CASE REPORT

Diagnosing neurosyphilis: a case of confusion

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SUMMARY

A Pakistani man aged 60 years presented with personality change, aggression, paranoid delusions and sexual disinhibition while being treated for severe chest sepsis in intensive care. Collateral history confirmed that these personality changes had been developing over the course of the previous 2 years. He was found to have positive syphilis serology during a routine confusion screen, and the possibility of neurosyphilis was raised. Cerebrospinal fluid examination revealed elevated protein but negative syphilis testing. Following multidisciplinary discussion, the decision was made to treat as neurosyphilis, which resulted in a significant improvement in symptoms. The genitourinary department was able to carry out thorough contact tracing. This case demonstrates the importance of including syphilis in a confusion screen as this patient was diagnosed following a low clinical suspicion. It also highlights some potential pitfalls and difficulties in the diagnosis of neurosyphilis and the importance of the use of a multidisciplinary team.

BACKGROUND

Neurosyphilis is an important diagnosis not to miss due to the potential benefit of receiving treatment and the value of contact tracing from a public health perspective. However, due to the relatively low background prevalence of syphilis: 5.6/100 000 population in 2011,¹ and the myriad of ways in which neurosyphilis can present, it is not always thought of as a differential diagnosis. In our case, for example, the diagnosis was made during a routine confusion screen, rather than clinical suspicion. With increasing rates of syphilis over the past decade, this is likely to become even more relevant.^{1 2} As our case illustrates, neurosyphilis is not always a straightforward diagnosis and diagnostic criteria are not universally agreed. Therefore, diagnosis relies on careful interpretation of test results in the context of the clinical situation. The input of a multidisciplinary team can help to decide on an appropriate treatment plan.

CASE PRESENTATION

Our patient was a Pakistani man aged 60 years with multiple comorbidities, including hypertension, type 2 diabetes mellitus, hypercholesterolaemia, ischaemic heart disease, chronic kidney disease and obesity.

His initial admission was to the intensive care unit due to severe chest sepsis, where he also sustained a non-ST-elevation myocardial infarction. During this admission, it was noted that his behaviour was extremely erratic: he was aggressive and violent towards staff, reported paranoid delusional beliefs and was sexually disinhibited. A psychiatric

assessment deemed that this was likely due to delirium on a background of undiagnosed frontal-temporal dementia. A Montreal Cognitive Assessment revealed a score of 15 out of 30. It was therefore arranged for him to be seen in the outpatient memory service following discharge.

However, he was readmitted 2 days after his discharge with drowsiness, and found to have a severe acute kidney injury, urinary tract infection and hypoglycaemia. While he was receiving medical treatment, his behaviour was noted to be similar to that of his previous admission.

A collateral history revealed that over the past 2 years, a significant behavioural change had occurred, with no apparent trigger. Our patient, once described as a polite, loving, well-respected community figure, demonstrated changes, including severe mood fluctuations, aggression, sexual disinhibition, self-exposure in public, racial abuse, breakdown of family relationships, short-term memory loss and paranoid delusions.

A working diagnosis of delirium on a background of dementia with persecutory delusions was considered and a trial of regular low-dose risperidone and lorazepam as required was started.

While on risperidone, a slight improvement was noted, as disruptive behaviour was now intermittent, but his paranoid delusions remained.

INVESTIGATIONS

It was noted that syphilis testing had been performed on admission as part of a confusion screen and was positive on initial and repeat testing.

Tests results included:

Serum rapid plasma reagin (RPR) positive 1:4;
Serum EIA total antibody positive;
Treponema pallidum particle agglutination assay (TPPA) positive 1:1280.

On further questioning of the patient following these test results, he was able to tell us that he had never previously been treated for syphilis. Owing to his confused and aggressive state at the time, however, we were unable to accurately ascertain whether he had ever noticed any signs of primary or secondary syphilis in the past. Full examination revealed no genital ulceration, lymphadenopathy or rash. He was found to have an ataxic gait with a positive Romberg's test.

A CT head and MRI were inconclusive and an EEG was unremarkable. A lumbar puncture was performed to assess for cerebrospinal fluid (CSF) evidence of neurosyphilis.

CSF results

Total antibody (EIA): not tested
TPPA: negative

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RPR: negative

Treponemal antibody NOT detected

CSF protein 500 mL/L

CSF white cell count <1

Multiple chest radiographs over the course of his admission revealed no structural cardiovascular abnormalities to suggest any cardiovascular involvement.

DIFFERENTIAL DIAGNOSIS

1. Neurosyphilis
2. Delirium on a background of frontotemporal dementia with persecutory delusions

TREATMENT

We consulted a multidisciplinary team, including the microbiology, psychiatry and genitourinary medicine (GUM) teams, regarding the diagnosis and management of this patient. There was a variety of opinions as to whether this represented a case of late latent syphilis, or whether this was indeed a case of active neurosyphilis requiring treatment, despite the negative CSF. It was decided to treat for neurosyphilis (benzylpenicillin 18–24 MU daily, given as 3–4 MU intravenous every 4 hours for 17 days).

