https://doi.org/10.1590/0004-282X-anp-2020-0178

ARTICLE

Small vessel occlusion and syphilis in patients with first-ever ischemic stroke

Oclusão de pequenos vasos e sífilis em pacientes com o primeiro acidente vascular cerebral isquêmico

Matheus Gomes FERREIRA[1], Valeria Cristina SCAVASINE[1], Giovanni Luís BREDA[2], Bernardo Montesanti Machado de ALMEIDA[2], Viviane de Hiroki Flumignan ZÉTOLA[1], Marcos Christiano LANGE[1]

ABSTRACT

Background: Syphilis is an endemic disease, particularly in low- and middle-income countries, with vascular involvement in large vessels (aortitis), but no clear relationship with stroke patients, except for those who presented with meningovascular neurosyphilis. **Objective:** To investigate the relationship between a positive history of syphilis determined by serological testing and ischemic stroke etiology, particularly small vessel disease (SVD). **Methods:** In total, 269 first-ever ischemic stroke patients admitted to the stroke unit were tested for syphilis. Patients with neurosyphilis were excluded. All patients were classified according to the ASCOD phenotyping as SVD — when SVD was the potential causal mechanism (S1) — or non-SVD — when SVD was uncertain (S2), unlike (S3), or not detected (S0). **Results:** Syphilis was positive in 32 (12%) patients. When comparing patients with positive and negative serology, the only significant difference was SVD as the causal mechanism (S1) in patients with positive results: 9 (28%) *vs.* 22 (9%), p<0.01. **Conclusion:** The current study showed that the frequency of positive syphilis serological test was higher in patients with first-ever ischemic stroke and SVD as the potential causal mechanism. This finding could be related to the endothelial dysfunction occurring in syphilis.

Keywords: Syphilis; Stroke; Cerebral Small Vessel Diseases.

RESUMO

Introdução: A sífilis é uma doença endêmica, especialmente em países de baixa e média renda, com acometimento vascular descrito em grandes vasos (aortite), porém nenhuma relação clara foi reconhecida em paciente com acidente vascular cerebral, exceto para aqueles com sífilis meningovascular. **Objetivos:** Investigar a relação entre história positiva de sífilis determinada pelo status sorológico e o mecanismo do acidente vascular cerebral isquêmico, particularmente doença de pequenos vasos. **Métodos:** Ao todo, 269 pacientes com AVC isquêmico foram testados para sífilis. Pacientes com diagnóstico de neurossífilis foram excluídos. Todos os pacientes foram classificados segundo o fenótipo ASCOD quando a doença de pequenos vasos era o mecanismo causal provável (S1) ou não-pequenos vasos quando este mecanismo era incerto (S2), pouco provável (S3) ou não detectado (S0). **Resultados:** O teste para sífilis foi positivo em 32 (12%) pacientes. Quando comparados, pacientes com sorologia positiva e o grupo com teste não reagente, a única diferença significativa foi a doença de pequenos vasos como mecanismo causal (S1) em pacientes com sorologia positiva: 9 (28%) *vs.* 22 (9%), p<0.01. **Conclusão:** O presente estudo mostra que o teste sorológico positivo para sífilis tem maior ocorrência em pacientes com o primeiro AVC isquêmico com a doença de pequenos vasos como um mecanismo causal possível. Tal achado pode estar relacionado à disfunção endotelial que ocorre durante a sífilis.

Palavras-chave: Sífilis; Acidente Vascular Cerebral; Doenças de Pequenos Vasos Cerebrais.

INTRODUCTION

Syphilis is a sexually transmitted systemic infection recognized since the late 14th century[1,2], caused by the *Treponema pallidum pallidum*[3]. Early and late forms have been described, with the latter further divided into latent (asymptomatic) and tertiary syphilis, which, in turn, can be classified as cardiovascular syphilis, neurosyphilis (NS), and peripheral gummatous syphilis. NS has a broad clinical spectrum, with five major subcategories: syphilitic

[1]Universidade Federal do Paraná, Hospital de Clínicas, Departamento de Neurologia, Curitiba PR, Brazil.

[2]Universidade Federal do Paraná, Hospital de Clínicas, Departamento de Doenças Infecciosas, Curitiba PR, Brazil.

