

Phlebology

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CCSVI, *Chlamydia pneumoniae* and multiple sclerosis clarification

Lewis expresses concern by our recent article describing the effect of a prolonged antibiotic protocol to treat persistent *Chlamydia pneumoniae* (Cpn) infection on the extracranial venous circulation in multiple sclerosis (MS).¹ In our article, we refer to the term chronic cerebro-spinal venous insufficiency (CCSVI) as referring to the venous disease associated with MS.² Is Lewis contending that there is no venous disease associated with MS? In addition, is Lewis contending that the meta-analysis which found nine studies satisfying the authors' criteria for inclusion, demonstrating a significant correlation between CCSVI and MS (odds ratio 1.885, $P < .0001$) with no significant heterogeneity of the studies ($I(2) = 18$, $P = .279$), was invalid?

Firstly, the presence of a venous disease associated with the lesions of MS goes back as far as 1863² and has been described in different ways by many physicians and researchers since that time.^{3–10} Zamboni re-ignited interest in the venous disease when he described obstructions in the extracranial circulation in the neck of MS patients (particularly in the internal jugular veins), then went on to claim that these obstructions could result in reflux flow in the intracranial cerebral veins, causing iron deposition in the cerebral tissues that triggered an immune response.^{11,12} Zamboni further postulated that these extracranial venous obstructions were due to venous truncular malformations that could possibly be treated by balloon venoplasty, which could in turn improve the symptoms of MS.¹³ Recently, Zamboni has published the results of the “Brave Dreams Trial” which has demonstrated that the balloon venoplasty technique is largely ineffective for MS patients.¹⁴ At this stage, we make clear that at no time have we stated that we agreed with Zamboni's concept of CCSVI. Nevertheless, there is considerable evidence that there is a venous disease affecting the extracranial (Internal jugular veins (IJV) and vertebral veins) and cerebral veins in MS.^{2–9}

Thibault¹⁵ in 2012 was one of the first to question Zamboni's concept of CCSVI, stating that the main

dilemma for this model of CCSVI and its claimed association with MS is that it assumed a congenital origin is pivotal to the development of MS which contradicts many of the known facts of MS, in particular, those related to epidemiology and geographical distribution.¹⁶ In addition, there was no pathological evidence that these ultrasound and radiologically diagnosed abnormalities are truncular venous malformations. Subsequent histological examination of the diseased IJVs provided an alternative mechanism of intraluminal fibrosis, the probable result of past resolved inflammatory or thrombotic process that involved the wall of the IJV.¹⁷

The infective venulitis theory developed by Thibault¹⁵ arose from the extensive epidemiological studies of John Kurtzke who hypothesised that clinical MS was a widespread (but then unknown) persistent infection of adolescents and young adults which only rarely lead to clinical MS after years of incubation.¹⁸ Cpn appeared to be the most likely pathogen that was consistent with Kurtzke's criteria and that was both associated with MS and was also capable of causing disease in both arteries and veins.^{19,20} In our present article, we have cited just 15 of the many positive references that associate the presence of Cpn with MS.

In contrast, Lewis cites two review articles that “fail to support the contention that *Chlamydia pneumoniae* is important in the pathogenesis of Multiple Sclerosis”. The first article by McKay et al.²¹ refers to two population studies. However, in the first of these studies, the Nurses' Health Study (NHS) and Nurses' Health Study II (NHS II) cohorts,²² seropositivity for Cpn was only moderately associated with the risk of relapsing-remitting MS (OR = 1.7; CI = 0.9–3.2), but was strongly associated with the risk of progressive MS (OR = 7.3; CI = 1.4–37.2). The Nurses Health study in fact supported a positive association between Cpn infection and progressive MS. The second study referred to by McKay was a prospective nested case-control study among three million US Army personnel and 121,466 members of the Kaiser Permanente Medical Care Program (KPMCP) cohort, that came to the conclusion that neither Cpn seropositivity nor serum anti-Cpn IgG antibody titres predicted risk of

developing MS.²³ However, due to the heterogeneity of results between cohorts, Munger et al. could not exclude the possibility that infection with *Cpn* may modify the risk of MS.

In the third article cited by McKay, Krametter et al.²⁴ studied humoral immune responses to *Cpn* in paired sera and cerebrospinal fluid (CSF) of patients with definite MS and other inflammatory and non-inflammatory neurological diseases. Seropositivity was not significantly different between these groups. However, *Cpn*-specific IgG titres were significantly higher in CSF of MS than in controls. Sixteen out of 52 seropositive MS patients (30.8%) showed intrathecal synthesis of *Cpn*-specific IgG but only 1 of 43 seropositive controls (2.3%) (Chi-square $P < .001$).

The next review article cited by Lewis from Libbey et al.²⁵ refers to six studies including a large meta-analysis all of which support a role of *Cpn* in multiple sclerosis and only one recent study of PCR testing targeting the bacterial *16S* rRNA gene that failed to detect *Cpn* DNA in CSF of MS patients.²⁶ However, it is well recognised that there are sensitivity issues in detecting the presence of *Cpn* DNA by this type of PCR testing.^{27,28}

The third study cited by Lewis that supposedly fails to support the contention that *Cpn* is involved in MS concludes that *Cpn* was more incident in the biological liquids of patients with multiple sclerosis than in healthy volunteers.²⁹ So, the evidence that Lewis presents that *Cpn* is not a significant factor in the development of MS could be argued to support the case.

Lewis then goes on to cite the study by Woessner et al. that reported that three 6-week courses of roxithromycin over the space of a year did not ameliorate the course of MS in a group of patients.³⁰ He appears to believe that this is further evidence that *Cpn* is not involved in the initiation and progression of the disease. However, this is a weak study for two reasons:

- It is well known that in chronic infections, *Cpn* enters a persistent state and relapse can occur even after a prolonged course of “anti-chlamydial” antibiotics. Conventional agents in fact force the organism into a persistent state that can relapse back to a normal replicating state when more favourable conditions return.^{31,32} This is described in our article and is the reason for the necessity of the prolonged, combined antibiotic protocol that was developed by the Vanderbilt University group.³³ It is interesting that Lewis, whilst citing the roxithromycin trial, fails to cite the minocycline combined with glatiramer acetate trial that did reveal benefit after nine months when compared with glatiramer acetate alone.³⁴

- With only 15 and 13 in the intervention and placebo groups, the study is underpowered to detect typical clinical changes in a continuous score (Expanded Disability Status Scale (EDSS) in this case); this study could only detect a Cohen’s *d* of over 1 at the usual power of 80% and type 1 error rate of 0.05, which is a very large effect size. The authors also did not report the mean or median scores at baseline and follow-up, which makes it difficult to independently assess the results. Hence, this study is not a robust negative result.

Finally, Lewis criticizes the design of our study which focuses on observing the changes in blood volumes flows in the extracranial veins of the neck after six months of the combined antibiotic protocol, inferring that we need to study clinically relevant end-points and disease progression. We completely agree and refer to the last sentence of the article: “Further research is required including a double-blind placebo controlled randomised trial using the CAP with ultrasound, magnetic resonance venography (MRV), and neurological MRI assessment along with clinical neurological assessment.” The reality however is that science is incremental and views our results as one step in working towards a trial with clinical endpoints.

To avoid such confusion in the future, the CCSVI terminology introduced by Zamboni will be replaced with the more precise descriptive term “Neck Vein Obstruction” in future publications by our group.

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