Prevalence of positive syphilis serology and meningovascular neurosyphilis in stroke and TIA admissions from a culturally diverse population (2005-2009)

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Abstract

Objective: To determine prevalence of positive syphilis serology and meningovascular neurosyphilis (NS) in transient ischaemic attack (TIA) and stroke admissions to a tertiary hospital serving a culturally diverse community.

Design and setting: Retrospective cohort analysis using routinely collected administrative data and medical records to identify TIA, stroke and other admissions with positive syphilis serology between 2005 and 2009. Direct medical record review confirmed diagnoses of meningovascular NS.

Main outcome measures: Prevalence of positive syphilis serology and meningovascular NS in stroke and TIA admissions

Results: Syphilis serology was requested in 27% (893/3270) of all TIA and stroke patients (2005-2009) of which 4% (38/893) were positive. Thirty-seven patients with positive serology had clinical characteristics consistent with meningovascular NS. Mean age was 72 ± 13 years; 65% were male and 38% had recorded birth in South-East Asia or the Pacific Islands. One of twelve suspected meningovascular cases with CSF analysis had a positive CSF VDRL. Three patients (8%) met diagnostic criteria for 'definite or probable' meningovascular NS. All 3 patients with 'definite or probable' meningovascular NS and 15 (44%) of the remainder who had positive serology without confirmation of NS were treated with intravenous penicillin.

Conclusion: In this culturally diverse Australian community, 4% of tested stroke and TIA patients were seropositive for syphilis. Less than 10% of seropositive patients met criteria for 'definite or probable' meningovascular NS. Lumbar puncture and penicillin were underutilised in stroke and TIA patients with positive serology.

Introduction

Syphilis is an acquired or congenital infection caused by *Treponema pallidum* subsp. *pallidum*. It is a global disease with a worldwide estimated incidence of 12 million new cases per year among adults.¹ Syphilis is most prevalent in developing countries but has re-emerged as a rare but important diagnosis in developed nations such as Australia.^{1,2} It can be divided into early and late forms with the latter further divided into latent (asymptomatic) and tertiary syphilis.³ Tertiary syphilis is classified as cardiovascular, neurosyphilis (NS) and late benign or peripheral gummatous syphilis.³⁻⁵ Patients with cardiovascular syphilis often have associated NS.⁵

The four major subcategories of NS are: asymptomatic; meningeal including ocular and auricular; meningovascular including central gummatous and parenchymatous (which includes general paresis); and tabes dorsalis.³⁻⁵ Patients with meningovascular NS may present with symptoms of transient ischaemic attack (TIA) or stroke, indistinguishable from atherothrombotic TIA and stroke.⁴

There is no 'gold standard' for the diagnosis of NS. The serum rapid plasma reagin (RPR) and venereal disease research laboratory (VDRL) tests are inexpensive non-treponemal tests that have a lower sensitivity and specificity than more expensive treponemal tests.³⁻⁶ Patients with positive RPR or VDRL serology require confirmation with a treponemal antigen test such as the Treponemal enzyme immunoassay (EIA) or *Treponema pallidum* particle agglutination test (TPPA).³ Cerebrospinal fluid (CSF) analysis is recommended in patients with positive syphilis serology and neurological symptoms and in the presence of HIV infection, especially where the serum RPR test titre is high (> 1:32).³

It is generally accepted that a positive CSF VDRL and/or raised CSF protein and pleocytosis indicate active central nervous system disease, although diagnostic sensitivity may be less than 50% [range 30-78%].^{3,6,7} False-positive results may be seen if CSF is contaminated with blood^{3,6} and CSF-TPPA

can be positive in adequately treated patients as well as asymptomatic NS. CSF-TPPA may remain positive indefinitely.^{3,6}

The age-adjusted notification rate of infectious syphilis in New South Wales (NSW) has significantly increased from 1.9 per 100,000 (3.3 per 100,000 in men and 0.6 per 100,000 in women) in 2002 to 6.4 per 100,000 (12.1 per 100,000 in men and 0.7 per 100,000 in women) in 2007.² Increase in the prevalence of infectious syphilis is likely to result in a surge of NS cases in coming decades.

South-Western Sydney (SWS) has one of the most culturally and linguistically diverse populations in Australia and has the second highest infectious syphilis notification rate in NSW at ~ 6 per 100,000 population.⁸

Syphilis is a potentially treatable cause of neurovascular disease. The present study is the first to report the modern prevalence of positive syphilis serology and neurosyphilis in TIA and stroke admissions in an Australian setting.