Matheus Gomes FERREIRA https://orcid.org/0000-0002-5288-4739; Valeria Cristina SCAVASINE https://orcid.org/0000-0002-2972-0971; Giovanni Luís BREDA https://orcid.org/0000-0001-7092-8830; Bernardo Montesanti Machado de ALMEIDA https://orcid.org/0000-0001-5293-3652; Viviane de Hiroki Flumignan ZÉTOLA https://orcid.org/0000-0001-8464-9488; Marcos Christiano LANGE https://orcid.org/0000-0002-0405-7157

Correspondence: Matheus Gomes Ferreira; E-mail: gomesferreira.m@gmail.com

Conflict of interest: There is no conflict of interest to declare.

Authors' contribution: MGF: data collection, study design, literature review, manuscript draft. VCS: manuscript review, data collection. BMMA: study design, data collection. GLB: study design, data collection. VHFZ: study design, manuscript review. MCL: study design, manuscript review, statistical analysis.

Received on April 26, 2020; Received in its final form on June 10, 2020; Accepted on July 7, 2020.

meningitis, meningovascular NS, general paresis, tabes dorsalis, and ocular NS[4].

Besides the relationship between NS and stroke, Kelley et al. were some of the first to call attention to the fact that stroke patients had a higher rate of positive syphilis serological tests compared to controls (24 *versus* 15%), although no correlation between stroke type and positive results was found[5].

Today, we have a better understanding of the pathophysiology of both conditions, particularly endothelial dysfunction, as shown by studies of lesions from secondary syphilis[6]. This study aimed to determine the relationship between a positive history of syphilis determined by serological testing and first-ever ischemic stroke (FEIS), exploring its association with the mechanism of cerebral ischemia, especially small vessel disease (SVD).

METHODS

This is a retrospective analysis of a prospective database of patients with FEIS admitted to the Hospital de Clínicas of the Universidade Federal do Paraná from January 2012 to July 2017. The study was approved by the local Research Ethics Committee, and the board waived the need for patient consent.

All patients underwent etiological investigation with at least computed tomography (CT) scans (one at admission and the other 24 h after symptom onset), electrocardiography, transthoracic echocardiography, and vascular ultrasound. Other tests, such as magnetic resonance imaging (MRI), 24-hour Holter monitoring, cerebrospinal fluid (CSF) analysis, CT angiography, and angiography, were performed on a case-by-case basis. Syphilis testing was carried out in two steps, following the Brazilian Ministry of Health guidelines[7]: first, a treponemal test (chemiluminescence) and, if positive, a non-treponemal test (venereal disease research laboratory — VDRL); when the treponemal test was positive, but the VDRL was non-reactive, a second treponemal test (indirect immunofluorescence: fluorescent treponemal antibody absorption — FTA-Abs) was performed to exclude a false-positive chemiluminescence result. Tests were considered positive when both chemiluminescence and VDRL were positive or when chemiluminescence and FTA-Abs were concordant. Cases with only a positive VDRL (with negative treponemal test) were categorized into the non-syphilis group due to the lack of specificity of the test. Patients in the syphilis group were submitted to CSF analysis. Cases with a reactive CSF-VDRL, pleocytosis, or elevated protein were subcategorized in the NS group[7], as presented in Figure 1.

The variables studied were age, sex, cerebrovascular risk factors (hypertension, diabetes, hyperlipidemia, and

