Psychosis in treated neurosyphilis: Is now the time to stop his antipsychotic?

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How would you handle this case?

Answer the **challenge questions** throughout this article

Mr. C, age 61, has a history of auditory and visual hallucinations and depression. Syphilis was diagnosed 13 years ago and treated with IV penicillin for 2 weeks. How would you approach his care?

CASE Hallucinations, impaired memory

Mr. C is a 61-year-old African American man who visits the outpatient clinic for management of antipsychotic therapy for psychosis and depression. His most recent inpatient psychiatric hospitalization for auditory and visual hallucinations, paranoia, and agitation was more than 10 years ago. He has been taking chlorpromazine, 100 mg/d, for 11 years. Mr. C reports that he has had no psychotic symptoms in the past 3 years; he continues taking chlorpromazine, he says, because it helps him sleep.

How would you proceed with Mr. C's care?

a) continue chlorpromazine because he has been symptom free
b) consider tapering and discontinuing chlorpromazine
c) obtain a more detailed history from Mr. C and perform additional tests

HISTORY Validation of diagnosis

Mr. C reports that, at age 48, he started hearing babies crying and started seeing dead infants crawling out of the incinerator at the hospital where he worked. He denies any psychiatric symptoms before that time. He stopped working 10 years ago because of his psychiatric symptoms and decline in cognition.

Subsequently, Mr. C had 3 inpatient psychiatric hospitalizations for auditory hallucinations; chlorpromazine, 100 mg/d, was prescribed for psychosis. Later efforts to discontinue chlorpromazine resulted in relapse of psychotic symptoms. Mr. C has no family history of psychiatric illness.

Mr. C's medical history is significant for aortic regurgitation, congestive cardiac failure, hypertension, and left-sided sensorineural hearing loss. He has a history of cocaine abuse from age 21 to 45, but denies using any other substances, including alcohol and nicotine.

Urine toxicology and routine blood tests are within normal limits. The QTc is slightly prolonged over the past 2 years, recording 512, 520, and 505 milliseconds on serial electrocardiograms.

Mr. C is able to perform simple abstractions. He has a goal-directed thought process, devoid of any preoccupation, paranoia, and perceptual abnormalities. Cognitive screening reveals significant impairment of

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memory, registration, calculation, attention, and visuospatial skills.

Careful review of Mr. C's history and medical records reveals a diagnosis of syphilis at age 48 after unprotected sexual intercourse. He recalls that he had a solitary genital lesion, which resolved over a few weeks. He then developed a slightly itchy, non-tender macular rash over his upper back, which he did not report to a physician. After a few months, he developed unsteady gait, blurry vision, and weakness of limbs, and had to crawl to the hospital. There, he was given a diagnosis of neurosyphilis. He also developed left-sided hearing loss during that time.

Mr. C was treated with aqueous penicillin G benzathine, 4 million units IV for 2 weeks. No follow-up cerebrospinal fluid (CSF) examination was documented after antibiotic treatment. He developed auditory and visual hallucinations and paranoia a few months after completing penicillin treatment. During the following year, he had 3 inpatient psychiatric hospitalizations for psychosis, agitation, and depressed mood.

How would you treat a patient with a history of neurosyphilis who presents with psychosis years after diagnosis?

a) repeat antibiotic treatment and stop the antipsychotic
b) repeat antibiotic treatment and continue the antipsychotic
c) attempt to discontinue the antipsychotic
d) continue the antipsychotic

The authors' observations

Mr. C's psychotic symptoms seem to be temporally related to his diagnosis of neurosyphilis at age 48. He and his family members deny that Mr. C had any history of psychosis or depression before the neurosyphilis diagnosis. All inpatient psychiatric hospitalizations were within 1 year of the neurosyphilis diagnosis.

Mr. C has been on a low dosage of chlorpromazine, which has significant antihistaminic action. Chlorpromazine also is known to cause QTc prolongation, especially in patients with heart disease.

TREATMENT Medication change

A serum rapid plasma reagin test is nonreactive, but *Treponema pallidum* particle agglutination is positive. MRI shows moderate atrophy suggestive of diffuse small-vessel disease.

Mr. C's psychotic symptoms are considered to be sequelae of neurosyphilis, based on (1) the presence of positive antibody tests, (2) residual neurologic deficits, (3) other suggestive sequelae (aortic regurgitation, sensorineural deafness), and (4) age-inappropriate gradual cognitive decline in the absence of other psychiatric history.

