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Perspective

Neurosyphilis: Concordance between cerebrospinal fluid analysis and subsequent antibiotic strategy for patients undergoing evaluation of a diagnosis of neurosyphilis

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ABSTRACT

Introduction: The confirmation or analysis and exclusion of a diagnosis of neurosyphilis has long presented a challenge for infectious diseases clinicians. The authors reviewed the concordance between cerebrospinal fluid (CSF) analysis and the subsequent antibiotic strategy for patients undergoing evaluation of a diagnosis of neurosyphilis.

Methods: All patients with positive serum syphilis serology referred for CSF analysis between January 2009 and May 2016 were included. Indications for CSF analysis were determined by review of the hospital electronic medical records. CSF parameters were determined from the hospital pathology database. Cases were defined as either 'confirmed', 'supportive' of, or 'not supportive' of a diagnosis of neurosyphilis based on existing definitions. Subsequent therapy was defined as for neurosyphilis, late latent primary syphilis or no therapy based on existing guidelines.

Results: Of 131 patients reviewed, 95.4% were male and HIV co-infected (74%). A confirmed diagnosis of neurosyphilis was met by fourteen patients (10.7%). All but two of these were treated with a neurosyphilis-directed regimen. Of the 58 patients treated with neurosyphilis antibiotics, 17.2% had no CSF findings suggestive of the diagnosis. Seventy-three patients were not treated for neurosyphilis; however 35 of these met the CSF criteria for a diagnosis supportive of neurosyphilis.

Conclusions: The results of routine CSF analysis in patients with a possible diagnosis of neurosyphilis are inconsistently applied in the clinical setting, calling into question the value of routine CSF. Empirical neurosyphilis treatment should be considered up front in patients with high pre-test probability of the diagnosis.

Introduction

Existing definitions of neurosyphilis require evidence of *Treponema pallidum* invasion of the central nervous system (CNS) and yet there is no single available cerebrospinal fluid (CSF) test that is both sensitive and specific enough for this purpose (Chang et al., 2011; Harding and Ghanem, 2012; Smibert et al., 2018). Syphilis notifications are increasing across Australia, Europe, and the USA (CDC, 2017; The Kirby Institute, 2016; European Centre for Disease Prevention and Control, 2016). Clinicians are more and more likely to see patients presenting with a possible diagnosis of neurosyphilis, and while there is a historical precedence for routine CSF examination in these patients, it is unclear how useful this test actually is in helping to direct therapeutic decisions.

Neurosyphilis presents both a troublesome clinical syndrome for patients and a diagnostic dilemma for physicians. It is a heterogeneous syndrome that may occur at any stage of the otherwise traditional temporal sequence of syphilis infection (i.e., primary, secondary, latent, and tertiary), with protean manifestations (Polanco et al., 2015). Add to this the insensitive and non-specific CSF tests available, and it is no wonder that clinicians struggle to confidently confirm or exclude a diagnosis of neurosyphilis.

This study was performed to review how the results of CSF analysis affected the subsequent therapeutic strategy in patients undergoing investigation of a potential diagnosis of neurosyphilis.

Materials and methods

This study included all patients with positive serum syphilis serology referred to a quaternary centre for lumbar puncture (LP) and CSF analysis in either the outpatient or inpatient setting

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between January 2009 and May 2016. Patients were identified from the hospital pathology database. Recorded parameters included CSF leukocyte count ($\times 10^6$/ml), protein (g/l), rapid plasma reagin (RPR), and fluorescent treponemal antibody absorption (FTA-ABS), and serum syphilis serology (enzyme immunoassay and RPR). The electronic medical records were examined for clinical presentation from which an indication for CSF analysis was determined. Cases were dichotomized into either symptomatic or asymptomatic. Symptomatic cases were further divided into those with meningitis, cranial neuropathy (in which those with ocular and otic symptoms were also included), cognitive decline, other neurology, and secondary syphilis with or without focal neurology. Indications for LP that did not meet any of these definitions were classified as 'other'. Patients with inadequate clinical records available to establish the indication for LP, those with negative or unavailable serum syphilis serology, and those with a confirmed alternative diagnosis were excluded. The research protocol was reviewed and approved by the Alfred Health Ethics and Research Governance Committee. Continuous variables were expressed as the median (with range) and categorical variables as the frequency (percentage). Proportional outcomes were compared using the Chi-square test or Fisher's exact test. A p-value of <0.05 was deemed statistically significant.

