

The effect of penicillin therapy on cognitive outcomes in neurosyphilis: a systematic review of the literature [☆]

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ABSTRACT

Objective: Neurosyphilis commonly presents with cognitive impairment, and penicillin remains the treatment of choice. However, despite a rapid increase in syphilis incidence, the effect of penicillin on long-term cognitive outcomes has not previously been evaluated. We therefore aimed to assess the effect of penicillin on cognitive function in neurosyphilis.

Methods: We performed a systematic review of all studies of neurosyphilis, where cognitive function was assessed objectively both before and after penicillin therapy for at least one patient. Where Mini-Mental State Examination (MMSE) scores were taken, we performed a paired-samples *t* test to assess the change in cognitive function and aimed to correlate this with change in serological titers.

Results: Nine studies met inclusion criteria. The one cohort study reported a nonsignificant overall improvement in MMSE, while amalgamation of case reports produced a significant improvement ($P = .02$) in MMSE after treatment. However, follow-up duration was inadequate, and data were insufficient to correlate changes in cognitive function with serological markers.

Conclusions: Despite evidence of short-term improvement, there are insufficient data to support the long-term benefit of penicillin therapy on cognitive function in neurosyphilis.

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1. Introduction

Neurosyphilis results from infection of the central nervous system by *Treponema pallidum*. Its clinical presentations include meningovascular syphilis, tabes dorsalis and dementia paralytica, and over 60% of psychiatric patients with neurosyphilis have overt dementia [1]. Penicillin has been the mainstay of treatment for many decades. Early studies of the effect of penicillin on cognitive function cited positive outcomes, but objective cognitive testing was not used [2]. Later research using objective cognitive testing reported no significant improvement after treatment [1].

Between 1997 and 2002, diagnoses of syphilis in genitourinary medicine clinics in the United Kingdom have increased by 141% in homosexual men and 213% in heterosexual men [3]. With recent studies using newer antibiotic agents [4], against a potential increase in the future incidence of syphilis-related dementia, a rigorous examination of the effect of penicillin therapy on cognitive outcomes in neurosyphilis is warranted.

We conducted a systematic review of cognitive outcomes following penicillin treatment in neurosyphilis. Our primary aim was to assess change in cognitive function after treatment, while our secondary aim was to assess the correlation between change in cognitive function and relevant serological titers.

2. Methods

2.1. Design and literature search

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched Web of Science and MEDLINE for papers dating from 1900 to August 2014 using the following search strategy: (syphilis OR neurosyphilis OR treponemal OR treponema OR syphilitic OR general paresis OR generalised paresis OR generalized paresis) AND (dementia OR cognitive impairment OR cognition OR memory). Published and unpublished articles were included, and reference lists of included papers were checked for additional publications. Fig. 1 shows the PRISMA flow diagram of the search.

2.2. Inclusion criteria

Studies were included if all of the following were met for at least one patient: (a) a diagnosis of neurosyphilis made clinically and with positive cerebrospinal fluid (CSF) serology, (b) penicillin-based treatment administered for at least 2 weeks and (c) a validated test of cognitive status performed before and at least 6 months after treatment. Exclusion criteria were (a) reanalysis of previously published data, (b) review article not presenting original data and (c) study not published in English.

[☆] Conflict of interest: None.