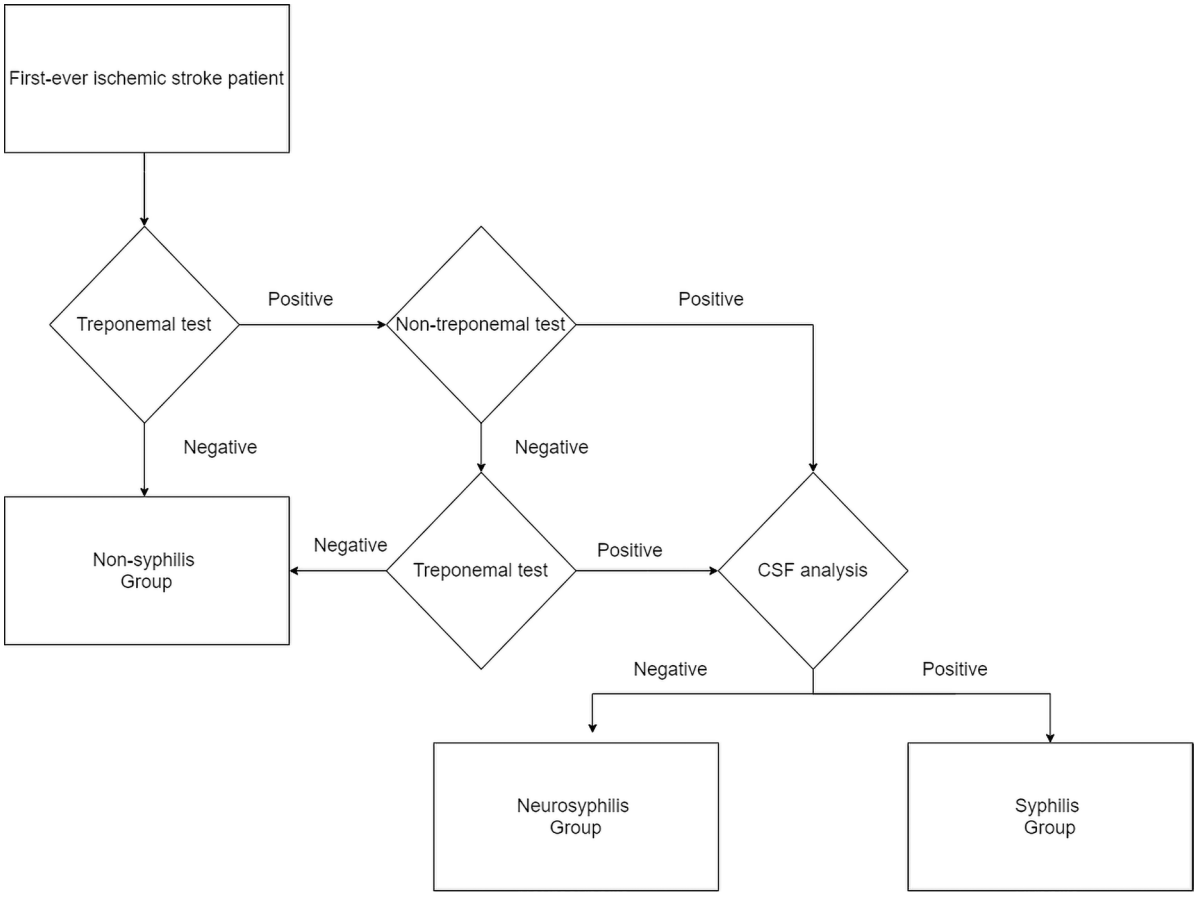

Figure 1. Diagnosis flowchart to classify first-ever ischemic stroke patients in the syphilis group in the study period.

tobacco use), presence of atrial fibrillation, National Institutes of Health Stroke Scale/Score (NIHSS) at admission, modified Rankin Score (mRS) at discharge and at the last visit, stroke recurrence, and mortality. The stroke mechanism was classified according to the TOAST phenotype[8] in large-artery atherosclerosis, cardioembolism, small vessel occlusive disease, stroke of other determined etiology, and stroke of undetermined etiology. All patients were also evaluated based on the ASCOD phenotyping[9] and classified into two groups: SVD — when SVD was potentially causal (S1) — and non-SVD — when SVD was uncertain (S2), unlike (S3), or not detected (S0).

Statistical analysis was performed in the software Statistica 8.0; NIHSS was presented as median and first (Q1) and third (Q3) interquartile range (median [Q1–Q3]). We assessed the statistical significance using Student's *t*-test for continuous variables and Fisher's exact test or chi-square test for qualitative variables. Statistical significance was set at $p<0.05$, with a 0.95 confidence interval.

RESULTS

Out of the 273 FEIS patients tested for syphilis in the study period, four were diagnosed with NS. Among the 269 cases that fulfilled the study inclusion criteria, 32 (12%) had a positive syphilis serological test, while the other 237 (88%) had negative results. When comparing patient characteristics between these two groups, 10 (31%) individuals in the positive result group presented a higher frequency of small vessel occlusive disease based on TOAST, in contrast to only 35 (14%) in the negative result group, p=0.039. The ASCOD phenotyping analysis revealed nine (28%) patients in the syphilis group with SVD as a potential cause (S1) compared to 22 (9%) in the non-syphilis group, p=0.004. No differences were found in other stroke subtypes or between these groups, including those related to outcome. Table 1 presents the demographic data and results.

