

Investigating the frequency of neuro-syphilis in stroke patients

Manizheh Jozpanahi

Department of Infectious Diseases, Zanzan University of Medical Sciences, Zanzan, Iran

Seyede Pegah Saeed

MD, Zanzan University of Medical Sciences, Zanzan, Iran

Abdol Amir Feizi

Department of Pathology, Zanzan University of Medical Sciences, Zanzan, Iran

Maedeh Ghorbani

MD, Zanzan University of Medical Sciences, Zanzan, Iran, ghrbnimahdie@gmail.com

Abstract

Introduction: Syphilis is an infectious disease that can involve the central nervous system at any stage and cause neurosyphilis. Arterial stenosis or occlusion caused by syphilitic arthritis can lead to ischemic stroke. Stroke is one of the most important causes of death and disability worldwide, and identifying its underlying factors is important. Therefore, the aim of this study was to investigate the frequency of neuro-syphilis in stroke patients.

Material and Methods: This cross-sectional study was conducted on hospitalized patients with a clinical diagnosis of ischemic stroke. At first, the people referred to the hospital with history and diagnosis of stroke were tested serologically for syphilis. In confirmed stroke patients, VDRL serological test was first performed for screening. Due to the fact that no positive cases were found in terms of screening with VDRL, the next stages of the research, which included confirmation tests with FTA-ABS and Lumbar Puncture, were not performed.

Results: A total of 224 people were included in the study. The average age of the subjects was 69.9 ± 13.87 . The screening test was reported negative in all subjects. According to gender, out of a total of 224 people, 100 people (44.6%) were women and 124 people (55.4%) were men. According to the place of residence, 85 people (37.9%) lived in the village and 139 people (62.1%) lived in the city. The frequency of marriage of the participants in the study was investigated and the results demonstrated that 222 (99.1%) were married and 2 (0.9%) were single. The frequency of disease outcome of the participants revealed that 185 (82.6%) of the patients recovered and 39 (17.4%) of the patients died, while none of the patients had syphilis. The prevalence of underlying disease showed that most of the patients, (139, 62%) had hypertension, followed by neurological disease (11, 4.9%).

Conclusion: Considering the negative results in all patients, it can be concluded that syphilis has been decreasing significantly in the city and Iran, and the cases of CNS vascular involvement in CVA patients are almost not related to syphilis. Syphilis as an underlying factor, currently does not play an important role in brain vascular events in this study.

Keywords: *Syphilis, Neuro-syphilis, Meningovascular syphilis, Stroke.*

INTRODUCTION

Syphilis is an infectious disease caused by the spirochete *Treponema pallidum* and transmitted through sexual contact or from mother to fetus (1). This disease is divided into primary, secondary, tertiary and latent syphilis. Primary syphilis produces an inflammatory response of chancre eight weeks after contact at the site of inoculation of spirochetes. Its most common site is the external genitalia, which recovers within 3 to 6 weeks. The secondary stage is associated with the entry of spirochetes into the blood and causes systemic manifestations. Secondary syphilis can affect any organ. Latent syphilis is a period that has no clinical manifestations and can be diagnosed with serological tests. Tertiary syphilis is a slowly progressive inflammatory process that can affect any organ and can cause clinical symptoms 5 to 30 years or even more after the initial infection. The clinical spectrum of tertiary syphilis includes neurosyphilis, cardiovascular syphilis and gumma syphilis (2-6).

In the primary stage of syphilis, Neurosyphilis refers to infection of the CNS. In most patients, the immune system intervenes and prevents long-term complications, but a small number of people develop asymptomatic or symptomatic neurosyphilis (7). The exact prevalence of neurosyphilis worldwide is largely unknown, but it is more common among HIV epidemics (8). A patient with neurosyphilis may be completely asymptomatic or present with acute syphilitic meningitis, tabes dorsalis, meningovascular syphilis, optic nerve atrophy, or paresis.

Asymptomatic neurosyphilis is characterized by reactive serology in cerebrospinal fluid with increased protein and pleocytosis (9). The diagnosis of neurosyphilis requires serological evidence of syphilis and CSF analysis,

however, the VDRL test, which is the gold standard for neurosyphilis diagnosis, has a sensitivity of 30-70%. Neurosyphilis is treated with high-dose penicillin for 10-14 days (10).