OUTCOME AND FOLLOW-UP

Following completion of his antibiotic course, his behaviour reverted back to his original personality. He was discharged with no further deterioration, and at the time of writing this report, 6 months after his discharge, he has made good progress and is being followed up in the older age psychiatry clinic. His risperidone dose is being weaned down gradually.

He was followed up by the GUM clinic following discharge for screening of other sexually transmitted infections, including hepatitis B, HIV, Chlamydia and gonorrhoea, which were all negative. Contact tracing was carried out and identified no further positive cases of syphilis.

His serum RPR will be repeated after 12 months after completing treatment to identify response.

DISCUSSION

Neurosyphilis is a form of tertiary syphilis, along with gummatous, and cardiovascular syphilis. Looking at data from the pre-antibiotic era, it would appear that in the natural course of the disease, approximately one-third of patients with syphilis would progress to tertiary syphilis.³

There are three broad syndromes within neurosyphilis. These are meningovascular, which can lead to focal arteritis and features consistent with stroke or transient ischaemic attack; tabes dorsalis which is characterised by involvement of the dorsal columns and leads to pain, parasthesiae and gait disturbance; and general paresis, which is the form of neurosyphilis that we propose that our patient was affected by.^{4 5} General paresis can present with an insidious onset dementia, personality change and psychosis. The psychiatric syndromes are widely varied, with grandiosity and delusions described in the literature as frequent components.⁴

Serological diagnosis of syphilis depends on non-treponemal and treponemal tests. Non-treponemal tests, commonly the Venereal Disease Research Laboratory (VDRL) slide test and the RPR test, have the advantage of providing a quantitative titre of positivity but can also feature false positives, particularly in the context of other chronic or acute diseases,

pregnancy or autoimmune conditions.⁶ The treponemal-specific antibody tests include agglutination tests, enzyme immunoassay tests and fluorescent treponemal antibody absorbed test (FTA-abs).⁶

The US Centers for Disease Control (CDC) states that a diagnosis of syphilis requires a positive serological non-treponemal and treponemal test.⁷ If there is a suspicion of neurosyphilis, then CSF examination should be performed, and a combination of positive serology and either an elevated CSF cell count or protein along with a reactive CSF-VDRL confirms neurosyphilis, in the context of clinical signs or symptoms. It is recognised that CSF-VDRL lacks sensitivity, so in the case of a negative result, FTA-abs testing of CSF is recommended, and it is stated that if this is negative, then neurosyphilis is highly unlikely.⁷ This is similar to the advice given by the British Association for Sexual Health and HIV, which states that a negative CSF treponemal test excludes a diagnosis of neurosyphilis.⁵

However, Harding and Ghanem⁸ in 2012 examined existing literature on diagnosis of neurosyphilis with CSF treponemal-specific antibody tests and concluded that the sensitivity of these tests is dependent on pretest probability, and that in a moderate-to-high probability situation, a negative test would not rule out a diagnosis of neurosyphilis. In the latest Public Health England guidelines, it is stated that where there is clinical suspicion 'it is doubtful whether a negative TPPA result can exclude neurosyphilis'.⁹

The other complicating factor in making the diagnosis in our patient was that he had recently received a prolonged course of penicillin-based antibiotics for severe chest sepsis. It is possible that this may have affected the results of the CSF analysis, leading to a false-negative result. According to Lishman 'neurosyphilis can occur in atypical or attenuated forms in the post-antibiotic era' and CSF examination may not be pathognomic.⁴

In our hospital, we conducted a multidisciplinary team meeting involving GUM, psychiatry and microbiology, in order to decide on a treatment strategy. While as a team, we could not be completely certain of the diagnosis, in view of the high CSF protein count, clinical signs and possible effect of a recent course of antibiotics, a decision was made to treat as neurosyphilis.

To the authors' knowledge, there are no existing case reports of patients with confirmed syphilis and possible neurosyphilis with treponemal antibody-negative CSF following a prolonged course of antibiotics. We were able to benefit from the experience of the GUM department in our hospital in contact tracing to allow further testing of potentially at-risk individuals.

Learning points

- ▶ The diagnosis of neurosyphilis in patients with negative treponemal tests in cerebrospinal fluid is not always straightforward, and individual patient management is best decided with a multidisciplinary team approach.
- ▶ The importance of inclusion of syphilis testing during a routine confusion screen is highlighted, as in this case, the diagnosis was made without pre-existing clinical suspicion or known risk factors.
- ▶ On diagnosis of a communicable disease such as syphilis, the public health importance must not be forgotten, and thorough contact tracing is essential.

Contributors All authors were involved in the care of the patient. The summary, Case presentation, Investigations, Differential diagnosis, Treatment and Outcome and follow-up sections were written primarily by AH. The Background and Discussion were written mainly by JP. AW reviewed and contributed to all sections. JP holds responsibility for the overall content as guarantor.

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