Clinical and laboratory features in patients with positive syphilis serology presenting with acute ischemic stroke or transient ischemic attack: a prospective cohort study

Pornpong Jitpratoom¹ and Adhiratha Boonyasiri²*

Abstract

Background: Neurosyphilis (NS) can lead to acute ischemic stroke (AIS) or transient ischemic attack (TIA). We compared the clinical characteristics and laboratory features among AIS and TIA patients who were syphilis-seronegative (control group) or had latent syphilis (LS) or NS to evaluate their stroke outcome.

Methods: This prospective cohort study was conducted on patients who had recently suffered AIS or TIA. After serological syphilis screening, clinical and laboratory data were collected, and brain imaging and spinal tap (serologically syphilis-positive patients only) were performed. Stroke outcome was re-evaluated approximately three months later.

Results: The 344 enrolled patients were divided into three groups: control group (83.7%), LS (13.1%), and NS (3.2%). A multivariate analysis revealed: 1) age of ≥70 years, generalized brain atrophy via imaging, and alopecia (adjusted odds ratio [AOR] = 2.635, 2.415, and 13.264, respectively) were significantly associated with LS vs controls; 2) age of ≥70 years (AOR = 14.633) was significantly associated with NS vs controls; and 3) the proportion of patients with dysarthria was significantly lower (AOR = 0.154) in the NS group than in the LS group. Regarding the NS patient cerebrospinal fluid (CSF) profile, only 2/11 cases had positive CSF-Venereal Disease Research Laboratory (VDRL) test results; the other nine cases were diagnosed from elevated white blood cell counts or protein levels combined with positive CSF fluorescent treponemal antibody absorption (FTA-ABS) test results. Regarding disability, the initial modified Rankin scale (mRS) score was lower in the control group than in the NS group (p = 0.022). At 3 months post-stroke, the mRS score had significantly decreased in the control (p < 0.001) and LS (p = 0.001) groups. Regarding activities of daily living, the 3-month Barthel Index (BI) score was significantly higher in control patients than in LS (p = 0.030) or NS (p = 0.002) patients. Additionally, the 3-month BI score was significantly increased in the control (p < 0.001) and LS (p = 0.001) groups.

Conclusions: Because syphilis was detected in many AIS and TIA patients, especially those aged ≥70 years, routine serological syphilis screening may be warranted in this population. Patients with syphilitic infection had worse stroke outcomes compared with NS patients.
Background
Syphilis is a sexually transmitted disease caused by infection with the spirochete Treponema pallidum. Syphilis incidence per 100,000 population in Thailand increased five times from 2.16 in year 2008 to 11.51 in year 2018 [1]. Also, between 2005 and 2011, a significant increase occurred in the annual prevalence of syphilis from 5.0% to 12.5%. Syphilis has been considered to be a major sexually transmitted disease in Thailand [2]. Infected individuals typically follow a disease course divided into primary, secondary, latent, and tertiary stages. Neurologic involvement, i.e., neurosyphilis (NS), occurs in up to 10% of patients with untreated syphilis [3]. NS is typically described as a late-stage manifestation, but neuroinvasion and neurological disease may occur at any stage of syphilis [4]. Meningovascular NS is an infectious inflammatory arteriopathy caused by the invasion of T. pallidum into the meninges, their arteries, and the surrounding arteries. Among NS patients, 14.09% develop ischemic stroke as a primary symptom, but only 0.31–0.25% of cases of acute ischemic stroke (AIS) and transient ischemic attack (TIA) are caused by NS [5–7].

At present, understanding of the prevalence and the clinical and laboratory characteristics of NS among patients with AIS or TIA is very limited; only a few studies on this topic have been conducted [6, 8]. To our knowledge, no studies have analyzed the outcome of patients with AIS or TIA at our hospital during the study period. There is extensive evidence supporting the use of mRS and BI scores for stroke outcome assessment, and AIS or TIA at our hospital during the study period were considered for study inclusion and screened for syphilis serology. Patients showing serological positivity for syphilis underwent a lumbar puncture. Patients were excluded from study participation if they showed signs or symptoms suggestive of increased intracranial pressure or had imaging results that indicated the same, or if they refused to undergo a lumbar puncture. Written informed consent was obtained from the patients or patients’ surrogates.

Methods
This prospective cohort study was conducted at Chumphonkhetudomsakdi Hospital, Thailand, from November 2019 to November 2020. All patients over 15 years of age presenting within 7 days of newly onset symptoms suggestive of increased intracranial pressure or had imaging results that indicated the same, or if they refused to undergo a lumbar puncture. Written informed consent was obtained from the patients or patients’ surrogates. Baseline patient characteristics, including atherosclerotic risk factors, neurological status severity, laboratory diagnosis of stroke, computed tomography (CT) brain scans, and syphilis serological profile, were collected. The enrolled patients were classified into the following three groups: syphilis-seronegative (control group), LS, and NS.

A presumptive diagnosis of syphilis required the use of two laboratory serologic tests: a treponemal test and a nontreponemal test [11]. Serological testing for syphilis in this study was conducted via a chemiluminescence microimmunoassay (CMIA; for treponemal tests) and rapid plasma reagin (RPR; for nontreponemal tests) in all included patients. If the treponemal test is positive but the nontreponemal test is negative, the laboratory will perform a treponemal test different from the one used for initial testing [11]. We chose the fluorescent treponemal antibody absorption (FTA-ABS) test as an alternative treponemal test. NS was diagnosed in patients with positive syphilis serology, clinical features consistent with AIS or TIA, and a reactive cerebrospinal fluid-Venereal Disease Research Laboratory (CSF-VDRL) test result. In cases where a non-reactive CSF-VDRL test result occurred but the patient had an elevated CSF leukocyte count (>5 white blood cells [WBCs]/mm³) or an elevated level of CSF protein (>45 mg/dL), NS was still diagnosed if a CSF fluorescent treponemal antibody absorption (CSF FTA-ABS) test yielded a reactive result. In this study, LS was defined as having syphilis seropositivity in the absence of clinical manifestations of primary, secondary, or tertiary disease [11]. All included cases that did not fall into the LS or NS groups were categorized as controls.

