



# The relationship of syphilis to small vessel stroke in the absence of neurosyphilis: real or imaginary?

A relação da sífilis com o acidente vascular cerebral na ausência de neurosífilis: real ou imaginário?

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In a prospective study from *Universidade Federal do Paraná* published in this issue of *Revista Arquivos de Neuro-Psiquiatria*, Ferreira and colleagues<sup>1</sup> demonstrated an association between small vessel stroke and positive syphilis serology after excluding patients with cerebrospinal fluid (CSF) findings consistent with neurosyphilis. The authors argue that this association is likely a consequence of endothelial dysfunction resulting from *Treponema pallidum* infection.

Abnormalities of the CSF in early syphilis had been commonly recognized in multiple studies dating from the early 20<sup>th</sup> century and indicated that *T. pallidum* frequently invaded the central nervous system during the hematogenous dissemination of early stages of infection. The presence of these CSF abnormalities was recognized to increase the risk of the subsequent development of symptomatic neurosyphilis<sup>2</sup>. Modern technology using polymerase chain reaction has confirmed that the organism is present in the CSF during primary and secondary syphilis in more than 25% of infected individuals<sup>3</sup>, though the rates of clinically recognized neurosyphilis in untreated syphilis, as revealed by the Oslo and Tuskegee studies, are substantially lower<sup>4</sup>. One form of neurosyphilis, referred to as meningovascular syphilis, usually occurs 6 to 7 years after initial infection, but may manifest in up to 6 months<sup>5</sup>. Typically, in meningovascular syphilis, large and medium sized intracranial arteries are affected; a condition referred to as Huebner's endarteritis. Histopathological examination reveals thickening of the arterial walls with separation of the intima concentrically or eccentrically from the internal elastic lamina by an inflammatory infiltrate comprised of monocytes and lymphocytes and often plasma cells and eosinophils. Inflammation of small vessels with intimal fibrosis leading to stroke is also a recognized form of meningovascular syphilis, although less common. Small vessel involvement is referred to as Nissl-Alzheimer endarteritis. There is evidence to suggest that, even in the absence of clinical meningovascular syphilis, cerebral blood flow abnormalities exist potentially due to a subclinical inflammatory state<sup>6,7</sup>.

In this study, the authors propose that individuals with first-ever ischemic stroke (FEIS) secondary to small vessel disease, statistically, are more often of positive syphilis serology in the absence of neurosyphilis than individuals with other forms of ischemic stroke. The authors performed a retrospective analysis of patients with FIES and separated them into those with positive and negative syphilis serologic testing. The mechanism of stroke (according to the TOAST and ASCOD phenotype) in each cohort was determined by the combination of vessel imaging, brain imaging, and cardiac evaluation. Based on the TOAST criteria, there was a higher percentage of patients (31 *versus* 14%) with positive syphilis serology testing who had a stroke secondary to small vessel disease. Similarly, based on the ASCOD phenotyping, there was a higher percentage (28 *versus* 9%) of small vessel disease strokes in patients who tested positive for syphilis.

The increased incidence of stroke secondary to small vessel disease in patients with syphilis was ascribed to an increased inflammation of endothelial cells within small vessels. More specifically, the authors propose that proteins expressed by *T. pallidum* led to an upregulation of the expression of intercellular adhesion molecule-1 (ICAM-1), E-selectin, and monocyte chemoattractant protein-1 (MCP-1). The upregulation and increased gene transcription of these molecules resulted in an increased migration of monocytes to endothelial cells

and increased membrane permeability, ultimately increasing the likelihood of small vessel occlusion.

One shortcoming of this study is the small sample size of 269 patients who met the inclusion criteria. A retrospective study by Xiang et al.<sup>7</sup> in 2020 comparing stroke patients with positive (n=668) and negative syphilis serology (n=785) found no significant difference in stroke secondary to small-vessel occlusions (p=0.637). Thus, repeating this study with a larger patient population may yield different results. Another limitation to the study is that the patients' HIV status is not

documented. There is a higher incidence of neurosyphilis, including meningovascular syphilis, in patients with HIV compared to the seronegative population<sup>5,8</sup>. HIV infection, even in the absence of neurosyphilis, is a risk factor for arterial ischemic strokes and, therefore, is a potential confounding variable contributing to small vessel disease<sup>9</sup>.

It is possible that infection with *T. pallidum* in the absence of neurosyphilis leads to increased inflammation within small vessels, causing stroke. Larger patient population and study cohort would be needed to substantiate this theory.

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