Definitions

A patient with a positive CSF RPR and with a clinical syndrome compatible with neurosyphilis and a positive serum syphilis serology was considered diagnostically 'confirmed' for neurosyphilis, as per existing definitions (JD R et al., 2015; AC S et al., 2015). An elevated CSF protein above the upper limit of normal (normal 0.15–0.40 g/l) and/or elevated CSF leukocyte count ($>5 \times 10^6$ leukocytes/μl in HIV-negative patients, or $>20 \times 10^6$ leukocytes/μl in HIV-positive patients) was considered 'supportive' of a diagnosis of neurosyphilis (JD R et al., 2015; AC S et al., 2015; CDC, 2018). Due to the high sensitivity of FTA-ABS, a positive CSF FTA-ABS in the absence of CSF red blood cell contamination (cut-off $>5 \times 10^6$ cells/ml) was selected as an additional criterion for a CSF examination supportive of a diagnosis of neurosyphilis (Harding). Asymptomatic neurosyphilis was defined by a positive serum RPR in those without focal symptoms and with one or more CSF abnormality (pleocytosis, elevated protein, or positive RPR) in those without focal symptoms but with positive serum syphilis serology (JD R et al., 2015; AC S et al., 2015). Indications for a LP in patients to investigate asymptomatic neurosyphilis were either in those HIV-positive patients with syphilis of unknown duration, or those with serofast serology.

For therapeutic analysis, patients were categorized by the treatment they received as for neurosyphilis, late latent syphilis, primary syphilis, or no therapy; this was determined by a review of the electronic medical records and based on national guidelines for the treatment of syphilis (CDC, 2018).

Results

Baseline demographics and characteristics

One hundred and seventy-five CSF specimens were subjected to syphilis serology testing between January 2009 and May 2016. Forty-four met the exclusion criteria and were not included in the subsequent analysis. No patient was included more than once. Baseline and clinical characteristics of HIV-positive and HIV-negative patients can be found in Table 1. The majority of patients were male (95.4%) and HIV co-infected (74%). Those with HIV had a median CD4 count of 494 cells/μl, while 42% had a suppressed viral load on antiretroviral therapy. A summary of CSF parameters of patients, dichotomized into symptomatic and asymptomatic, is presented in Table 2.

Positive CSF RPR

The criteria for a confirmed diagnosis of neurosyphilis were met by 14 patients (10.7%). These patients presented with a range of syndromes including cranial neuropathy (ocular ($n=1$) and otic ($n=2$)), secondary syphilis with cranial neuropathy (ocular + secondary syphilis ($n=1$) and otic + ocular + secondary syphilis ($n=1$)), secondary syphilis ($n=1$), cognitive decline in an HIV-positive patient ($n=1$) and HIV-negative patient ($n=1$), other neurology ($n=1$), other ($n=3$), and asymptomatic ($n=2$). All but two patients (85.8%) with a positive CSF RPR were treated with a regimen of antibiotics appropriate for neurosyphilis.

Treated for neurosyphilis

A neurosyphilis antibiotic regimen was administered to 44.3% (58/131) of all patients (Table 3). While 21.1% of patients treated for neurosyphilis had a confirmed diagnosis (with a positive CSF RPR), a further 34 (58.7%) had CSF findings supportive of a neurosyphilis diagnosis with positive FTA-ABS ($n=23$) and/or CSF protein >0.4 g/l ($n=16$) and/or CSF white cell count (WCC) above the upper limit cut-off ($n=10$). There were 12 (17.2%) patients who were treated with a neurosyphilis regimen with no CSF findings suggestive of the diagnosis. These patients had a range of clinical presentations including cranial neuropathy (tinnitus ($n=3$) and diplopia ($n=1$)), asymptomatic ($n=2$), meningitis ($n=1$), cognitive decline ($n=1$), and other neurology (radiculopathy ($n=2$)).