For stroke outcome, modified Rankin scale (mRS) [12] and Barthel Index (BI) [13] scores were obtained at the time of enrollment (initial baseline scores). In the third month after the stroke, a telephone follow up was conducted. There is extensive evidence supporting the use of mRS and BI scores for stroke outcome assessment, and...
these scores have also been used to evaluate the validity and reliability of assessment administered over the telephone as compared with face-to-face assessment [14–20].

**Statistical analysis**

All statistical analyses were performed using PASW Statistics version 18.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to summarize demographic characteristics such as patient age and sex. Quantitative data are presented as the mean ± standard deviation or median (25th percentile, 75th percentile), and qualitative data are presented as the frequency (percentage). A chi-squared test or Fisher’s exact test was performed on categorical variables, such as patient sex, across the control group, LS, and NS groups. A one-way ANOVA or the Kruskal–Wallis H test was used to compare the quantitative data of the three groups. Unadjusted pairwise comparisons are reported, and once Bonferroni’s adjustment has been applied, the p-value required for significance is 0.016. All predictors identified as significant were subsequently tested in a multivariable analysis. Multinomial logistic regression was used to estimate the adjusted odds ratio (AOR) of the LS and NS groups with controls as the comparison group via a manual backward step. The CSF profiles of the LS and NS groups were compared using a Fisher’s exact test and Mann–Whitney U test. The Wilcoxon signed-rank test was used to compare the initial and 3-month mRS and BI scores.

**Ethics approval**

The study was approved by the human research ethics committee of the Faculty of Medicine, Thammasat University (Ref: MTU-EC-OO-0-080/62) and informed consent obtained from each participant. All methods were carried out in accordance with relevant guidelines and regulations such as the Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the International Practice (ICH-GCP).

**Results**

**Demographic characteristics of the AIS and TIA population**

A total of 344 patients were recruited in this study (Fig. 1). The mean patient age was 65 (range: 17–97) years, and 60.8% of the participants were men. Most of the patients had an AIS (n=327; 95.1%), and the rest had a TIA (n=17, 4.9%). The most common atherosclerotic risk factor was hypertension (64.0%), followed by dyslipidemia (43.9%) and smoking (40.7%). The patients were categorized by the trial of ORG 10172 in acute stroke treatment (TOAST) classification [21] into five subtypes: (1) large-artery atherosclerosis (30.2%); (2) cardioembolism (16.3%); (3) small-vessel occlusion (46.5%); (4) stroke of other determined etiology (5.8%); and (5) stroke of undetermined etiology (1.2%).

**Comparison of the clinical characteristics and laboratory features of control, LS, and NS patients**

Patients were divided into three groups according to their serological results: controls (83.7%), LS (13.1%), and NS (3.2%). For the HIV status, the testing was not routinely performed because it was not included in the study protocol, which raised concerns about patients’ rights and appropriateness in the AIS and TIA investigations. The results of a univariate analysis of the clinical characteristics and laboratory features of the three groups are shown in Table 1. A multivariate analysis revealed that, compared with controls, the factors significantly associated with LS were age of ≥70 years (AOR = 2.635), generalized brain atrophy on imaging (AOR = 2.415), and alopecia (AOR = 13.264) and the factor significantly associated with NS was age of ≥70 years (AOR = 14.633). The multivariate analysis also identified a significantly lower incidence of dysarthria among NS patients than among LS patients (AOR = 0.154).

**Clinical characteristics, CSF profiles, and therapeutic treatment of syphilis patients**

The clinical characteristics and CSF profiles of the 11 NS patients are shown in Table 2. The CSF profiles of the NS patients revealed that the mean WBC count was 4.9 cells/mm³, the lymphocyte percentage was 72%, the level of CSF protein was 111 mg/dL, and the CSF/serum glucose ratio was 0.57. The CSF-VDRL tests results were reactive in only two NS cases (the other nine NS cases were diagnosed on the basis of an elevated WBC count or protein level in combination with a reactive CSF FTA-ABS test result). A comparison of the CSF profiles of the LS and NS patients (Table 3) revealed no significant differences in the WBC count, but the CSF protein level in the NS group was significantly higher than that in the LS.
Table 1  Clinical characteristics and laboratory features of patients without or with latent syphilis or neurosyphilis