Because we are concerned about the prolonged QTc, chlorpromazine is discontinued. Haloperidol, 5 mg at bedtime, is started. The neurology team does not recommend antibiotic treatment because symptoms have been stable for years. Mr. C refuses a lumbar puncture.

Mr. C returns to the outpatient clinic monthly. He is psychiatrically stable without any worsening of psychosis. Cognitive impairment remains stable over the next 6 months. Haloperidol is tapered to 2 mg at bedtime 6 months after initial evaluation. Mr. C remains psychiatrically stable on subsequent follow-up visits.

continued

Clinical Point

Chlorpromazine is known to cause QTc prolongation, especially in patients with heart disease

Table 1

5 Stages of syphilis

Stage	Symptoms
Primary syphilis	Chancre in genitalia (often unnoticed)
Secondary syphilis	Maculopapular, non-tender rash; fever; lymphadenopathy; condyloma latum (genital)
Latent syphilis	Asymptomatic; serum nontreponemal and treponemal antibody tests are positive
Tertiary syphilis	Multiple organ-system involvement: Nerve involvement (deafness), aortic root dilation, aortitis, gummas (liver, bone, skin, spleen)
Neurosyphilis	Any stage can progress to neurologic involvement. Most common presentation is asymptomatic pupillary afferent defect (Argyll Robertson pupil). Focal symptoms include aphasia, paresis, blurry vision, hearing loss, seizures, ataxia, bowel or bladder incontinence, tabes dorsalis, loss of position and vibration senses, progressive ataxia, and sudden and severe pain, loss of balance, delirium, hydrocephalus, transverse myelitis, and stroke-like small vessel changes

Clinical Point

Psychiatric patients are at higher risk of acquiring syphilis because of substance use, lack of education on safer sex, and impulsive behavior

The authors' observations

Mr. C's psychotic symptoms persisted after standard antibiotic treatment of neurosyphilis and lapsed when he stopped taking antipsychotic medication 10 years after the initial treatment of neurosyphilis. He carried a diagnosis of schizophrenia for many years, even though his psychotic symptoms were atypical for the presentation of schizophrenia.

It is important to understand the natural course of syphilis, its implication on psychiatric symptom production, and long-term psychiatric prognosis.

Syphilis is a sexually transmitted infectious disease caused by *T pallidum*, a spirochete, that has varied clinical presentations. Osler called syphilis the "great imitator" for its array of system involvement, ranging from asymptomatic infection and afferent pupillary defect to depression, psychosis, and dementia. With wide use of penicillin, the rate of neurosyphilis declined steadily during the mid 1990s. By 1997, the overall rate reached its lowest point in the United States; in 1999 the Centers for Disease Control and Prevention released a national plan to eliminate syphilis.[1] By 2004, however, prevalence had increased to 4.7/100,000. It is thought that this increase is mainly associated with substance use (especially crack cocaine) and HIV co-infection. Most cases were distributed in economically depressed geographical areas.

Psychiatric patients are at higher risk of acquiring the infection because of substance use, lack of education on safer sex practices, and impulsive behavior.

Stages of syphilis

Syphilis does not follow a step-wise progression. One-third of cases progress to the tertiary stage, even many years after initial infection, without adequate treatment.[2]

Almost 10% syphilis cases present with neurologic symptoms,[3] and neurologic involvement can occur at any stage of disease progression. The most common symptoms of syphilis are presented in ***Table 1***.

A range of psychiatric symptoms have been reported among patients with syphilis, including anhedonia, suicidality, mania, grandiosity, persecutory delusions, auditory and visual hallucinations, paranoia, and cognitive impairment. The incidence of psychiatric symptoms is not clearly described in literature.

Diagnosis and treatment

Neurosyphilis, at any disease stage, should be suspected if a patient:

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Table 2

Diagnostic tests and treatment protocol for syphilis

Phase of diagnosis	Tests	Treatment
Presumptive	CSF VDRL: Non-reactive, CSF protein >50 g/dL or CSF blood cell count >10/mm^3	**Primary and secondary disease:** Penicillin G benzathine, 2.4 million units IM, single dose **Tertiary disease:** Aqueous penicillin G, 3 to 4 million units IV, every 4 hours for 10 to 14 days
Confirmed	CSF VDRL: Positive. When VDRL test is negative, specific treponemal antibody tests, such as TPPA and TPHA, are helpful. Specific antibody tests and VDRL both negative: Syphilis is ruled out	**Latent disease:** Penicillin G benzathine, 2.4 million units IM, weekly for 3 weeks **Tertiary disease:** Aqueous penicillin G, 3 to 4 million units IV, every 4 hours for 10 to 14 days
Follow-up	Nontreponemal test titer should decrease 4-fold after 6 months of successful treatment of primary and secondary syphilis and 12 to 24 months after successful treatment of latent infection. TPPA and TPHA can be positive throughout life	If the initial CSF had a high red blood cell count, repeat CSF every 6 months until normal Consider retreatment when blood count does not decrease in 6 months or returns to normal in 2 years