Not treated with positive CSF serology

Seventy-three patients were not treated for neurosyphilis, receiving a range of syphilis antibiotic regimens (Table 2). However, 35 of these patients met CSF criteria for a diagnosis supportive of neurosyphilis with an elevated protein ($n=33$) and/or positive FTA-ABS ($n=8$) and/or WCC above the upper limit ($n=1$). Clinical syndromes in these cases included asymptomatic ($n=8$), otic symptoms in the setting of secondary syphilis ($n=1$), other cranial neuropathy ($n=1$), cognitive decline ($n=10$), other neurology ($n=3$), other ($n=9$), other neuropathy in the setting of secondary syphilis ($n=2$), and asymptomatic ($n=8$).

Table 1
Baseline characteristics and clinical indications for CSF analysis.

	HIV-positive (Total = 97)	HIV-negative (Total = 34)
Age (years), median (IQR)	45 (38–53)	51 (37–66)
Sex, male (%)	96 (99)	29 (85)
CD4 cells/μl (median) (IQR)	494 (327–729)	NA
VL (copies/μl) available (%)	82 (85)	NA
Suppressed VL (%)	41 (42)	NA
Median copies/μl (IQR)	9565 (316–42 000)	NA
Symptomatic (%)	72 (74)	27 (79)
Meningitis	4	0
Isolated cranial neuropathy	20	9
Cognitive decline	12	7
Other neurology	4	3
Secondary syphilis	5	0
Secondary syphilis with focal neurology	1	2
Other syndrome	26	6
Asymptomatic (%)	25 (26)	7 (21)

CSF, cerebrospinal fluid; IQR, interquartile range; NA, not applicable; VL, viral load.

Table 2
Serum and CSF characteristics of symptomatic and asymptomatic patients undergoing lumbar puncture to assess for neurosyphilis.

	Symptomatic $n = 99$	Asymptomatic $n = 32$
Serum RPR, median (IQR)	16 (4–28)	16 (8–64)
≥1:32	38 (38)	14 (44)
≥1:256	15 (15)	0
CSF RPR positive (%)	12 (12.1)	2 (6.3)
CSF FTA-ABS positive (%)	29 (29)	7 (22)
CSF WCC (cells/μl), median (range)	8.5 (0–341)	1 (0–3)
WCC ≥20 cells/μl (%)	8 (8)	1 (3)
CSF protein (g/l), median (range)	0.48 (0.35–0.6)	0.38 (0.3–0.51)
Protein ≥0.4 g/l (%)	63 (64)	15 (44)
Treatment		
15 days IV benzylpenicillin (%)	47 (47)	11 (34)
3 × IM benzylpenicillin (%)	10 (10)	7 (22)
1 × IM benzylpenicillin (%)	6 (6)	2 (6)
No treatment (%)	36 (36)	12 (38)

CSF, cerebrospinal fluid; RPR, rapid plasma reagin; IQR, interquartile range; FTA-ABS, fluorescent treponemal antibody absorption; WCC, white cell count; IV, intravenous; IM, intramuscular.

Table 3
CSF characteristics of those treated for neurosyphilis compared to those not treated for neurosyphilis.

	Treated for NS		*p*-Value
	Yes $n = 58$ (%)	No $n = 73$ (%)	
HIV-positive (%)	41 (68)	58 (79)	0.246
Asymptomatic (%)	11 (19)	21 (29)	0.195
CSF diagnostic for NS[a]	12 (20.7)	2 (2.7)	0.001
CSF supportive of diagnosis of NS[b]	34 (58.7)	34(46.6)	0.171
CSF not supportive of diagnosis of NS	12 (20.1)	37 (50.1)	<0.001

CSF, cerebrospinal fluid; NS, neurosyphilis.
[a] Positive RPR on CSF.
[b] Positive FTA-ABS and/or elevated CSF protein above the upper limit of normal (normal 0.15–0.40 g/l) and/or elevated CSF leukocyte count ($>5 \times 10^6$ leukocytes/μl in HIV-negative or $>20 \times 10^6$ leukocytes/μl in HIV-positive).