|                        | 1. Controls | 2. Latent syphilis | 3. Neurosyphilis | p-value* | P1 (1 vs 2) | P2 (1 vs 3) | P3 (2 vs 3) |
|------------------------|-------------|-------------------|-----------------|----------|-------------|-------------|-------------|
| n                      | 288         | 45                | 11              |          |             |             |             |
| Male sex, n (%)        | 171 (59.4%) | 30 (66.7%)        | 8 (72.7%)       | 0.460    | 0.35        | 0.38        | 0.70        |
| Age, mean ± SD (years) | 63.07 ± 15.20 | 73.09 ± 12.55     | 79.82 ± 8.54    | <0.001   | <0.001      | <0.001      | 0.099       |
| TIA, n (%)             | 17 (5.9%)   | 0 (0.0%)          | 0 (0.0%)        | 0.262    | 0.14        | 1.00        |
| HIV-positive, n/tested patients (%) | 1/66 (1.5%) | 0/25 (0.0%)       | 0/5 (0.0%)      | 1.000    | 1.00        | 1.00        |
| Stroke risk factor     |             |                   |                 |          |             |             |             |
| Diabetes mellitus, n (%) | 90 (31.3%) | 9 (20.0%)         | 2 (18.2%)       | 0.217    | 0.12        | 0.36        | 0.89        |
| Hypertension, n (%)    | 184 (63.9%) | 28 (62.2%)        | 8 (72.7%)       | 0.808    | 0.83        | 0.55        | 0.51        |
| Chronic kidney disease, n (%) | 53 (18.4%) | 14 (31.1%)        | 4 (36.4%)       | 0.062    | 0.048       | 0.14        | 0.74        |
| Dyslipidemia, n (%)    | 128 (44.4%) | 18 (40.0%)        | 5 (45.5%)       | 0.851    | 0.58        | 0.95        | 0.74        |
| Atrial fibrillation, n (%) | 47 (16.3%) | 6 (13.3%)         | 3 (27.3%)       | 0.532    | 0.61        | 0.34        | 0.26        |
| Smoking, n (%)         | 121 (42.0%) | 16 (35.6%)        | 3 (27.3%)       | 0.481    | 0.52        | 0.37        | 0.73        |
| Stroke symptoms        |             |                   |                 |          |             |             |             |
| Motor weakness, n (%)  | 263 (91.3%) | 42 (93.3%)        | 10 (90.9%)      | 1.000    | 1.00        | 1.00        | 1.00        |
| Visual disturbance, n (%) | 70 (24.3%) | 8 (17.8%)         | 3 (27.3%)       | 0.604    | 0.34        | 0.82        | 0.48        |
| Vertigo, n (%)         | 86 (29.9%)  | 8 (17.8%)         | 2 (18.2%)       | 0.187    | 0.094       | 0.40        | 0.97        |
| Sensory abnormalities, n (%) | 140 (48.6%) | 18 (40.0%)       | 7 (63.6%)       | 0.321    | 0.28        | 0.33        | 0.16        |
| Language, n (%)        | 61 (21.2%)  | 13 (28.9%)        | 1 (9.1%)        | 0.296    | 0.30        | 0.47        | 0.26        |
| Dysarthria, n (%)      | 212 (73.6%) | 35 (77.8%)        | 5 (45.5%)       | 0.089    | 0.55        | 0.040       | 0.033       |
| Location of acute lesion from imaging |         |                   |                 |          |             |             |             |
| Middle cerebral artery, n (%) | 97 (33.7%) | 15 (33.3%)        | 2 (18.2%)       | 0.591    | 0.880       | 0.27        | 0.28        |
| Anterior cerebral artery, n (%) | 4 (1.4%) | 0 (0.0%)         | 0 (0.0%)        |          |             |             |             |
| Posterior cerebral artery, n (%) | 10 (3.5%) | 0 (0.0%)         | 0 (0.0%)        |          |             |             |             |
| Basilar artery, n (%)  | 8 (2.8%)    | 1 (2.2%)          | 1 (9.1%)        | 0.269    | 0.30        | 0.47        | 0.26        |
| Subcortical white matter, n (%) | 41 (14.2%) | 9 (20.0%)        | 3 (27.3%)       | 0.591    | 0.880       | 0.27        | 0.28        |
| Posterior limb of internal capsule, n (%) | 28 (9.7%) | 6 (13.3%)        | 0 (0.0%)        |          |             |             |             |
| Basal ganglia, n (%)   | 33 (11.5%)  | 4 (8.9%)          | 0 (0.0%)        | 0.432    | 0.28        | 0.34        | 0.16        |
| Others, n (%)          | 43 (14.9%)  | 8 (17.8%)         | 3 (27.3%)       | 0.851    | 0.58        | 0.95        | 0.74        |
| Not identified, n (%)  | 24 (8.3%)   | 2 (4.4%)          | 2 (18.2%)       |          |             |             |             |
| Old cerebral infarction on imaging, n (%) | 103 (35.8%) | 26 (57.8%)      | 5 (45.5%)       | 0.017    | 0.005       | 0.51        | 0.46        |
| Generalized brain atrophy on imaging, n (%) | 100 (34.7%) | 28 (62.2%)      | 8 (72.7%)       | <0.001   | <0.001      | 0.010       | 0.51        |
| History of syphilis symptoms |             |                   |                 |          |             |             |             |
| Chancre, n (%)         | 9 (3.1%)    | 3 (6.7%)          | 0 (0.0%)        | 0.470    | 0.21        | 1.00        | 1.00        |
| Oral ulcer, n (%)      | 8 (2.8%)    | 1 (2.2%)          | 0 (0.0%)        | 1.000    | 1.00        | 1.00        | 1.00        |
| Rash, n (%)            | 16 (5.6%)   | 4 (8.9%)          | 0 (0.0%)        | 0.472    | 0.33        | 1.00        | 0.58        |
| Alopecia, n (%)        | 7 (2.4%)    | 8 (17.8%)         | 0 (0.0%)        | <0.001   | <0.001      | 1.00        | 0.33        |
| Lymphadenopathy, n (%) | 0 (0.0%)    | 1 (2.2%)          | 0 (0.0%)        | 0.163    | 0.14        | 1.00        |             |
| Urogenital wart, n (%) | 6 (2.1%)    | 1 (2.2%)          | 0 (0.0%)        | 1.000    | 1.00        | 1.00        | 1.00        |
group (p=0.013). All NS patients were treated with 24 million units of aqueous crystalline penicillin G per day, administered intravenously as 4 million units every 4 h for 14 days. Among the 45 LS patients, 36 patients were injected with benzathine penicillin G intramuscularly as three doses of 2.4 million units at 1-week intervals, 6 patients took 100 mg of doxycycline orally twice daily for 28 days, 2 cases were fatal before treatment was initiated, and the remaining case refused treatment.