CSF: cerebrospinal fluid; TPHA: *T pallidum* hemagglutination assay; TPPA: *T pallidum* particle agglutination; VDRL: Venereal Disease Research Laboratory test

Source: References 2-5

Clinical Point

Almost 10% of syphilis cases present with neurologic symptoms, and neurologic involvement can occur at any stage of disease progression

continued

Related Resources

- Centers for Disease Control and Prevention. Syphilis—STD fact sheet. https://www.cdc.gov/std/syphilis/stdfact-syphilis.htm.
- Drago F, Merlo G, Ciccarese G, et al. Changes in neurosyphilis presentation: a survey on 286 patients [published online June 15, 2016]. J Eur Acad Dermatol Venereol. doi: 10.1111/jdv.13753.

Drug Brand Names

Chlorpromazine • Thorazine
Haloperidol • Haldol
Penicillin G benzathine • Bicillin

Clinical Point

Psychiatric symptoms can persist for many years with or without residual neurosyphilis symptoms, possibly because of permanent neuronal loss

- exhibits suggestive symptoms
- does not respond to antibiotic treatment
- has late latent syphilis
- is immunocompromised.

Lumbar puncture and examination of CSF is the most useful diagnostic test. Dark field microscopy to reveal *T pallidum* is definitive, but only is applicable during the primary stage. The role of dark field microscopy of the CSF sample to diagnose neurologic involvement has not been established. Tests and treatment protocol are described in ***Table 2***[2-5] (***page 57***).

Treatment of psychiatric symptoms of neurosyphilis

There are inconsistent and limited data about the prevalence of psychiatric symptoms in neurosyphilis. A retrospective study[6] of 161 patients with neurosyphilis in South Africa reported that 50.9% exhibited a complex spectrum of symptoms that included delirium and dementia. Of treated patients, 17% continued to have residual symptoms during follow-up.

A review of the literature did not reveal any widely accepted guideline for screening for neurosyphilis in general psychiatry practice or a treatment protocol for psychiatric symptoms. This lack of guidance could be attributed to the rarity of the disease, cost-benefit analyses, and low specificity of antibody tests. In the literature, syphilis screening is recommended as a routine protocol when evaluating and treating dementia.[7]

In most studies, a diagnosis of neurosyphilis was confirmed by CSF examination; however, many of these studies did not report a specific follow-up CSF examination protocol. Most of these patients were treated with an antipsychotic with partial improvement in symptoms, even after standard antibiotic protocol.[8]

First- and second-generation antipsychotics and mood stabilizers have been shown to be useful in the acute treatment of psychosis and agitation.[8] In few instances, the psychotropic medication was continued beyond several months and the patient was placed in a long-term care facility. Psychiatric symptoms persisted for many years with or without residual neurosyphilis symptoms, possibly because of permanent neuronal loss.

Clinical considerations

It often is difficult to distinguish a preexisting psychiatric disorder *made worse by* neurosyphilis from a secondary psychiatric disorder *caused* by neurosyphilis. The 2 might coexist, or psychiatric symptoms could be wrongly attributed to schizophrenia because of a lack of careful clinical evaluation.

Bottom Line

Neurosyphilis is a rare and challenging disease. Neuropsychiatric symptoms, such as anhedonia, hallucinations, delusions, and cognitive impairment, can persist years after antibiotic treatment. Clinical collaboration with neurology and infectious disease is ideal. When indicated, repeat treatment with antibiotics might alleviate some residual psychiatric symptoms.

Often, the follow-up diagnostic protocol for neurosyphilis is not followed; as a result, the need for re-treatment remains unclear. Rarity of the disease makes it difficult to perform a prospective, randomized study to determine the duration and effect of long-term psychiatric treatment.

Close follow-up and consideration of the risk vs benefit of psychotropic medication is key. Because there are no proven guidelines for the length of treatment with antipsychotics, it is prudent to minimize their use until psychiatrically indicated. Side effects, such as (in Mr. C's case) changes in the QTc interval, should warrant consideration of discontinuing psychotropic medication. Interdisciplinary collaboration with neurology and infectious disease will improve the overall outcome of a complex clinical presentation.

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