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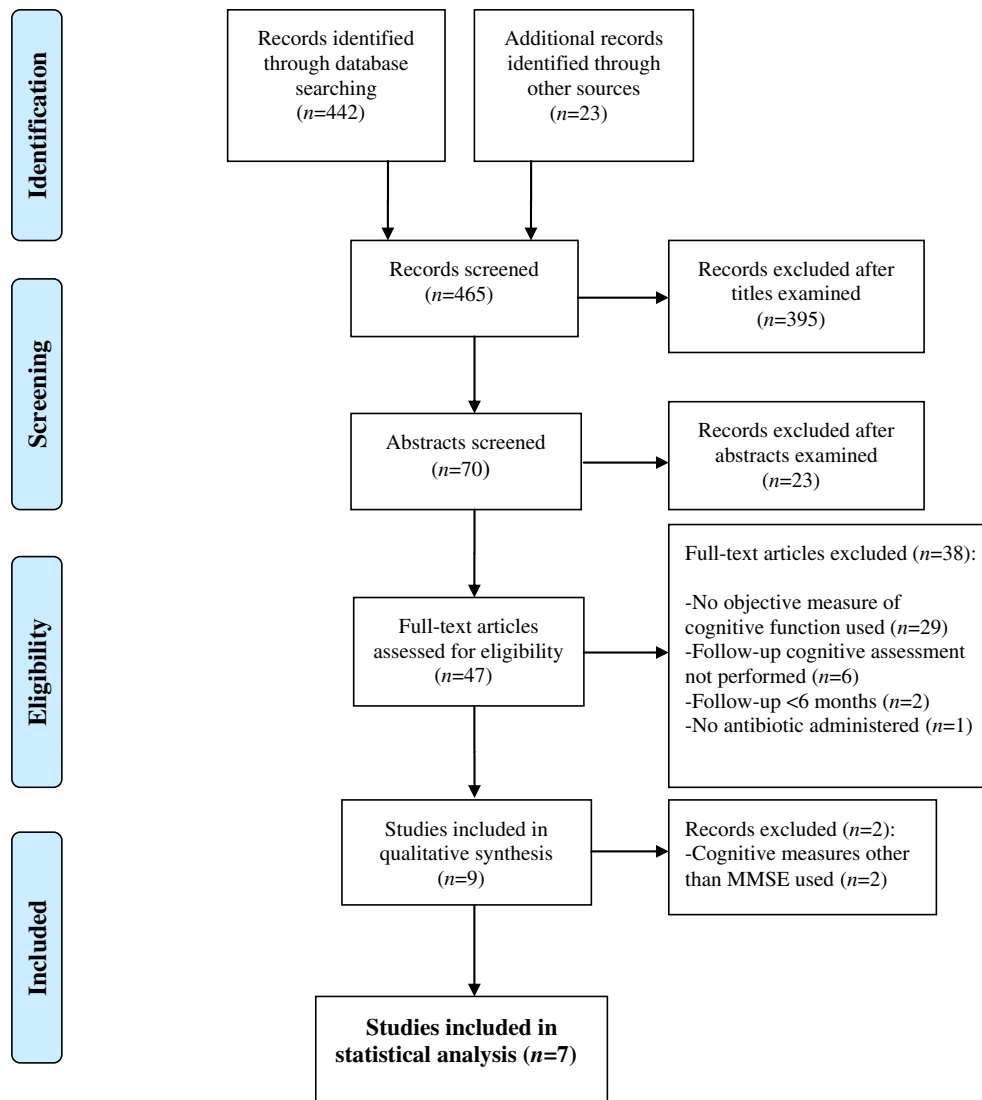


Fig. 1. PRISMA flow diagram of search.

2.3. Data extraction

The following data were extracted: year, sample size, design, age, gender, duration of psychiatric symptoms, treatment, HIV status, follow-up period (if more than one, the longest duration used), CSF syphilis serology before and after treatment, and any coexisting psychopathology.

2.4. Data analysis

We amalgamated Mini-Mental State Examination (MMSE) scores of case reports both before and after treatment and performed a paired-samples *t* test to assess for any significant change, planning also to assess the statistical correlation between changes in MMSE scores and changes in serological titers.

3. Results

3.1. Overview

Nine studies met inclusion criteria, comprising a total of 21 patients with mean age 42.8 years. Seven were case reports [4–10], one was a cohort [1], and one was a case series [11]. Study characteristics are summarized in Table 1.

3.2. Diagnosis

Alongside clinical features of neurosyphilis, positive CSF serology was present in all patients, although baseline titers were variable and often not stated.

3.3. Treatment

Benzylpenicillin treatment was used in all studies, except for two in which it was used in combination with a cephalosporin, while one used cephalosporin alone.

3.4. CSF serology

Change in CSF serology was variable and often not stated. Roberts et al. demonstrated a significant correlation between decrease in Venereal Disease Research Laboratory (VDRL) titer and improvement in MMSE [1].

3.5. Coexisting psychopathology

Affective features and disorientation were common at baseline in the case reports, while Roberts et al. found a high prevalence of psychosis and affective features.

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