DISCUSSION

The current study showed a higher frequency of positive syphilis tests in patients with stroke, predominantly in those with SVD as the potential cause of the event.

Syphilis is considered an endemic disease in Latin America, with an estimated prevalence of positive tests of 2.6% in the general population[3,10]. This investigation identified 12% of positive tests in stroke patients, which is close to previous studies, whose values were between 4 and 8.4%[11,12].

The association between syphilis and SVD observed in the present study could result from recent pathophysiological data. Some proteins expressed by *Treponema pallidum*, such as Tp0965[13] and Tp17[14], have demonstrated the capacity to activate endothelial cells, ultimately leading to the up-regulation and expression of vascular endothelial growth factor (VEGF) and adhesion molecules by the endothelium, such as

Table 1. Patient characteristics and comparison between both groups.

Sample	Syphilis (32)	Non-syphilis (237)	p
Age (mean±SD)	63.5±14.5	61.16±14.6	0.113
Females n (%)	16 (50)	110 (46)	0.71
Hypertension n (%)	26 (81)	168 (70)	0.309
Diabetes mellitus n (%)	13 (40)	63 (26)	0.147
Hyperlipidemia n (%)	20 (62)	106 (44)	0.088
Smoker n (%)	11 (34)	64 (27)	0.507
Atrial fibrillation n (%)	7 (21)	32 (13)	0.28
NIHSS at admission (median 1–3)	7 (3–14)	7 (3–13)	0.368
Thrombolysis therapy n (%)	9 (28)	89 (37)	0.334
S1 n (%)	9 (28)	22 (9)	0.004
S2 n (%)	1 (3)	13 (5)	1
S1S2 n (%)	10 (31)	35 (14)	0.039
Recurrence n (%)	2 (6)	24 (10)	0.75
Mortality n (%)	8 (25)	32 (13)	0.112
Vascular mortality n (%)	2 (6)	11 (4)	0.657
mRS <3 at discharge among the living n (%)	17 (53)	152 (64)	0.319
mRS <3 at discharge among all n (%)	17 (53)	152 (64)	0.295
mRS <3 at the last visit among the living n (%)	19 (59)	140 (59)	0.426

SD: standard deviation; NIHSS: National Institutes of Health Stroke Scale; S1: small vessel disease as a potential causal mechanism; S2: uncertain small vessel disease; mRS: modified Rankin Score.

ICAM-1, E-selectin, and VCAM-1[13,14]. Furthermore, studies of primary and secondary syphilis lesions have documented the role of interleukin-6 (IL-6) and increased vascular permeability during their development[15]. All of these features are common to the pathogenesis of SVD, as recently described[16]. Therefore, an inflammatory endothelial mechanism could play an important role in a pathological process, eventually resulting in the development of SVD and stroke, a relationship that resembles the one associated with stroke in general[17] and myocardial infarction specifically[17,18].

The clinical impact of the syphilis diagnosis could not be confirmed, as both groups had similar results to all other variables, including outcome. Therefore, even if syphilis could accelerate the endothelial dysfunction, this acceleration might depend on other stroke risk factors, which could even trigger or exacerbate a vascular inflammatory response and consequent endothelial dysfunction associated with SVD.

This study has limitations, such as the small sample, the retrospective analysis, and the assessment of only clinical features; no biomarker study was performed to confirm the hypothesis of this relationship, but the results replicate previous findings in medical literature and further raise the question of a common pathway for distinct pathologies.

In conclusion, more than 10% of FEIS patients presented positive syphilis serological tests, which were more common in the small vessel occlusive disease mechanism, based on two different classifications. This finding could be related to the endothelial dysfunction occurring in syphilis. Future studies could focus on biomarkers related to endothelial dysfunction and their relationship with SVD and syphilis.