Discussion

This study reviewed the experience of a quaternary HIV and infectious diseases centre of CSF analysis to investigate patients with a suspected diagnosis of neurosyphilis. It was found that while only 10.7% of the cohort met existing definitions of neurosyphilis, 44.3% were treated with a neurosyphilis-directed antibiotic regimen. Conversely, it was found that 35 patients (26.7% of the cohort) had CSF findings supportive of a diagnosis of neurosyphilis but did not receive neurosyphilis therapy. These observations suggest that clinicians are making therapeutic decisions in spite of the results of CSF analysis.

A tendency for clinicians to 'upscale' to neurosyphilis treatment in patients with no CSF findings supportive of the diagnosis was observed, with 17.2% of those treated for neurosyphilis without meeting diagnostic criteria. However, these patients presented with clinical syndromes strongly associated with neuroinvasion of treponemes, including ocular and otic neuropathies, which left untreated are associated with high morbidity (JD R et al., 2015). While we can only speculate regarding the rationale behind the individual clinician's therapeutic strategy, and how much weight is given to CSF findings in making these decisions, the authors anecdotal experience, supported by the present study data, would suggest that clinicians are aware of the limitations of available CSF tests and are concerned about the risk of under-treating treponemes in the CNS. These concerns appear to lead to empirical treatment of patients with a high pre-test probability of the diagnosis, regardless of CSF findings. This observation forms the basis for questioning the necessity of routine CSF analysis in patients with a likely diagnosis of neurosyphilis. We suggest that given the current limitations of CSF syphilis diagnostics, empirical neurosyphilis treatment should be considered up front in patients with high pre-test probability of the diagnosis.

Limitations of CSF syphilis serology are well described, with recent suggestions that such testing might in fact be better suited to exclude a diagnosis of neurosyphilis rather than confirming it. This is based on the robust sensitivity of FTA-ABS in CSF (Harding and Ghanem, 2012). However, as highlighted by Harding et al. in their review of the limitations of CSF treponemal testing, the negative predictive value of any test is dependent on the prevalence of the condition in the population in which it is undertaken. Therefore, in a patient with a high pre-test probability, a negative CSF FTA-ABS is unable to exclude the diagnosis with sufficient confidence. It was observed that a negative FTA-ABS was not sufficient evidence for clinicians to not treat for neurosyphilis in this cohort, as 11 patients were treated for neurosyphilis despite negative CSF FTA-ABS. (Some of these patients had supportive CSF features for neurosyphilis, others did not.) Conversely, a positive FTA-ABS did not result in automatic neurosyphilis therapy, as eight patients with positive FTA-ABS were not treated for neurosyphilis (none of these eight CSF samples had red blood cells, which supported an intrathecal origin of the antibodies rather than contamination of the CSF with serum antibodies during the lumbar puncture).

There are a number of limitations to this study. First, this was a retrospective observational chart review, where detailed documentation describing the clinician's rationale for therapy was often lacking. Some patients were referred for evaluation from peripheral centers, occasionally with limited documentation of clinical symptoms. Long-term follow-up of the patients was not available, in particular those who left the center after treatment for follow-up at primary facilities. So, while this review is interesting, further prospective studies with clinically meaningful definitions of neurosyphilis are needed to establish the true utility of CSF evaluation in the diagnostic work-up of neurosyphilis. Neurosyphilis is not currently a notifiable condition in most countries. We would advocate for mandating notification of neurosyphilis diagnosis to help better characterize the burden of disease and look more critically at the value of current approaches to diagnosis.

The long-term consequences of untreated CNS treponemal infection are well documented, in both the historical and contemporary setting, with a potentially enormous burden of morbidity and mortality associated with untreated syphilis (Ghanem, 2010). This study demonstrated that the results of routine CSF analysis in patients with a possible diagnosis of neurosyphilis are inconsistently applied in the clinical setting. This observation forms the basis for our question to the broader infectious diseases community as to whether there are legitimate grounds to consider empirical therapy for patients with a high pre-test probability of neurosyphilis without routine CSF analysis.

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Ethics approval

Granted by the Alfred Health Ethics and Research Governance Committee.

Conflict of interest

The authors have no conflicts of interest to declare.

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