Subjects and Methods

This a retrospective, observational study of consecutive stroke and TIA admissions to Liverpool Hospital (LH), between January 1st 2005 and December 31st 2009, utilising routinely collected administrative data. LH is the tertiary referral centre for SWS, a previously described metropolitan and rural area with a population of ~800,000.⁹ Hospital policy is to admit all Emergency presentations of stroke and TIA to the stroke service.¹⁰

Data were extracted from routinely collected administrative datasets, including the NSW Health Department Health Information Exchange (HIE) data-base, a census of all hospital admissions using the ICD-10-AM diagnostic coding system¹¹ and local electronic medical records (eMR Cerner version 2010.10).

Ethics approval was obtained from the SWS Area Health Service Research Ethics Committee.

Case ascertainment

Two strategies were used to identify seropositive TIA and stroke patients.

1) Identification of all hospital admissions with a diagnosis of syphilis.

All LH patients with a principal or secondary ICD-10-AM discharge diagnosis of syphilis (A50.0-9, A51.0-5, A51.9, A52.0-3, A52.7-9, A53.0, A53.9), in the 5 year study period (2005-9), were identified in the HIE database.

2.) Identification of all TIA and stroke admissions with positive syphilis serology.

All LH patients with a principal or secondary discharge diagnosis of TIA and stroke (ICD-10-AM I60.0-9, I61.0-9, I62.0, I62.1, I62.9, I63.0-9, I64, G45.0-9) were identified in the HIE database (2005-2009). All underwent electronic medical record system analysis to identify those patients with positive syphilis serology or a CSF VDRL analysis. Patients with negative TPPA serology were excluded.

Medical record review

Co-authors DC, ST and SD reviewed the hospital medical records of all patients with an ICD-10 diagnosis of syphilis and patients with a diagnosis of TIA or stroke with positive syphilis serology to confirm diagnoses of syphilis, TIA and stroke. Clinical characteristics of suspected meningovascular NS were identified and patients were classified as having a 'probable' or 'definite' diagnosis of NS, 'positive serology without confirmation of NS' or an 'other' clinical syphilis diagnosis (eg cardiovascular). Past or admission treatment for syphilis was determined from the medical record.

Diagnosis of meningovascular NS

Meningovascular NS diagnosis was determined by co-author medical record review. Patients with positive syphilis serology, clinical features consistent with meningovascular NS and a positive CSF VDRL were categorised as 'definite' meningovascular NS. Patients with clinical features consistent with meningovascular NS, positive syphilis serology and a negative CSF VDRL were categorised as 'probable' meningovascular NS if there was a CSF pleocytosis (> 5 white cell/mm³). Patients with positive syphilis serology and clinical features consistent with meningovascular NS were categorised as having 'positive serology without confirmation of NS' if CSF protein was raised (>0.45 g/L) without pleocytosis or if CSF analysis was normal (Table 1). The remaining patients with positive syphilis serology and no features of meningovascular NS or a documented past history of treatment were categorised as 'other' syphilis (eg cardiovascular) or a 'non-syphilis' related presentation and excluded from further analysis.

Statistical methods

All eligible sero-positive patients admitted to LH between 2005 and 2009, as identified by case ascertainment methods 1 and 2, were included in the analysis of baseline demographic and patient clinical data. Data were analysed according to age, gender, place of birth, RPR serology, CSF results, syphilis treatment and the presence of 'positive serology without confirmation of NS', or a 'probable' or 'definite' diagnosis of meningovascular NS.

Statistical analysis of mean, median and standard deviation (SD) values were performed using SPSS Statistics version 18.0.

Results

Patients with an ICD-10-AM hospital diagnosis of syphilis

There were 354,824 admissions to LH in the period 2005-09. Twenty-two patients had a principal or secondary ICD-10-AM hospital diagnosis of syphilis (Figure 1).

Seven patients had symptoms and signs consistent with a diagnosis of general paresis, 5 had focal neurological symptoms and signs including symptoms of stroke and TIA consistent with meningovascular NS, 2 had symptoms and signs consistent with tabes dorsalis, 2 had ocular NS and 4 had 'other' syphilis diagnoses. Two patients diagnosed with syphilis had 'non-syphilis'-related presentations.

Seropositive TIA and stroke patients (Figure 1)

There were 3270 TIA and stroke admissions determined by ICD-10 coding between 2005 and 2009. Syphilis serology was requested in 27% (893/3270) of TIA and stroke patients, of whom 38 (~4%) were seropositive. Three seropositive TIA and stroke patients were also captured by case ascertainment method 1 (ICD-10-AM diagnoses of syphilis, Figure 1). Of the remaining 35 seropositive TIA and stroke patients, 32 had symptoms and signs consistent with a meningovascular NS presentation. One patient with a TIA or stroke diagnosis had an 'other' syphilis diagnosis and 2 had 'non-syphilis'-related presentations including 1 patient with a documented past history of treatment for NS.

