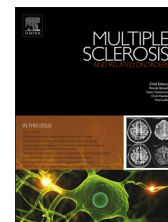




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REVIEW

Observations on the brain vasculature in multiple sclerosis: A historical perspective



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History

Abstract

Objectives: To review the literature on vascular aspects of multiple sclerosis (MS) specifically pathological observations of the perivenular distribution of MS lesions and venous pathology in MS. **Methods:** Comprehensive literature search from 2012 back to 1839.

Results: One hundred and thirty two papers from 1839 to 2012 were included in this study. Multiple authors observed central venules in MS lesions as a feature of MS with the first specific mention by Rindfleisch in 1863. Recent high field strength MRI has reintroduced the perivenular distribution of MS lesions to a new generation, and has suggested that there is disease specificity to this distribution. In addition Putnam and others in the 1930s hypothesized that venous disease was causative for MS. Treatments based on these observations have included anticoagulation, hyperbaric oxygen therapy, and recently endovascular venous procedures. The significance of these findings in terms of MS pathogenesis has been debated over the same period of time.

Conclusions: While the controversy over venous disease in MS is new, the observation of perivenular MS plaques and venous theories about MS pathogenesis are as old as the history of MS research.

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1. Introduction

It is common in medicine for observations to be made and then become lost or obscured by other events in a certain field. In the case of multiple sclerosis (MS), both the perivenular distribution of lesions and the hypothesis that larger veins may be involved in MS have been noted many times over the past 160 years, with varied interpretations regarding the potential role of blood vessels in MS pathogenesis. In this study we review the literature exploring the relationships between the venous system and the central nervous system in MS.

2. Methods

We performed a literature search focused on vascular observations relating to MS from 1946 to 2011 (OvidMEDLINE, OvidOLDMEDLINE), with hand searched references of articles earlier than Ovid databases dating back to 1839. The search included the following search terms: multiple sclerosis, vascular, pathophysiology, vein, jugular, azygous, and venous (multiple sclerosis and (vascular or vein or jugular or azygous or venous.mp.)). We performed a secondary search using the same terms in Google Scholar (<http://scholar.google.com/>). We also performed a text search using McAlpine's Multiple Sclerosis 1998 and 1955 editions, Churchill Livingstone, London; Multiple Sclerosis, Principles of Neurology, Adams et al., McGraw-Hill, 1997, USA; and Multiple Sclerosis, the History of a Disease, T. Jock Murray, 2005, Demos, New York. Studies were included in the final reviewed group of papers if they met the following criteria:

- (1) Primary papers referring to multiple sclerosis which discussed vein, venule, or venous sinus appearance or pathology in the multiple sclerosis population.
- (2) Languages limited to English, French, and German to provide for translation.
- (3) We excluded multiple studies from one group if they reviewed similar findings or populations.
- (4) We did not comprehensively review the literature after the observations by Zamboni et al. (Zamboni as they were not germane to the historical record prior to his papers. However we did look at the frequency of publications over time prior to and after 2009).
- (5) We excluded articles on retinal venous changes in MS unless they were connected with studies looking at brain or systemic venous changes.

3. Results

Our initial search yielded 1420 articles of which all abstracts were reviewed. Of the 1420, we excluded 1237 articles which did not meet all inclusion criteria. We excluded articles specifically dealing with the presence of retinal vessel abnormalities unless they referred to how this would relate to brain vascular change, as well as many articles which referred to vessels only in passing.

We reviewed the remaining 183 articles from the Medline search, a Google scholar search and the hand searched texts using the above criteria. Of these only the articles which were primary sources or which commented directly upon the sociology of vascular theories for MS were included in the final manuscript. A final 102 articles met inclusion criteria were utilized in this review, though not all were included in the final reference list.

4. Early history

4.1. 1820s-1930s

Early observations of blood vessels in MS focused on descriptions of the anatomy and histology of the disease's plaques. In his classic pathological text, French anatomist Jean Cruveilhier ([Cruveilhier, 1928-1842](#)) in a series of pathological manuscripts dated 1829-1842 provides some of the earliest descriptions of the MS plaque. Cruveilhier compared areas of sclerosis with the results of embolism, noting "*curious irregular scars 'almost like areas of embolism'*". Thus Cruveilhier alluded to a vascular relationship without specifically documenting a perivenular distribution of lesions.

Georg Eduard von Rindfleisch was the Chair of Pathology at the University of Würzburg. In 1863 he described vessel changes in autopsied brains of MS patients and first noted that a blood vessel was often prominently positioned in the center of MS plaques ([Rindfleisch, 1863](#)). He also noted that the vessels show changes typically found in chronic inflammatory processes, with thickened walls and the accumulation of cells in the adventitia. He observed that the vessels seemed dilated and the capillaries appeared double walled with 'round cells' between layers.

Hugo Ribbert, a German Professor of pathology at the University of Bonn, suggested in 1882 that the cause of MS lay in the blockage of capillaries by minute thrombi ([Ribbert, 1882](#)). He noted the accumulation of small 'nuclei' (likely leukocytes) around vessels and described changes

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