References

1. Halperin JJ. Spirochetal Infections of the Nervous System. In: Aminoff MJ, Josephson SA. Aminoff's Neurology and General Medicine. 5th ed. London. Elsevier Inc.; 2014. p.817-31.
2. Arora N, Schuenemann VJ, Jäger G, Peltzer A, Seitz A, Herbig A, et al. Origin of modern syphilis and emergence of a pandemic *Treponema pallidum* cluster. Nat Microbiol. 2016 Dec;2:16245. https://doi.org/10.1038/nmicrobiol.2016.245
3. Kojima N, Klausner JD. An update on the global epidemiology of syphilis. Curr Epidemiol Rep. 2018 Mar;5(1):24-38 https://doi.org/10.1007/s40471-018-0138-z
4. French P, Gomberg M, Janier M, Schmidt B, van Voorst Vader P, Young H, et al. IUSTI: 2008 European Guidelines on the Management of Syphilis. Int J STD AIDS. 2009 May;20(5):300-9. https://doi.org/10.1258/ijsa.2008.008510
5. Kelley RE, Bell L, Kelley SE, Lee SC. Syphilis detection in cerebrovascular disease. Stroke. 1989 Feb;20(2):230-4. https://doi.org/10.1161/01.str.20.2.230
6. Macaron NC, Cohen C, Chen SC, Arbiser JL. Cutaneous lesions of secondary syphilis are highly angiogenic. J Am Acad Dermatol. 2003 Jun;48(6):878-81. https://doi.org/10.1067/mjd.2003.504
7. Brazil. Ministério da Saúde. Technical manual for diagnosis of syphilis. Brasília: Ministério da Saúde; 2016.
8. Adams Jr. HP, Bendizen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993 Jan;24(1):35-41. https://doi.org/10.1161/01.str.24.1.35
9. Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Wolf ME, Hennerici MG. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). Cerebrovasc Dis. 2013;36(1):1-5. https://doi.org/10.1159/000352050
10. Borges CR, Almeida SM, Sue K, Koslyk JLA, Sato MT, Shiokawa N, et al. Neurosyphilis and ocular syphilis clinical and cerebrospinal fluid characteristics: a case series. Arq Neuro-Psiquiatr. 2018 Jun;76(6):373-80. https://doi.org/10.1590/0004-282X20180054
11. Cordato DJ, Djekic S, Taneja SR, Maley M, Beran RG, Cappelen-Smith C, et al. Prevalence of positive syphilis serology and meningovascular neurosyphilis in patients admitted with stroke and TIA from a culturally diverse population (2005-09). J Clin Neurosci. 2013 Jul;20(7):943-7. https://doi.org/10.1016/j.jocn.2012.08.011
12. Dharmasaroja PA, Dharmasaroja P. Serum and cerebrospinal fluid profiles for syphilis in Thai patients with acute ischemic stroke. Int J STD AIDS. 2012 May;23(5):340-5. https://doi.org/10.1258/ijsa.2011.011207
13. Zhang RL, Zhang PJ, Wang QQ. Recombinant *Treponema pallidum* protein Tp0965 activates endothelial cells and increase the permeability of endothelial cell monolayer. PLoS One. 2014 Dec;9(12):e115134. https://doi.org/10.1371/journal.pone.0115134
14. Zhang RL, Wang QQ, Zhang JP, Yang JL. Tp17 membrane protein of *Treponema pallidum* activates endothelial cells *in vitro*. Int Immunopharmacol. 2015 Apr;25(2):538-44. https://doi.org/10.1016/j.intimp.2015.02.028
15. Carlson JA, Dabiri G, Cribier B, Sell S. The immunopathobiology of syphilis: manifestations and course of syphilis are determined by the level of delayed-type hypersensitivity. Am J Dermatopathol. 2011 Jul;33(5):433-60. https://doi.org/10.1097/DAD.0b013e3181e8b587
16. Wiseman SJ, Doubal FN, Chappell FM, Valdés-Hernández MC, Wang X, Rumley A, et al. Plasma biomarkers of inflammation, endothelial function and hemostasis in cerebral small vessel disease. Cerebrovasc Dis. 2015;40(3-4):157-64. https://doi.org/10.1159/000438494
17. Smeeth L, Thomas SL, Hall AJ, Hubbard R, Farrington P, Vallance P. Risk of myocardial infarction and stroke after acute infection or vaccination. N Engl J Med. 2004 Dec;351(25):2611-8. https://doi.org/10.1056/NEJMoa041747
18. Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. N Engl J Med. 2019 Jan;380(2):171-6. https://doi.org/10.1056/NEJMra1808137