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Title: Management of neurosyphilis: time for a new approach?

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Management of neurosyphilis: time to reconsider the utility of routine CSF analysis?

Syphilis has been afflicting humans for over 500 years and no manifestation of the infection has been as troublesome as that of neurosyphilis. Existing definitions of neurosyphilis require evidence of *T. 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, Michelow et al). We are currently in the midst of a local Australian syphilis epidemic with notification rates increasing from 5.1 cases per 100,000 men per year in 2005 to 15.9 cases per 100,000 men in 2014, particularly in the population of men who have sex men (2). Similarly, notifications are increasing across Europe and the United States (3, 4). Whilst syphilis is notifiable, in most countries, a diagnosis of neurosyphilis is not, so there has been no published data documenting a rise in neurosyphilis diagnoses per se, however anecdotally this appears to be the case. Clinicians everywhere are more and more likely to see patients presenting with a possible diagnosis of neurosyphilis. Now is a useful time to re-examine the limitations and pitfalls of available diagnostics and possibly consider a new approach of treating such patients with consistent eye, ear or other neurological symptoms with 15 days of intravenous penicillin without the requirement for CSF examination. .

The neurotropic nature of *T. pallidum* has been appreciated for well over a century with early attempts to abort dissemination and central nervous system (CNS) disease, even by excision of primary chancres, proving futile! Experimentally, *T. pallidum* is detectable within the bloodstream within 48 hours and in the cerebrospinal fluid (CSF) within 2 weeks following cutaneous inoculation (5,6). During the early twentieth century large cohorts of patients underwent lumbar puncture and CSF analysis in an

attempt to address the question regarding the prevalence of neuroinvason of *T. pallidum*. It was found that 15-30% of all stages of syphilis were associated with CSF abnormalities (predominantly elevations in protein and white cell counts) – the overwhelming majority without localising symptoms to the CNS (7,8). These findings have been replicated in contemporary studies in the HIV era leading to the concept of 'asymptomatic neurosyphilis', a syndrome believed to be the precursor of symptomatic neurosyphilis (9,10). However, the variables promoting progression from asymptomatic neurosyphilis to symptomatic neurosyphilis are unknown, although advanced immunosuppression with low CD4 count in the HIV population has long been thought to be a risk factor (11,12,13). The value of screening HIV patients with low CD4 count and positive serum syphilis serology for evidence of asymptomatic neurosyphilis and subsequent treatment of patients with a 'CSF paretic formula' (characterised by elevated protein and white cell count but, negative serology) as for neurosyphilis is still a cause for ongoing debate (14,15). An open-label, prospective randomised clinical trial at the University of Washington (Clinical Trials Registry number NCT02031146) hopes to answer this question by demonstrating that a strategy of immediate LP followed by therapy based on CSF findings results in better serological and functional outcomes in patients at 6 and 12 months.

Whilst a number of diagnostic algorithms exist for neurosyphilis possibly the most widely accepted is described by Sena et al. in the Manual of Clinical Microbiology (16). This algorithm mandates that a patient must have a positive serum treponemal test and a clinical syndrome compatible with neurosyphilis with one of three CSF tests positive; a reactive CSF VDRL, a positive *T. pallidum* PCR or identification of treponemes in nervous tissue by histological methods (16). Therefore, based on these criteria, a diagnosis of neurosyphilis is possible at any clinical stage of syphilis infection. This is

in keeping with the scientific literature, including local experience at our institution, where CNS invasion with treponemes has been demonstrated at all clinical stages (ie. Primary, secondary, tertiary) of infection **(1,**7,8,9**)**. Unfortunately, despite being the best available, there are still significant limitations with Sena et al's definition. We have not widely used the CSF VDRL in Australia for more than 20 years and the RPR (Rapid Plasma Reagin) that has largely replaced the VDRL is not validated for use in CSF nor is it as sensitive as the VDRL (67% vs. 58%) (16). Whilst hope was held that a *T. pallidum* PCR would have sufficient sensitivity to increase the diagnostic accuracy of CSF analysis, this has not proven to be the case. A study published in 2016 analysed 40 CSF samples from patients with documented neurosyphilis using a nested PCR targeting the *tpp47 gene.* Disappointingly the PCR gave a sensitivity of only 42.5% with a specificity of 97% when compared to a diagnosis based on clinical assessment and existing CSF diagnostic tests (18). *T. pallidum* PCR has found its place in the diagnosis of primary syphilis with superficial swabs of lesions of primary syphilis containing sufficient concentrations of treponemes for detection. Finally, examination of nervous tissue to demonstrate invasion of treponemes is neither justifiable or practical in the majority of cases and is likely to be limited in the future to animal and autopsy studies. The search for more sensitive and specific markers of CNS invasion of *T. pallidum* continues. Recent approaches include the use of quantitative CSF:serum ratios of treponemal antibodies (ie. FTA-ABS) with higher ratios presumed to be indicative of intrathecal antibody production (19). These approaches attempt to improve sensitivity also by estimating permeability of the blood brain barrier with an albumin quotient. Whilst these techniques, and others, appear to improve the sensitivity of existing CSF serology they are considerably more labour intensive than existing techniques and are yet to be validated or widely applied. CSF cytokine and chemokine profiling of patients

with neurosyphilis have led to an expanding library of novel markers that correlate with CNS inflammatory responses and invasion of the CNS (19,20,21). A prospective study looking at the utility of CSF levels of chemokine CXCL 13 and *T. pallidum* DNA PCR to improve diagnostic accuracy in patients with suspected neurosyphilis has recently begun recruiting in Shanghai (Clinical Trials Registry number ChiCTR-DDD-16009591). Validation of these indicators will be difficult and further work is required before these tests can be confidently incorporated into any existing neurosyphilis diagnostic algorithm.

So, neurosyphilis continues to present both troublesome clinical syndromes for patients and a diagnostic dilemma for physicians. We are limited by a lack of understanding of disease pathogenesis, the unavailability of CSF tests with both an adequate sensitivity and specificity to confirm or exclude the diagnosis and considerable barriers to further clinical research. Furthermore, 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 manifestations that can include meningitis, meningovasculitis with stroke, uveitis and visual disturbance and otosyphilis that may present with vertigo, tinnitus or hearing loss. Late complications of untreated neurosyphilis include cognitive impairment, dementia, psychosis, general paresis and tabes dorsalis. 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. Furthermore, later stages of syphilis are associated with low titre non-treponemal tests and an even lower chance of CSF abnormalities. Therefore, CSF examination in these patients is likely to be even less useful. Armed with an understanding of the limitations of CSF serology is now the time to have the discussion and collectively consider an alternative approach to patients who present with a

clinically compatible syndrome with positive serum syphilis serology? We know of instances at our institution where patients with a high pre-test probability of neurosyphilis but negative CSF serology have been treated presumptively with 15 days of intravenous benzylpenicillin. Given the late consequences of untreated neurosyphilis and the current limitations with CSF analysis and tests perhaps patients, at any stages of syphilis infection, with symptoms consistent with neurosyphilis and positive serum serology should be offered treatment with 15 days of benzylpenicillin? This then raises the question regarding the value of lumbar puncture and CSF analysis as part of a diagnostic evaluation in this cohort. In the light of our current local syphilis epidemic perhaps now is the time to collectively review and reconsider our approach to this troublesome clinical syndrome.

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Summary Points/Abstract

Given the long term sequelae of untreated neurosyphilis and insensitive tests to detect treponemes in the CSF, questions regarding the utility of a lumbar puncture (LP) and CSF analysis to either confirm or exclude neurosyphilis are raised.

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