Stroke is a heterogeneous syndrome and the determination of risk factors and its treatment depends on the specific pathogenesis of stroke (11). Risk factors for stroke can be classified as modifiable and non-modifiable. Age, sex, race, and ethnicity are nonmodifiable risk factors for ischemic and hemorrhagic stroke, while hypertension, smoking, diet, and physical inactivity are commonly reported modifiable risk factors. Recently described risk and risk factors for stroke include inflammatory disorders, infection, pollution, and atrial fibrillation independent of atrial fibrillation (12, 13).

Stroke is one of the most important causes of death and disability in the world, and it is important to identify its underlying factors. Many studies have been conducted on the risk factors of its occurrence, but infectious factors have been less studied as underlying causes. In Iran, no study has been conducted regarding this underlying cause in recent years. Therefore, the aim of this study is to investigate the frequency of neurosyphilis in stroke patients.

Materials and Methods

This cross-sectional study was conducted on patients hospitalized in the first six months of 2021 in Valiasr Hospital, Zanjan, Iran, with a clinical diagnosis of ischemic stroke. The number of hospitalized patients with a clinical diagnosis of ischemic stroke was equal to 224, and all these patients were examined in this study.

Procedure

At first, the people referred to the hospital with history and diagnosis of stroke were tested serologically for syphilis. In confirmed stroke patients, VDRL serological test was first performed for screening. Due to the fact that no positive cases were found in terms of screening with VDRL, the next steps including confirmatory tests with FTA-ABS and Lumbar Puncture were not performed.

Data analysis

Data analysis was done using SPSS version 26 software. Qualitative variables were reported as number (percentage) and quantitative variable of age was reported as mean (standard deviation).

Ethical considerations

The ethics committee of the University of Medical Sciences approved the study (IR.ZUMS.REC.1400.379). This study was performed in accordance with Declaration of Helsinki. Data accessed were pseudo-anonymised prior to use. Approval was granted by the Research Council of the Faculty of Medicine.

Results

A total of 224 patients were included in the study. The average age of the subjects was 69.9 ± 13.87 . Table 1 shows the frequency of the age variable of the participants in the study. The screening test was reported negative in all subjects. The study subjects consisted of 100 (44.6%) women and 124 (55.4%) men.

Table 1: Frequency of age variable of people participating in the study

Variable	Category (Year)	Number
Age	20-30	1 (0.4%)
	30-40	2 (0.8%)
	40-50	17 (7.5%)
	50-60	29 (12.9%)
	60-70	50 (22.3%)
	70-80	58 (25.8%)
	80-90	53 (23.6%)
	90-100	14 (6.25%)

85 people (37.9%) lived in the village and 139 people (62.1%) lived in the city. The frequency of marriage of the participants in the study was investigated and the results showed that 222 (99.1%) were married and 2 (0.9%) were single.

In Table 2 shows the frequency of the underlying disease of the participants in the study. The results showed that most of the patients (62%, 139 individuals) had hypertension, followed by neurological disease (4.9%, 11 cases).

Table 2: Frequency of underlying disease of people participating in the study

Variable	Category	Number
Underlying disease	Non-Underlying disease	40 (17.85%)
	Hypertension	139 (62%)
	Diabetic	70 (31.25%)
	Cardiac disease	57 (25.4%)
	Infraction	50 (22.3%)
	Nervous disease other	11 (4.9%)
	Cancer	23 (10.2%)

Frequency of smoking and opium use is summarized in Table 3 and the results showed that 195 (87.1%) of the patients had no smoking or opium use.

Table 3: Frequency of smoking and opium

Variable	Category	Number
Smoking and opium	No smoking and opium	195 (87.1%)
	Smoking	22 (9.8%)
	Smoking and opium	4 (1.8%)
	opium	3 (1.3%)

The frequency of disease outcome of the participants in the study showed that 185 (82.6%) of the patients recovered and 39 (17.4%) of the patients died, while none of the patients had syphilis.