Meningovascular NS in patients presenting with symptoms of TIA or stroke.

Three patients fulfilled criteria for 'definite' or 'probable' NS:

- 1.) A 42-year-old Fijian-born male with a past history of oral antibiotic therapy for a chancre in 1991 presented in 2005 with a 2 month history of fluctuating headache, confusion and dysphasia. A CT

brain scan demonstrated a hypodensity in the left fronto-temporal region. An MRI brain revealed a large left fronto-temporal lesion with associated oedema, thick enhancing rim, adjacent dural enhancement and restricted diffusion. His serum RPR titre was 64, CSF analysis identified a pleocytosis (52 lymphocytes/mm³), raised CSF protein (0.52 g/L) and positive CSF VDRL. A brain biopsy identified a necrotising inflammatory abscess-like process with mononuclear response and endarteritis, consistent with a cerebral gumma, which was confirmed by a positive treponemal polymerase chain reaction (PCR) of biopsy material. The patient significantly improved following 15 days of intravenous benzyl penicillin.

2) A 77-year-old Korean-born female with a past history of diabetes mellitus and hypertension presented in 2009 with recurrent falls and visual hallucinations. There was no past history of venereal disease. CT and MRI brain demonstrated bilateral temporal intracerebral haemorrhages (ICH). Her serum RPR titre was 1, CSF analysis identified a pleocytosis (17 lymphocytes/mm³) and raised CSF protein (1.32 g/L). CSF VDRL test was negative. The patient was treated with 15 days of intravenous benzyl penicillin. She gradually improved and was discharged home after a period of rehabilitation.

3.) A 67-year-old Tongan-born male with a past history of hypertension and dyslipidaemia presented in 2008 with left hemiparesis due to a right basal ganglia infarct confirmed on MRI brain. There was no past history of venereal disease. His serum RPR titre was 2, CSF analysis identified a pleocytosis (10 lymphocytes/mm³) and raised CSF protein (0.65 g/L). CSF VDRL was negative. He was treated with daily intramuscular procaine benzyl penicillin for 15 days and discharged home after a period of rehabilitation.

Thirty-four patients had 'positive serology without confirmation of NS'. All presented with symptoms of TIA or stroke including 18 with cortical infarction, 5 with basal ganglia infarction, 3 with brainstem or cerebellar infarction, one with thalamic infarction, 5 with TIA and 2 with ICH. CSF analysis was

performed in 9 of the 34 patients, of whom 6 had raised CSF protein without pleocytosis and 3 had normal CSF analyses. Eight patients had a documented reason for not performing a lumbar puncture (LP) including six patients who refused LP, 1 patient who was noted to be of non-English speaking background, suggesting issues of consent and 1 who had a past history of treatment for NS.

All 3 patients with a diagnosis of 'definite' or 'probable' meningovascular NS received 15 days of intravenous benzyl penicillin therapy. Fifteen patients (44%) who had 'positive serology without confirmation of NS' were treated with 15 to 21 days of intravenous benzyl penicillin or intramuscular procaine benzyl penicillin therapy.

Discussion

This is the first modern Australian study to report the prevalence of syphilis serology in hospitalised TIA and stroke patients. Four percent of tested TIA and stroke patients had positive syphilis serology in this culturally and linguistically diverse community. Patients born in South-East Asia and the Pacific islands made up over two-thirds of seropositive stroke and TIA patients.

The clinical manifestations of NS are highly variable and patients with meningovascular NS may present with symptoms and signs indistinguishable from an ischaemic stroke due to atheromatous disease.^{4,6,12-14} NS has been reported in patients with cortical infarction causing dysphasia, hemiparesis and hemianopia and subcortical lacunar infarction causing hemiparesis or hemianaesthesia.^{4,15} It is also a well recognised cause of stroke in young patients, particularly those originating from areas where syphilis is prevalent.^{13,15}

The vast majority of patients in the present study did not fulfil criteria for a diagnosis of 'definite' or 'probable' NS. Most did not undergo LP or had a non-diagnostic CSF analysis.^{4,6}