**Comparison of disability and activities of daily living (ADL) outcomes among the control, LS, and NS groups**

After study enrollment, the initial mRS and BI scores were first recorded, and then the investigation for syphilitic infection was performed, followed by treatment if necessary. An evaluation was conducted via telephone three months later. The mRS scores, which represent the degree of disability due to stroke and range from 0 (no symptoms) to 6 (death), at the initial and 3-month timepoints are compared in Table 4. The initial mRS score in the control group was significantly lower than that in the NS group (p=0.022), reflecting a mild disability at the initial evaluation of patients without syphilis. The 3-month mRS score was significantly decreased from the baseline score in the control (p<0.001) and LS (p=0.001) groups, indicating good recovery from disability in these patients. Additionally, the BI score was used to measure performance in
Table 2  Clinical characteristics and CSF profiles of neurosyphilis patients (all CMIA-serological positive)

| Case | Age  | Sex | Symptoms | Underlying conditions | Serology | WBC (cells/mm³) | N% | L% | RBC (cells/mm³) | Protein (mg/dL) | Sugar (mg/dL) | CSF/glucose ratio | CSF VDRL | CSF FTA-ABS | Location of lesion | 3-month outcome |
|------|------|-----|----------|-----------------------|----------|-----------------|----|----|----------------|----------------|---------------|-----------------|----------|-------------|-------------------|-----------------|
| 1    | 85   | M   | hemiparesis, hemianesthesia | DM, HT, smoking | RPR non-reactive FTA-ABS: reactive | 1   | 0   | 100 | 0             | 83             | 66            | 0.46 | NR | R | no definite lesion | mRS: 4, BI: 40 |
| 2    | 85   | F   | hemiparesis | HT, DLP, CAD | RPR titer 1:4 | 1   | 0   | 100 | 0             | 46             | 68            | 0.58 | NR | R | no definite lesion | mRS: 6, BI: 0  |
| 3    | 77   | M   | hemiparesis, blurred vision, vertigo, hemianesthesia | HT | RPR titer 1:4 | 7   | 29  | 71  | 4,000         | 71             | 72            | 0.55 | 1.4 | NR | brainstem | mRS: 4, BI: 90 |
| 4    | 63   | M   | hemiparesis, hemianesthesia | HT, DLP, AF | RPR: weakly reactive | 4   | 50  | 50  | 1,000         | 139            | 78            | 0.62 | NR | R | BA territory | mRS: 5, BI: 0   |
| 5    | 80   | M   | hemiparesis, blurred vision, vertigo, hemianesthesia | DM, HT | RPR: weakly reactive | 1   | 100 | 0   | 0             | 170            | 63            | 0.52 | NR | WR | brainstem | mRS: 2, BI: 100 |
| 6    | 94   | F   | aphasia | HT, DLP | RPR non-reactive FTA-ABS: reactive | 2   | 50  | 50  | 0             | 390            | 80            | 0.61 | NR | R | subcortical white matter | mRS: 6, BI: 0   |
| 7    | 78   | M   | hemiparesis, dysarthria, hemianesthesia | Alcoholism | RPR non-reactive FTA-ABS: reactive | 17  | 7   | 93  | 1,000         | 78             | 58            | 0.68 | NR | R | thalamus | mRS: 4, BI: 65   |
| 8    | 74   | M   | hemiparesis, dysarthria | DLP, smoking, CVD | RPR titer 1:16 | 18  | 67  | 33  | 18,000        | 51             | 74            | 0.61 | NR | WR | MCA territory | mRS: 5, BI: 0   |
| 9    | 72   | M   | hemiparesis, dysarthria, hemianesthesia | smoking | RPR titer 1:1 | 1   | 0   | 100 | 0             | 90             | 69            | 0.62 | NR | R | subcortical white matter | mRS: 2, BI: 95   |
| 10   | 89   | M   | hemiparesis, blurred vision | HT, DLP, CAD | RPR titer 1:1 | 1   | 0   | 100 | 0             | 59             | 64            | 0.41 | NR | R | subcortical white matter | mRS: 4, BI: 40   |
Table 2 (continued)

| Case | Age (years) | Sex | Symptoms | Underlying conditions | Serology | WBC (cells/mm³) | N% | L% | RBC (cells/mm³) | Protein (mg/dL) | Sugar (mg/dL) | CSF/serum glucose ratio | CSF VDRL | CSF FTA-ABS | Location of lesion | 3-month outcome |
|------|-------------|-----|----------|-----------------------|----------|----------------|-----|----|----------------|----------------|-------------|-----------------------|-----------|-------------|-------------------|-----------------|
| 11   | 81          | F   | hemiparesis, dysarthria, hemianesthesia | RPR: non-reactive | FTA-ABS: reactive | 1    | 0   | 100  | 0   | 50          | 65            | 0.68        | 1.2                  | NR        | MCA territory | mRS: 5, BI: 0     |

Mean ± SD

4.91 ± 6.5 27 ± 34 72 ± 34 2181 ± 5381 111 ± 100 68 ± 66 0.57 ± 0.085

AF atrial fibrillation, BA basilar artery, BI barthel index, CAD coronary artery disease, CMIA chemiluminescent microparticle immunoassay, CSF cerebrospinal fluid, CVD cerebrovascular disease, DLP dyslipidemia, DM diabetes mellitus, F female, FTA-ABS fluorescent treponemal antibody absorption, HT hypertension, L lymphocyte, M male, MCA middle cerebral artery, mRS modified Rankin scale, N neutrophil, NR non-reactive, R reactive, RBC red blood cell, RPR rapid plasma reagin, SD standard deviation, VDRL Venereal Disease Research Laboratory test, WBC white blood cell, WR weakly reactive.
ADL, with scores ranging from 0 (totally dependent) to 100 (normal ADL). There was no significant difference in the initial BI scores among the three groups. However, the 3-month post-stroke BI score was significantly higher in the control group than in the LS ($p = 0.003$) and NS ($p = 0.002$) groups, reflecting better ADL performance at this timepoint among patients without syphilis. The 3-month post-stroke median BI score was significantly increased from the initial BI score in the control ($p < 0.001$) and LS ($p = 0.001$) groups, indicating good recovery with respect to ADL performance among these patients.