Discussion

Stroke is one of the important causes of death and disability in the world, and it is important to identify its underlying factors. Many studies have investigated the risk factors of stroke, but the underlying infectious factors have been less investigated. In Iran, the underlying cause has not been enough studied in recent years (14). Based on this, we aimed to determine the prevalence of syphilis in stroke patients in Zanjan city, Iran.

In this study, people referred to the hospital with history and diagnosis of stroke were tested serologically for syphilis. In confirmed stroke patients, VDRL serological test was first performed for screening, and the results of all samples were negative. A cohort study by Martins et al. estimated the prevalence of syphilis and neurosyphilis in Brazil in 2020. They reviewed the medical records of patients who were admitted to the CCU due to TIA or stroke. From 2015 to 2016, 1,436 people were hospitalized, of which 1,119 people were checked for syphilis serology tests. Among these, 143 people had positive syphilis serology, CSF analysis was positive in 53 people, and VDRL was found positive in 8 people. The results of this study determine the

relationship between syphilis and stroke, and also note that positive syphilis serology is frequently observed in Brazil (15).

Pei-Xiang et al. conducted a retrospective study in 2020 with the aim of determining the role of syphilis in narrowing and stenosis of cerebral arteries. They examined the patients who were admitted to the CCU between 2016 and 2018. Among the hospitalized patients, 668 patients were serologically positive for syphilis and 785 were syphilis negative. The percentage of positive syphilis serology among stroke patients was reported as 88.1%. In patients who had a stroke with positive syphilis, the stenosis of large vessels was 31.1%, while 7.24% of large vessels had stenosis among syphilis negative patients. Furthermore, it was found that intracranial vessel stenosis was more among syphilis patients with stroke, and serologically positive patients were younger and mostly men (16).

Pintado et al. conducted a prospective and cross-sectional study in Thailand in 2019 at Srinagar Hospital. Their aim was to investigate the prevalence of syphilis in acute ischemic stroke patients. They examined 466 patients in terms of VDRL and TPPA. The prevalence of syphilis among these patients was found to be 12.6%, and the average age of syphilis-positive patients was also calculated to be 75.2 years, which was different from the average age of syphilis-negative patients (63.7 years). But other factors such as age and gender were not found to be statistically different. This study demonstrated that the prevalence of syphilis in the patients of Khon Kean city was moderate (17).

Dharmasarojas et al. designed a study in which the CSF and serum of patients hospitalized for acute stroke were examined for neurosyphilis. In mentioned study, the number of WBC and Pr

was investigated in the serum of RPR and TPPA patients and in the CSF fluid. Out of 284 patients, 24 (8.4%) had positive TPPA. Furthermore, 7 patients (2.5%) were diagnosed with symptomatic neurosyphilis. 85.7% of symptomatic patients had WBC in their CSF above 20 cells /mm³, and less than 50% of symptomatic patients had a protein level in their CSF above 50 mg/dL, where there was no significant difference with non-syphilitic individuals. The results of this study show that the amount of WBC and protein level is important for determining the true cases of symptomatic neurosyphilis and reducing false positive cases, especially in countries with a high prevalence of *treponema pallidum* (18).

Okeke et al. conducted a retrospective study in Portugal with the aim of investigating the prevalence of neurosyphilis among stroke patients. During a period of 44 months, 525 patients were admitted to CCU, of which 309 patients underwent routine tests. Lumbar puncture was performed for those who had a positive test and CSF was analyzed. 309 out of 525 patients were negative for syphilis, but 12 patients were positive, among which 72.3% had neurosyphilis (19).

Cordato et al. (2012) investigated the prevalence of serologically positive syphilis patients and meningovascular neurosyphilis in stroke and TIA patients. This study was conducted retrospectively in 2009-2005. Out of 3270 patients who came to this center due to stroke, 893 (27%) of stroke patients were examined. 38 out of 893 of these patients were serologically positive for syphilis. 37 of the serologically positive ones had symptoms compatible with meningovascular neurosyphilis. One of these patients had a positive CSF analysis for VDRL. They concluded that Syphilis testing should be

included as part of routine tests for stroke and TIA (20).

