TORBEN FOG

The Topography of Plaques in Multiple Sclerosis

MUNKSGAARD

ACTA NEUROLOGICA SCANDINAVICA
SUPPLEMENTUM 15 · VOLUME 41, 1965

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With Special Reference to Cerebral Plaques

BY

TORBEN FOG, M. D.

Drawings by
ROSELIL HAMMERICH

MUNKSGAARD
COPENHAGEN 1965

Translated from the Danish
by *Harry Cowan*, B.Sc.

PRINTED IN DENMARK
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Preface

My intention has been to carry out a thorough analysis of the so-called vascular pathogenesis of plaque formation in multiple sclerosis. The present study, therefore, is based both on the literature and on my own investigations. Certain sections of Chapter I have been taken from my thesis in Danish on the lesions of the spinal cord in multiple sclerosis. I hope that the present study will contribute to elucidating the formation of plaques throughout the entire nervous system, although the analysis of detail in the study concerns the telencephalon only.

The work could only be carried through as a result of the exceedingly great help and interest which I received from my assistants, as it would have been impossible for me to complete these time-consuming investigations alone. My warmest thanks are extended to them all.

The embedding and cutting of the numerous hemisphere sections were done on Jung's macrotome by my two technical assistants, Mrs. *Karen Konow* and Mrs. *Anne-Marie Rahbek*. The care with which this was carried out and arranged was a necessary condition for the work being done at all.

Mr. *Aage Andkjær Hansen* provided the necessary technical assistance to make possible the work of drawing the diagrams on Bourges acetate foil. Mr. Andkjær Hansen constructed the necessary apparatus himself, and his technical inventiveness and precision made this work possible. He also carried out all the photographic work.

Last, but not least, I must mention the artist, Mrs. *Roselil Hammerich,* who made all the drawings in the study. Her quite outstanding precision and ability, and her sense for sober scientific accuracy, have been responsible for this study fulfulling its intention: a presentation and documentation of the plaques in the telencephalon.

The National Multiple Sclerosis Society in Denmark has provided economic support for the entire work, including the costly printing. The heavy expenses associated with this study have to be viewed in the light of the significance which such a clarification of the morphology of these plaques must have for our future work in multiple sclerosis.

CHAPTER I

Introduction

REMARKS ON THE HISTORY OF THE VASCULAR HYPOTHESIS

It is a general observation that the largest plaques are found in the white matter of the central nervous system. This does not imply that multiple sclerosis is exclusively a "leucoencephalitis". Plaques can be found everywhere, no sites are wholly free, although there do seem to be certain so-called sites of predilection. In the case of the cerebrum these are the periventricular zones around the lateral ventricles, the medulla of the hemisphere and the subcortical zones. *Hallervorden* (1940) actually considers that when there is absence of periventricular sclerosis, doubt may be cast on the correctness of the diagnosis. In the more clinically localized forms of multiple sclerosis: the spinal, pontine, cerebral type, etc., autopsy shows plaques in many other sites in addition (*Hallervorden* (1940)). *Siemerling & Räcke* (1911) in three cases found plaques in the medullary substance only, and in two cases, mainly in the cortex. *Steiner* (1931, p. 385) states that the entire central nervous system is involved in the process, although there is preference for the white matter. The gray matter is often affected only as a continuation of the lesions in the white matter. Periventricular sclerosis is particularly dominant. Small plaques often show a dependence on the vascular system, but this does not apply to all plaques, in which the vessel only apparently forms the centre, as then there is often "eine örtlich kennbare Lösung von dieser Bindung" (p. 359). *Marburg* (1936, p. 637) remarks with regard to the localization in general that plaques are sited perivascularly and subependymally. The perivascular localization is true only with limitations. *Dawson* (1916, p. 662), in his classic monograph, states that the sites of predilection are around the vessels corresponding to the branches of the end arteries, i.e. around the ventricles and at the sites where the vessels subdivide, namely at the transitions between the gray and the white matter, and also at the places where much neuroglia is found preformed, i.e. periventricularly, pericentrally, in the chiasma, posteromedially, marginally and perivascularly. It is remarkable that he finds periventricular plaques in only 6 of his nine cases of multiple sclerosis!

Borst (1903) has collected the entire European literature prior to 1903. He concludes that the plaques are mainly seen in the boundary between cortex and medulla, periventricularly and subpially in the spinal cord, around the central canal and at the sites of entry of the large vessels. It is also obvious to *Borst* that in one way or another, plaques possess a relationship with the vascular system.

The localization of the plaques, and the dependence of their form on the vascular system, are problems which recur in almost all investigations on multiple sclerosis, and have always occupied authors very strongly in all major studies of the morbid anatomy of the disease. *Strähuber* (1903) lists no less than 19 authors who found intimate relations between vessel and plaques, while ten did not. This relationship plays a major role for Borst in his theory (1903, p. 137). *Marburg* (1906, 1930), in his theory, pays considerable attention to the perivascular plaques, but he reports that plaques may be found which are not perivascular, and where the extent of the plaques in no way corresponds to any vascular territory. His point of view follows that of *Falkiewicz* (1926), who bases his opinions on an investigation of the plaque relationship in the spinal cord. *Siemerling & Räcke* (1911), in discussing the pathogenesis, give the vessels a central place, because of the perivascular site which they found in 7 cases. *Anton & Wohlwill* (1912) cut serial sections of plaques and came to the conclusion that over a stretch, a plaque covers a central vessel like a mantle, but plaques never correspond to the area of capillary distribution of the vessels. *Dawson* (1916) also prepared plaques as serial sections, and concluded (p. 619) that it can be confirmed that the branches of a main vessel are the ones which are affected by plaques, and that it is these primary small zones, each associated with its own branch, that finally become confluent. But "the changes appear within, but do not coincide with the areas of distribution of the arteries, and it may be extremely difficult to determine the territory of an artery" (p. 619–20). In the case of the periventricular plaques, *Dawson* (p. 621) considers that these lie around the subependymal vessels, from which they digitate into the white matter. The apparently isolated islets are mutually connected by bridges of more or less demyelinated tissue, lying around a central vessel. This appears to be confirmed by *Döhring*'s studies (1940), whereas both *Steiner* (1931) and *Hallenvorden & Spatz* (1933) find that these periventricular plaques are an actual noxious influence from the ventricular fluid, as these plaques cannot be explained on the basis of any vascular genesis.