### Discussion

Meningovascular NS is a rare cause of stroke that occurs in approximately 10% of NS cases and in approximately 3% of all syphilis cases (22, 23). Previous studies conducted in Australia and Portugal, countries with a very low prevalence of syphilis, found the prevalence of positive syphilis serology results among patients who presented with an acute stroke to be 4% and 3.72%, respectively (6, 24, 25). In Thailand, a 2011 study found that the prevalence of syphilis among patients who presented with an acute stroke was 8.4% (11), which is only half of the syphilis prevalence found by our present study (16.3%). Our data indicate that syphilis remains a major problem in Thailand.

Meningovascular NS often presents with a stroke among patients younger than 50 years of age and typically occurs within 10 years of syphilitic infection (6, 26–28). Regarding studies conducted before the year 2000 (29, 30), up to 74% of meningovascular NS patients who presented with a stroke were under the age of 50 years. However, the epidemiology of NS has changed over the last decade. A recent study conducted in Portugal revealed a mean age of 76 years in NS patients who presented with a stroke and reported several cerebrovascular risk factors for ischemic stroke. This finding showed a trend similar to that of our study, in which the median age of meningovascular NS patients was 80 years old. Moreover, the multivariate analysis comparing patients without and with LS or NS (Table 3) revealed that an age of $\geq 70$ years was an independent factor associated with LS and NS. This result emphasizes that in the AIS and TIA population, the age of most syphilis-infected patients was higher than that of the typical patient with meningovascular NS, as described above. Therefore, routine serological screening for syphilis may be warranted in AIS and TIA patients aged 70 years or older, especially in regions with a high prevalence of syphilis.

Although the incidence of meningovascular NS continues to rise, only a few studies have focused on syphilis in elderly patients with typical ischemic stroke or TIA who present with atherosclerosis and cardiovascular risk factors. Through neuroimaging, we found that generalized brain atrophy was a factor associated with LS and showed a trend towards being a factor associated with NS (in the univariate analysis, the comparison of control

### Table 3

|                          | Total (n = 56) | Latent syphilis (n = 45) | Neurosyphilis (n = 11) | p-value* |
|--------------------------|---------------|--------------------------|------------------------|----------|
| WBC (cells/mm$^3$), median (P25, P75) | 1 (1, 4) | 1 (1, 3) | 1 (1, 7) | 0.471 |
| N (%), median (P25, P75) | 0 (0, 50) | 0 (0, 50) | 7 (0, 50) | 0.714 |
| L (%), median (P25, P75) | 67 (28, 100) | 67 (0, 100) | 93 (50, 100) | 0.238 |
| RBC (cells/mm$^3$), median (P25, P75) | 0 (0, 1000) | 0 (0, 1000) | 0 (0, 1000) | 0.713 |
| Protein (mg/dL), median (P25, P75) | 57 (42, 80) | 54 (40, 71) | 78 (51, 139) | 0.013 |
| Sugar (mg/dL), median (P25, P75) | 66 (59, 79) | 65 (57, 79) | 68 (64, 74) | 0.657 |
| CSF/serum glucose ratio, median (P25, P75) | 1 (1, 1) | 1 (1, 1) | 1 (1, 1) | 0.665 |

CSF cerebrospinal fluid, FTA-ABS fluorescent treponemal antibody absorption, L lymphocyte; P25, 25th percentile, N neutrophil, n number, P75 75th percentile, RBC red blood cell, VDRL Venereal Disease Research Laboratory test, WBC white blood cell

* Fisher’s exact test was performed to assess the association between qualitative CSF profile and two syphilis groups: Latent syphilis and Neurosyphilis. Mann–Whitney U test was used to compare the median of the quantitative CSF profiles between the two groups.
group with NS yielded a \( p \)-value of 0.01, but this difference was not significant in the multivariate analysis. Several case reports have shown generalized brain atrophy via imaging in NS patients who presented with a progressive cognitive decline (24, 31–33). However, for LS, there was no obvious evidence for an association with generalized brain atrophy. Therefore, this result requires confirmation from additional studies.

Alopecia has historically been associated with syphilis infection (34–36). In the present study, alopecia was a factor significantly associated with LS as compared with controls. However, no patient in the NS group presented with this symptom, which may be a consequence of the small sample size in that group.

The multivariate analysis comparing LS and NS revealed that the proportion of patients with dysarthric symptoms of stroke was significantly lower in the NS group than in the LS group (AOR = 0.154). Previous studies have reported that dysarthria is a symptom of NS, (24, 33, 37), but the observations from the present work do not support that finding; however, this discrepancy may stem from the confounding effect of our small sample size.