It is interesting to note that a study similar to our results that all the studied subjects were negative for syphilis was not found. This point is consistent with the very rare cases of syphilis in our society and indicates a very high level of control in infected and patient cases, which is a very positive point.

Conclusion

According to the negative results in all patients, it can be concluded that syphilis has decreased significantly in the city and country of Iran. Cases of CNS vascular involvement in CVA patients are almost not related to syphilis. Syphilis as an underlying factor, currently does not play an important role in brain vascular events, which is considered a great success for our public health.

Reference

- Lasagabaster, M. A. and L. O. Guerra (2019). "Sífilis." *Enfermedades Infecciosas y Microbiología Clínica* 37(6): 398-404.
- Radolf, Justin D., and Sanjiv Kumar. "The *Treponema pallidum* outer membrane." *Spirochete Biology: The Post Genomic Era* (2017): 1-38.
- Gonzalez, H., I. Korapnik, and C. Marra. "Seminar in neuropathology." *Neurosurgery* 39.4 (2019): 448-455.
- Saylor, D. and C. Marra (2021). *Neurological Complications of Syphilis. Neurological Complications of Infectious Diseases*, Springer: 111-129.
- Ahamed, S., et al. (2009). "Case of neurosyphilis presented as recurrent stroke." *Oman Medical Journal* 24(2): 134.
- Tan, Haur Wey, et al. "Intracranial vessel wall imaging with magnetic resonance imaging:

- current techniques and applications." *World neurosurgery* 112 (2018): 186-198.
- Shi, Min, et al. "Young male with syphilitic cerebral arteritis presents with signs of acute progressive stroke: a case report." *Medicine* 98.48 (2019).
- Liu, L.-L., et al. (2012). "Ischemic stroke as a primary symptom of neurosyphilis among HIV-negative emergency patients." *Journal of the neurological sciences* 317(1-2): 35-39.
- De Souza, Ronaldo Lopes, et al. "Prevalence of syphilis in female sex workers in three countryside cities of the state of Pará, Brazilian Amazon." *BMC Infectious Diseases* 20.1 (2020): 1-8.
- Lanamtieng T, Kasemsap N, Meesing A. Serologic Prevalence of Syphilis in Acute Ischemic Stroke. *J Med Assoc Thai* 2019; 102:114.
- Boehme, A. K., et al. (2017). "Stroke risk factors, genetics, and prevention." *Circulation research* 120(3): 472-495.
- Kovacs, Gabor G. "Invited review: neuropathology of tauopathies: principles and practice." *Neuropathology and applied neurobiology* 41.1 (2015): 3-23.
- Kasper, Dennis, et al. *Harrison's principles of internal medicine*, 19e. Vol. 1. No. 2. New York, NY, USA: Mcgraw-hill, 2015.
- Peeling, R., et al. (2017). "Benzaken." *AS Syphilis. Nat. Rev. Dis. Prim* 3: 17073.
- Martins, Rodrigo Targa, et al. "Frequency of screening and prevalence of neurosyphilis in stroke population." *Cerebrovascular Diseases* 49.3 (2020): 301-306.
- Xiang, L., et al. (2021). "Positive syphilis serology contributes to intracranial stenosis in ischemic stroke patients." *Brain and Behavior* 11(1): e01906
- Pintado Maury, I., et al. (2019). "Neurosyphilis prevalence at a Portuguese stroke unit care." *Aging Clinical and Experimental Research* 31(8): 1155-1161.
- Dharmasaroja, P. A. and P. Dharmasaroja (2012). "Serum and cerebrospinal fluid profiles for syphilis in Thai patients with acute ischaemic stroke." *International journal of STD & AIDS* 23(5): 340-345.
- Okeke, N. L., and C. B. Hicks. "Treatment of syphilis: a systematic review." *JAMA* 312.18 (2014): 1905-17.
- Cordato, D. J., et al. (2013). "Prevalence of positive syphilis serology and meningovascular neurosyphilis in patients admitted with stroke and TIA from a culturally diverse population (2005–09)." *Journal of Clinical Neuroscience* 20(7): 943-947.