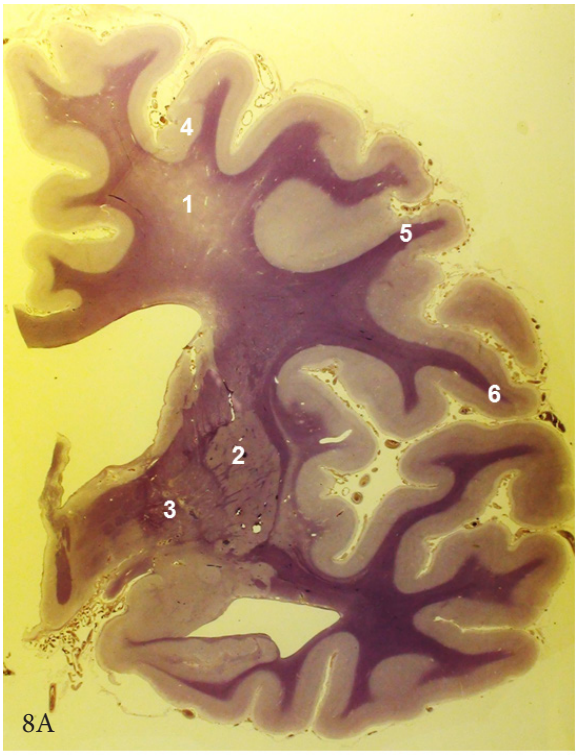
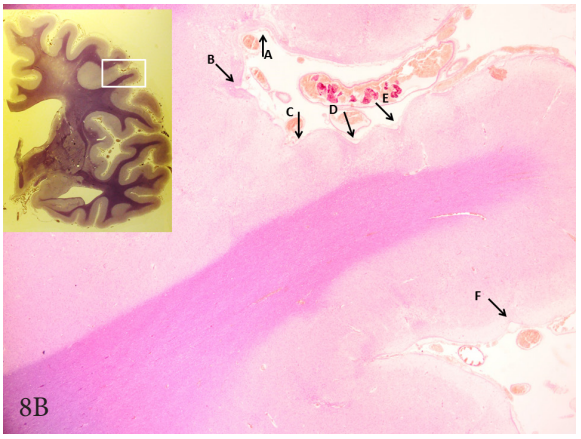


Figure 7. Coronal section of a cerebral hemisphere (celloidin, haematoxylin-eosin staining). All gyri in the territory of the middle cerebral artery present significant atrophy and innumerable small infarcts, giving them the appearance of being worm-eaten (*état vermoulu*). In contrast, the gyri of the medial face, in the territory of the middle cerebral artery, are smooth and normal.





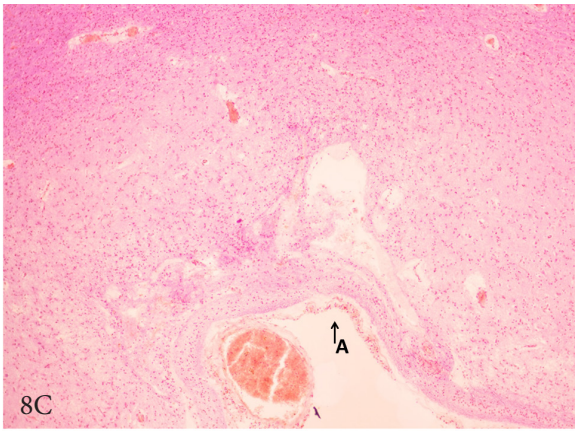


Figure 8. A) Coronal section of a cerebral hemisphere (paraffin, phosphotungstic acid haematoxylin staining). The macroscopic appearance seems largely normal, with the exception of ventricular dilation and a degree of subcortical myelin pallor. However, histological study reveals the characteristic lesions of arteriolosclerosis in 6 locations: *1)* subcortical white matter demyelination; *2)* status cribrosum; *3)* lacunar infarcts; and *4-6)* cortical microinfarcts. B) Photomicrograph of the area labelled 5 in Figure 8A. Various microinfarctions give the cortex the appearance of granular atrophy. C) Magnified image of the area labelled A in Figure 8B. Compare to Léri's photomicrograph (Figure 3).

parkinsonism, especially those of neurodegenerative origin, is neuropathological examination. In the main examples of these entities, Parkinson's disease and Alzheimer disease, neuropathological stages have been established according to the density and spatial distribution of lesions in the brain; this enables us to draw a correlation, albeit imperfect, with clinical signs. Staging is facilitated by the homogeneity of elemental lesions that can be quantified in these processes: Lewy bodies or neurites in Parkinson's disease and senile plaques and neurofibrillary tangles in Alzheimer disease.

However, it is very difficult to establish a similar correlation with qualitative and quantitative data in the study of cerebral vascular pathology, despite proposals to expand and harmonise neuropathological studies.[49,64-66] There are two reasons for this: *1)* the heterogeneity of the lesions that may coexist in the same brain; and *2)* the more or less random distribution of lesions, for which reason a complete quantitative study would have to follow the methodology proposed by Mme. Dejerine, with the whole brain being processed in serial sections, a considerable undertaking that is impossible in everyday practice.

Therefore, in vivo or ex vivo volumetric studies of the whole brain with a 7T MRI scanner may serve as a subrogate for this unviable complete neuropathological study. After neuropathological validation of MRI images of cortical microinfarcts, it will be possible to perform quantitative studies of their density and spatial distribution and establish their true contribution to cognitive impairment and parkinsonism secondary to vascular pathology.

With this information, a considerable burden of cortical microinfarcts, an unperceived *état vermoulu*, may explain certain incongruities that are frequently noted in clinical practice, such as patients with dementia or parkinsonism and presenting vascular risk factors but in whom ordinary neuroimaging studies reveal few subcortical lesions.

Conflicts of interest

The author has no conflicts of interest to declare. This study has received no public or private funding.

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