To further investigate abnormalities of the CSF profiles in our study, we allowed the diagnosis of NS with TIA or AIS from criteria that was proposed by the previous study in Thailand (7). There is a frequency of absence of CSF-cell elevation in the majority of our NS cases. The cause is not yet clear. But it may be assumed that one of the consequences of ageing is a decline in the immune response (mean age of NS was about 80 years old) (38–40). In 4 NS patients who had elevated red blood cells (RBC) in their CSF from traumatic tap, only one of them had CSF VDRL positivity with CSF RBCs of 4,000 cells/mm\(^3\), which is rarely a false positive result because, from Izzat et al. data, the amounts of CSF RBCs required to cause the CSF conversion have to be at least 12,000 cells/mm\(^3\) (41). The other 3 RBC contaminated NS patients had CSF VDRL negative with CSF FTA-ABS positive. When blood is contaminated, a CSF FTA-ABS is frequently false-positive, but in the context of a consistent clinical scenario, diagnosis and treatment for NS should be given (11, 42–45). Only 18.2% of our patients (n = 2/11) with TIA or AIS related to NS had positive CSF VDRL results; thus, combining CSF VDRL results with CSF FTA-ABS results was useful to diagnose NS in AIS and TIA patients.

The degree of stroke-related disability in the NS group was initially severe compared with that in the control group, and the severity of disability did not significantly improve over the subsequent three months. Moreover, the performance of ADL at 3 months post-stroke in the NS group was significantly worse than that in the control group and had improved significantly less from the baseline assessment compared with the control and LS groups. In LS patients, the ADL performance at 3-months post-stroke was significantly worse than that in control patients. This stroke outcome demonstrates that an occult syphilitic infection is associated with a poor recovery, which may be from systemic infection combined with ageing and cerebral infarction pushing individual microglia toward proinflammatory phenotypes, compromising the connectivity of neuronal networks (46, 47). This effect of persistent

| Table 4 | Outcome comparison of patients without and with latent syphilis and neurosyphilis |
|---------|---------------------------------------------------------------------------------|
|         | Controls | Latent syphilis | Neurosyphilis | \( p \)-value | P1 | P2 | P3 |
| Modified Rankin Scale* | | | | | | |
| Initial (points), median (P25, P75) | 4 (3, 5) | 5 (4, 5) | 5 (4, 5) | 0.022 | 0.095 | 0.022 | 0.12 |
| 3 months (points), median (P25, P75) | 2 (1, 4) | 3 (2, 5) | 4 (4, 5) | | | | |
| \( p \)-value (difference between initial and 3-month scores) | < 0.001 | 0.001 | 0.236 | | | | |
| Change from initial (3-month score–initial score), median (P25, P75) | -1 (-2, 0) | -1 (-2, 0, 5) | 0 (-1, 0) | 0.077 | 0.124 | 0.076 | 0.448 |
| Barthel Index** | | | | | | |
| Initial (points), median (P25, P75) | 50 (30, 75) | 50 (20, 65) | 55 (10, 60) | 0.204 | 0.14 | 0.27 | 0.69 |
| 3 months (points), median (P25, P75) | 100 (50, 100) | 90 (5, 100) | 40 (0, 90) | 0.001 | 0.030 | 0.002 | 0.095 |
| \( p \)-value (difference between initial and 3-month scores) | < 0.001 | 0.001 | 0.838 | | | | |
| Change from initial (3-month score–initial score), median (P25, P75) | 25 (0, 44) | 25 (-5, 40) | -10 (-20, 25) | 0.028 | 0.274 | 0.012 | 0.076 |

*The Kruskal–Wallis H test was used to compare median of the outcomes between the three groups

*Scores on the modified Rankin scale (mRS) range from 0 (no symptoms) to 6 (death)

**The Barthel Index (BI) scores range from 0 (totally dependent) to 100 (normal activities of daily living)
immune activation in the brain can result in neurodegeneration and a decreased ability to improve (48).

There are a few limitations to our study. The number of NS patients was small and may not have been sufficient to demonstrate many factors associated with having NS. However, we were able to identify some associated factors, such as old age, alopecia, and generalized brain atrophy, that could be used to trigger clinical suspicion of NS among patients with AIS or TIA. A multicenter prospective study and long-term follow-up are needed to provide further support for these associations.

Conclusions

This study displayed interesting hint characteristics which indicate to explore history and serological screening for syphilis in the acute ischemic cerebrovascular population. The AIS and TIA patients with one or more of aging more than seventy years old, a history of alopecia and generalized brain atrophy on the imaging were at risk for the *T. pallidum* infection. During the investigation for diagnosis of NS which based on CSF analysis, sending CSF VDRL and CSF FTA-ABS test at the same time was useful for confirming an NS diagnosis in a real-world situation which can avoid suffering from repeat lumbar puncture due to the low rate of CSF VDRL test result-positivity. Lastly, both NS and LS patients have a worse stroke consequence as compared with control patients that demonstrate by the mRS and BI score. From the electronic literature review, this is the first study that has shown the impact of the syphilitic infection on the prognosis of the AIS and TIA patients, which is the new evidence of connectivity between the infectious disease and the cerebrovascular disease.

Abbreviations

AIS: Acute ischemic stroke; AF: Atrial fibrillation; ANOVA: Analysis of variance; AOR: Adjusted odds ratio; BA: Basilar artery; BI: Barthel index; BUN: Blood urea nitrogen; CAD: Coronary artery disease; CIOMS: Council for International Organizations of Medical Sciences; CMA: Chemiluminescence microimmunoassay; Cr: Creatinine; CSF: Cerebrospinal fluid; CSF FTA-ABS: Cerebrospinal fluid fluorescent treponemal antibody absorption; CSF-VDRL: Cerebrospinal Fluid-Venereal Disease Research Laboratory; CT: Computed tomography; CVD: Cerebrovascular disease; DLP: Dyslipidemia; DM: Diabetes mellitus; F: Female; FTA-ABS: Fluorescent treponemal antibody absorption; GCP: Good clinical practice; GFR: Glomerular filtration rate; HIV: Human immunodeficiency virus; HT: Hypertension; ICH: International Conference on Harmonization; INR: International normalized ratio; IL: Illinois; L: Lymphocyte; LDL: Low-density lipoprotein; LS: Latent syphilis; M: Male; MCA: Middle cerebral artery; mRS: Modified Rankin Scale; n: Number; N: Neutrophil; NR: Non-reactive; NS: Neurosyphilis; PASW: Predictive analytics software; PT: Prothrombin time; PTT: Partial thromboplastin time; R: Reactive; RBC: Red blood cell; RPR: Rapid plasma reagent; SD: Standard deviation; SPSS: Statistical Package for the Social Sciences; TIA: Transient ischemic attack; TOAST: Trial of ORG 10172 in acute stroke treatment; T. pallidum: Treponema pallidum; USA: United States of America; VDRL: Venereal Disease Research Laboratory; WBCs: White blood cells; WR: Weakly reactive.