In the case of the cortical plaques, *Schob* (1907) was the first to show that these were situated perivascularly, and follow a cortical vessel

with branches. *Steiner* agrees with *Schob* only to a certain extent, as he sees in the form of the cortical plaques what he in fact considers to be a proof of a diffusion of the noxious influence from the meninges (p. 385). Finally, *Putnam & Adler* (1937) state that small plaques lie around contorted veins.

Pette wrote in 1928 "Der Beweis einer gesetzmässigen Abhängigkeit jeder Herdbildung vom Gefässsystem könnte zweifellos dann als erbracht gelten, wenn es nachzuweisen gelänge, dass das Versorgungsgebiet eines ganzen Gefässtammes in einen Herd aufgeht. Dieser Nachweiss ist bisher nicht erbracht worden." (Emphasis by *Pette*, p. 116–17). In a corresponding manner *Hallervorden* (1940) writes: "Die Herden entsprechen nicht den Ernährungsgebieten einer Arterie oder den Abflussgebieten einer Vene". (p. 213).

There is therefore more or less agreement as to the sites of predilection for plaque formation in the brain, and likewise as to the perivascular localization of at any rate some of the plaques. With regard to this perivascular localization, it is now more or less agreed that plaques do not correspond to the capillary territory of one single vessel. *Dawson* is not quite sure as to the extent of an arterial vascular territory. *Hallervorden* believes that plaques do not correspond to the drainage area of a vein, while *Putnam* establishes his theory of venous thrombosis, in which a fresh zone of degeneration arises close to a vein, should this thrombose.

The thrombosis theory of Putnam (1930, 1931, 1935, 1936, 1937 and 1939) reawakened interest in the "vascular genesis" of plaque formation. We will not recall the experimental prerequisites for this theory, nor the studies of *Putnam* and his co-workers. *Putnam*'s theory was that plaques form in consequence of a primary thrombosis of the small veins of the central nervous system.

It must be admitted that this theory has few or no supporters to-day. But it is to *Putnam*'s credit that he reawakened interest in the role of the veins. Four independent investigators have, in fact, made a special effort to develop this theory, *Dow & Berglund* (1942), *Broman* (1947, 1949), *T. Fog* (1948, 1950) and *Zimmermann & Netsky* (1950). As my studies exclusively concerned conditions in the spinal cord, these conditions will be discussed first.

THE SPINAL PLAQUES

In 1948–1950 I studied serial sections of spinal cord in typical cases of multiple sclerosis. Conditions here are very clearly presented, and the

vascularization is generally well known. *Borst* (1903, p. 89), on the basis of his study of the literature, states that plaque localization in the spinal cord is mostly subpial, around the central canal and at the sites of entry of the large vessels. *Anton & Wohlwill* (1912) identify their cases of encephalomyelitis disseminata with multiple sclerosis, and state that plaques show symmetry. In particular, those plaques are discussed which lie in the ventral funiculus alongside the ventral median fissure, and which are delimited centrally by a convex boundary which also involves the adjacent territory of the gray matter. In addition many central plaques were found, and the centrally placed dorsal funiculus plaques were dominant in this area. *Schob* (1907) mentions the dorsal and lateral funiculi. The symmetry is striking. *Dawson* (1916, p. 620) finds no particular sites of predilection, except that the plaques in the dorsal funiculus are found especially around the dorsal median sulcus, and in the lateral funiculi their site corresponds most frequently to the lateral pyramidal tracts. *Marburg* (1936, p. 635) writes that it is the white matter of the spinal cord which is preferably attacked. The dorsal funiculus is attacked more frequently than the lateral and ventral funiculi. The plaques are often "säumbildend", are symmetrical, and do not spare the ventral median fissure. *Pette* (1942) arrives at the same result as *Marburg*. *Falkiewicz* (1926) has a very interesting material, consisting of the spinal cord from 12 typical cases of multiple sclerosis. He describes 2–3 blocks from each case and reaches the following conclusions with regard to the localization of the plaques: The sites of predilection are the dorsal areas of the lateral funiculi and the ventro-lateral areas of the lateral funiculi. Plaques are not uncommonly seen along the ventral median fissure, being in the form of bands, symmetrical and pointed ventrally, and finally, in the case of the plaques of the dorsal funiculus, showing typical form and localization (see below).

In the case of the spinal cord, the same uncertainty holds with respect to the plaque-vessel relationships as described above in the case of the brain.

The wedge-shaped plaques of the lateral funiculi of the spinal cord have led to analogies with infarction formation. (*Borst* (1903, p. 137), *Strähuber* (1903), *Siemerling & Räcke* (1911), *Schob* (1907), *Dawson* (1916, p. 618) and many others). *Dawson* (1916, p. 618) identifies *Mager*'s (1900–02) acute myelitic foci with sclerotic plaques. The wedge-shape is supposed to arise as a result of the relationship of the small radicular arteries, which according to *Kadyi* (1889) supply the lateral funiculi with arterial blood. The rounded, centrally-placed shape is the result of these arteries being divided into ascending and descend-