Although there is no 'gold standard' for the diagnosis of NS, a positive CSF VDRL or raised CSF protein with pleocytosis are important indicators of NS.^{6,16} There are well described exceptions to

this 'rule'. Conde-Sendin and colleagues reported an overall CSF VDRL sensitivity of 67% in 43 patients diagnosed with meningovascular, meningeal and general paresis categories of NS.⁴ Lee and colleagues have reported a case of dementia in which the patient had left temporal lobe hyperintensities on MRI, an initial normal CSF analysis and negative CSF VDRL on repeat CSF analysis, despite positive treponemal PCR on temporal lobe biopsy.¹⁷ In a large review of 156 cerebral gumma cases, CSF analysis was positive in just 31 (65%) of 48 tested patients and CSF VDRL was negative in 38% of 21 tested patients.¹⁸

Only 12 sero-positive patients in the present study underwent LP, with 8 patients having some documented reason for not performing this test. One possible explanation for the underuse of LP is that the clinical team considered the positive syphilis serology to be incidental, not appreciating a possible causative relationship or the importance of CSF analysis in this setting. Other possible reasons for the 'under-utilisation' of CSF analysis might include undocumented patient refusal or previous syphilis treatment, dysphasia or a non-English-speaking background confounding consent and the presence of LP contraindications such as antithrombotics or raised intracranial pressure.

Many TIA or stroke patients with positive syphilis serology did not receive definitive syphilis treatment during their admission. This is despite a 4-10% conversion of untreated syphilis to NS.⁴ It is possible that clinicians did not appreciate the significance of positive syphilis serology in this setting. A history of previous syphilis treatment not documented in medical records and poor prognosis with large strokes also may have influenced the apparent under-treatment of sero-positive patients.

It is unclear why clinicians requested syphilis serology in only 27% of TIA and stroke admissions and whether the 4% sero-positive rate reflects the prevalence in all stroke and TIA patients. A prospective study would be required to determine its 'true' prevalence. Usual caveats also apply

when using administrative data sets not intended for research, although coding for stroke and TIA has been well validated.¹⁹⁻²¹

In conclusion, syphilis testing should be considered as part of the diagnostic work-up of TIA and stroke, particularly in ethnically diverse populations. The majority of patients presenting to LH with positive syphilis serology and a TIA or stroke did not fulfil diagnostic criteria for 'definite' or 'probable' meningovascular NS. LP was under-utilised at LH and the majority of patients with positive serology were not given definitive treatment whilst in hospital although a decision not to perform a LP or treat with benzyl penicillin may have been justified.

Competing Interests

None identified

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Table 1. Classification of types of suspected meningovascular NS presentations.

<u>Type of Syphilis</u>	<u>Treponemal serology</u>	<u>CSF findings</u>	<u>Clinical Findings</u>
<i>'Definite' NS</i>	+	+ve VDRL	Features of NS
<i>'Probable' NS</i>	+	CSF pleocytosis	Features of NS
<i>'Positive serology without confirmation of NS'</i>	+	↑ CSF protein or normal CSF	Features of NS
<i>'Other' syphilis or a 'non-syphilis'-related presentation</i>	+		No features of NS

NS = neurosyphilis; CSF = cerebrospinal fluid; VDRL = Venereal Disease Research Laboratory

Table 2. Demographics of patients with TIA or stroke symptoms and positive syphilis serology at Liverpool Hospital 2005-2009

		Suspected Meningovascular NS
Population number		37
Mean age $\pm$ SD, years		72 $\pm$ 12.9
Gender	Male Female	24 (65%) 13 (35%)
Country of birth	SE Asia Pacific Islands* Other (Europe/South America) Australia/UK	15 (41%) 10 (27%) 10 (27%) 2 (5%)
Previous reported venereal disease		6 (16%)

* Fiji, New Zealand, Philippines, Samoa, Tonga

Table 3.

Classification, test results and treatment history in patients with TIA or stroke symptoms and positive syphilis serology at Liverpool Hospital

2005-2009.

	Occurrences	Serum RPR Titre		CSF		Treatment Given
		Positive	median $\pm$ SD	performed	cell > 5 protein > 0.45	
'Definite/Probable'	Meningovascular	3	2 $\pm$ 36.1	3	3	3 (100%)
'Possible'	Meningovascular	24	4 $\pm$ 14.6	9	0	15 (44%)

RPR = Rapid Plasma Reagin

CSF = Cerebrospinal Fluid

SD = Standard Deviation

Figure 1. Meningovascular neurosyphilis (NS) in patients with a hospital diagnosis of syphilis, TIA and stroke, Liverpool Hospital, 2005-2009.

* International Classification of Diseases –Australian Modified diagnostic codes

+ Electronic Medical Record (eMR Cerner)