Acknowledgements

We thank Katie Oakley, PhD, from Edanz (www.edanz.com/ac) for editing a draft of this manuscript.

Author contributions

PJ has been involved in research. By requesting permission for human research from ethics committee, including data collection, interpreted the patient data regarding the neurological disease, analyzed basic statistical data and was a major contributor in writing the manuscript. AB edited research proposal project, calculated the number of populations to be studied, interpreted the patient data regarding the infectious disease, analyzed data with advanced statistics, edited the manuscript and sent for submission. Both authors read and approved the final manuscript.

Funding

No funding.

Availability of data and materials

Individual level data cannot be shared publicly because of patient confidentiality under current Thai legislation. The data that support the findings of this study are available from Chumphonkatudomsak Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Chumphonkatudomsak Hospital and the appropriate ethics committee.

Declarations

Ethics approval and consent to participate

The study was approved by the human research ethics committee of the Faculty of Medicine, Thammasat University (Ref: MTU-EC-OO-0-080/62) and informed consent obtained from each participant. All methods were carried out in accordance with relevant guidelines and regulations such as the Declaration of Helsinki, The Belmont Report, CIOMS Guidelines and the International Practice (CH-GCP).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

1 Division of Medicine, Chumphonkatudomsak Hospital, Chumphon, Thailand.

2 Department of Research and Development, Faculty of Medicine Sirinaj Hospi-
tal, Mahidol University, Bangkok, Thailand.

Received: 28 May 2022   Accepted: 22 August 2022

Published online: 30 August 2022

References

1. Chaiyamahapurk S, Kitiyaovamarn R. Syphilis: resurgence. Dis Contr J. 2021;47(2):199–208.

2. Leeyaphan C, Jiamton S, Prasertworonun N, Maneeprasopchoke P, Omchaoen VJ. Clinical and epidemiological characteristics of patients with syphilis: 5 year-case study from Thailand. J Med Assoc Thai. 2014;97(9):963–8.

3. Gjestland T. The Oslo study of untreated syphilis; an epidemiologic investigation of the natural course of the syphilitic infection based upon a re-study of the Boeck-Bruusgaard material. Acta Derm Venerologica. 1955;35(Suppl 34):3–368 (Annex I–LVI).

4. Golden MR, Marra CM, Holmes KK. Update on syphilis: resurgence of an old problem. JAMA. 2003;290(11):1510–4.

5. Liu LL, Zheng WH, Tong ML, Liu GL, Zhang HL, Fu ZG, et al. Ischemic stroke as a primary symptom of neurosyphilis among HIV-negative emergency patients. J Neurol Sci. 2012;317(1–2):35–9.

6. Pintado Maury I, Alves M, Fonseca T. Neurosyphilis prevalence at a Portuguese stroke unit care. Aging Clin Exp Res. 2019;31(8):1155–61.
7. Dharmasarjo PA, Dharmasarjo P. Serum and cerebrospinal fluid profiles for syphilis in Thai patients with acute ischaemic stroke. Int J STD AIDS. 2012;23(5):340–5.

8. Targa Martins R, Castilhos RM, Silva da Silva P, Costa LS. Frequency of screening and prevalence of neurosyphilis in stroke population. Cerebrovasc Dis. 2020;49(3):301–6.

9. Marra CM, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, Jones T. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. Sex Transm Dis. 2012;39(6):453–7.

10. Harding AS, Ghanem KG. The performance of cerebrospinal fluid treponemal-specific antibody tests in neurosyphilis: a systematic review. Sex Transm Dis. 2012;39(4):291–7.

11. Workowski KA, Bachmann LH, Chan PA, Johnston CM, Muzny CA, Park I, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep. 2021;70(4):1–187.

12. Banks JL, Marotta CA. Outcomes validity and reliability of the modified Rankin scale: implications for stroke clinical trials: a literature review and synthesis. Stroke. 2007;38(3):1091–6.

13. Quinn TJ, Langhorne P, Stott DJ. Barthel index for stroke trials: development, properties, and application. Stroke. 2011;42(2):1146–51.

14. Shinar D, Gross C, Bronstein K, Licata-Gehr E, Eden D, Cabrera A, et al. Reliability of the activities of daily living scale and its use in telephone interview. Arch Phys Med Rehabil. 1987;68(10):723–8.

15. Kornier-Bitensky N, Wood-Dauphinee SJA. Barthel Index information elicited over the telephone Is it reliable? Am J Phys Med Rehabil. 1995;74(1):9–18.

16. Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V, et al. Simplified modified rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. Stroke. 2011;42(8):2276–9.

17. Della Pietra GL, Savio K, Oddone E, Reggiani M, Monaco F, Leone MAJS. Validity and reliability of the Barthel index administered by telephone. Stroke. 2011;42(7):2077–9.

18. Dennis M, Mead G, Doubal F, Graham CJS. Determining the modified Rankin score after stroke by postal and telephone questionnaires. Stroke. 2012;43(3):851–3.

19. Baggio JA, Santos-Pontelli TE, Cougo-Pinto PT, Camilo M, Silva NF, Antunes P, et al. Validation of a structured interview for telephone assessment of the modified Rankin Scale in Brazilian stroke patients. Cerebrovasc Dis. 2014;38(4):297–301.

20. Prasad K, Kumar A, Misra S, Yadav AK, Johri S, Sarkar R, et al. Reliability and validity of telephonic Barthel Index: an experience from multi-centric randomized control study. Acta Neurol Belg. 2018;118(1):53–9.

21. Chung JW, Park SH, Kim N, Kim WJ, Park JH, Ko Y, et al. Trial of ORG 10172 for ischemic stroke lesions diagnosed by diffusion-weighted imaging. J Am Heart Assoc. 2014;3(4):e001119.

22. Hooshmand H, Escobar MR, Kopf SW. Neurosyphilis. A study of 241 patients. JAMA. 1972;219(6):726–9.

23. Singh AE, Romanovski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. Clin Microbiol Rev. 1999;12(2):187–209.

24. Mehrabian S, Raycheva M, Tantalo LC, Maxwell CL, Ho EL, Sahi SK, et al. Neurosyphilis with dementia and bilateral hippocampal atrophy on brain magnetic resonance imaging. BMC Neurol. 2012;12:96.

25. Kojima N, Klausner JD. An update on the global epidemiology of syphilis. Clin Microbiol Rev. 1999;12(2):187–209.

26. Behrouz R, Malek AR, Chichikov RI. Meningo-vascular syphilis: revisiting an old adversary. Practical Neurology. 2011;32–7.

27. Behrouz R, Malek AR, Chichikov RI. Meningo-vascular syphilis: revisiting an old adversary. Practical Neurology. 2011;32–7.

28. Simon RP. Neurosyphilis. Arch Neurol. 1985;42(6):606–13.

29. Merritt HH, Adams RO, Solomon HC. Neurosyphilis. Neurosyphilis 1946. pp. 443.

30. Kirkpatrick JB. Neurologic infections due to bacteria, fungi and parasites. In: Davis RL, Robertson DM, editors. Textbook of neuropathology. 2nd Edn. Baltimore: Williams & Wilkins; 1971:719–803.

31. Zilko U, Wimbberger D, Lindner K, Zier G, Grisold W, Schindler E. MRI in patients with general pariesis. Neuroradiology. 1996;38(2):120–3.

32. van Eijden P, Welling JH, Linn FH, Scheltens P, Bissels GJ. Progressive dementia and mesiotemporal atrophy on brain MRI: neurosyphilis mimicking pre-senile Alzheimer’s disease? Eur J Neurol. 2008;15(2):e14–5.

33. Toptan T, Ozdilek B, Kenangil G, Ulker M, Domac FM. Neurosyphilis: a case report. North Clin Istamb. 2015;2(1):66–8.

34. Tognetti L, Cinotti E, Perrot JL, Campoli M, Rubegni P. Syphilitic alopecia: uncommon trichoscopic findings. Dermatol Pract Concept. 2017;7(3):55–9.

35. Hernández-Bel P, Unamuno B, Sánchez-Carazo JL, Febrer I, Alegre V. Syphilitic alopecia: a report of 5 cases and a review of the literature. Actas Dermosifiliogr. 2013;104(6):512–7.

36. Qiao J, Fang H. Moth-eaten alopecia: a sign of secondary syphilis. CMAJ. 2013;185(1):61.

37. Nitrini R, de Paiva ARB, Takada LT, Brucki SMD. Did you rule out neurosyphilis? Dement Neurocogn Disord. 2010;4(4):338–45.

38. Montecino-Rodriguez E, Berent-Maaz B, Dorshkind K. Causes, consequences, and reversal of immune system aging. J Clin Investig. 2013;123(3):958–65.

39. Weyand CM, Goronzy JJ. Aging of the immune system. Mechanisms and therapeutic targets. Ann Am Thorac Soc. 2016;13(Suppl 5):S422–8.

40. Haynes L. Aging of the immune system: research challenges to enhance the health span of older adults. Front Aging. 2020;1:602108.

41. Izzat N, Bartruff J, Glicksman J, Holder W, Knox JB. Validity of the VDRL test on cerebrospinal fluid contaminated by blood. Br J Vener Dis. 1971;47(3):162.

42. Delany P. False positive serology in cerebrospinal fluid associated with a spinal cord tumor. Neurology. 1976;26(6):591.

43. Henao-Martinez AF, Johnson SC. Diagnostic tests for syphilis: new tests and new algorithms. Neurol Clin Pract. 2014;4(2):114–22.

44. Marra CM, Maxwell CL, Dunaway SB, Sahi SK, Tantalo LC. Cerebrospinal fluid Treponema pallidum particle agglutination assay for neurosyphilis diagnosis. J Clin Microbiol. 2017;55(6):1865–70.

45. Satyaputra F, Hendry S, Braddick M, Sivabalan P, Norton R. The laboratory diagnosis of syphilis. J Clin Microbiol. 2021;59(10):e00100-e121.

46. Kamel H, Iadeoca CIA. Brain-immune interactions and ischemic stroke: clinical implications. Arch Neurol. 2012;69(5):576–81.

47. Valdés-Ferrer SI, Benkendorff A, Sankowski RJ. Persistent inflammatory states and their implications in brain disease. Curr Opin Neurol. 2020;33(3):341–6.

48. Sankowski R, Mader S, Ippolito JM. Syphilitic alopecia: uncommon trichoscopic findings. Dermatol Pract Concept. 2015;5(1):24–8.