Is it General Paresis?

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ABSTRACT

The manifestations of central nervous system syphilis are unfamiliar to a differential of patients with dementia to many physicians today as a result of the relative rarity of this condition. This is a report of a patient with syphilis and dementia in an 88 year old Hispanic female. General Paresis is a progressive disease of brain leading to mental and physical deterioration. The clinical manifestations usually appear about 15-20 years after primary infection. It is important to keep tertiary syphilis in the differential diagnosis of dementia.

Key words: Syphilis, Paresis, Dementia

"Knowing syphilis in all its manifestations and relations, and all other things clinical will be added into you".

Sir William Osler, 1897

Syphilis is one of the most interesting diseases of humans. The disease has been of great historical significance for the practice of medicine, and for many persons who played important roles in the history of western world (1). Syphilis has expanded rapidly during the past two decades. The increase started gradually in the 1970s, due to the alteration in sexual behavior. The overall incidence increased slowly until 1982 and then declined slightly until 1986 (2). The number of reported cases of syphilis, including primary, secondary and congenital syphilis, has been rapidly rising since 1987 (3,4).

Case Report

This is a report of a patient with syphilis and dementia. An 88 year old Hispanic female presented with multiple problems. The daughter noted over the last year that her mother became less talkative than before. She is quite most of the time and she is usually not oriented to time, place and person. She still remembers the immediate family, but she cannot engage in long conversations. Her Folstein Mini-Mental score was 17/30, her geriatric depression scale was 14/30. Other associated problems include urinary incontinence and gait disturbance. Her neurological examination revealed: The left pupil is 7 millimeters with minimal reaction to light. The right pupil was 45 millimeters and reactive to light. Normal heart sounds S1 and S2, regular rhythm with no gallop or rail. Unequal pupils with one of them reactive to light; the other not reactive, pupils react normally to convergence accommodation. The rest of the cranial nerves were intact with good gag reflex. Reflexes are +2 all over; no nystagmus. Babinski was positive on the left side, muscle power was 3/5, unsteady gait. Laboratory study revealed a positive VDRL, a positive FTA. Her CT scan of the brain was normal. Ophthalmology examination revealed interstitial keratitis. The patient was hospitalised in 1987. Lumbar puncture was attempted three times but failed. She received treatment with IV penicillin for 10 days.

Primary Syphilis:
The typical lesions (Chancre) of the untreated illness typically appears from 10 to 90 days (average 3 weeks) from exposure. The lesion is normally single but may be multiple, and while it is normally painless and connected with regional adenopathy, exceptions occur (5).

Secondary Syphilis:
Classically, secondary Syphilis is featured by macular or papular lesions on the palms and soles. Nevertheless, the rash frequently begins on the trunk and spreads to the extremities ultimately embracing the whole body. It usually evolves six to eight weeks after the chancre has healed (2). It is also linked with systemic symptoms, including low grade fever, malaise, myalgia and generalised lymphadenopathy (6). Meningitis, iritis, glomulerulonephritis and hepatitis are infrequent but potential manifestations of secondary syphilis (Table 1) (5). The differential diagnosis of secondary Syphilis is broad, which accounts for the disease's historical name as "the great imitator" (5). The family of the patient did not recall any illness that resembles the above.

Latent Syphilis:
The latent stage has no clinical manifestations. It is divided into an early phase and a late phase. The Centers for Disease Control currently uses a one year cutoff to differentiate between early and late latent infection (2). Latent Syphilis follows the secondary stage of infection in the untreated patient. Roughly 25% of patients in the early latent stage will have at least one relapse of mucocutaneous symptoms, which may be helpful in the clinician's evaluation and management (7). Up to 35 percent of untreated persons with latent syphilis acquire the late sequelae of tertiary syphilis (7).

Tertiary Syphilis
Tertiary Syphilis is an ongoing, inflammatory disease that can effect any organ system. Among the untreated patients in the Oslo study who progressed to tertiary disease, cardiovascular Syphilis developed in 10%, neurosyphilis in 10% and gummatous Syphilis in 15% (7).

Neurosyphilis
The manifestation of the central nervous system readily recognised by practicing physicians three or four decades ago are unfamiliar to many physicians today as the result of relative rarity of this condition, as happened with our patient. A helpful schema for classification of neurosyphilis is shown in (Table 2). Although this classification indicates the existence of distinctive individual forms of neurosyphilis, features of several of the entities commonly coexist.

Table 1: Clinical Manifestations of Secondary Syphilis

Manifestation	Percentage of cases
Skin rashes	90
Macular, maculopapular, papular, pustular lesions, Condylomata, lata	
Mouth and throat lesions	35
Mucous patches	
Erosions or ulcers	
Genital lesions	20
Chancre	
Condylomata lata	
Constitutional Symptoms	70
Fever, malaise, myalgia, pharyngitis, arthralgia	
Central nervous system	
Asymptomatic	8-40
Symptomatic (headache, meningismus)	1-3
Generalised lymphadenopathy	50
Renal disorders	<10
Glomerulonephritis	
Nephrotic syndrome	
Gastrointestinal manifestations	<10
Hepatitis	
Intestinal wall invasion	

Table 2. Classification of Neurosyphilis

Asymptomatic neurosyphilis
Early
Late
Meningeal neurosyphilis
Acute syphilitic meningitis
Spinal syphilitic pachymeningitis
Meningovascular neurosyphilis
Cerebral form
Spinal form
Parenchymatous neurosyphilis
General Paresis
Tabes dorsalis
Optic atrophy
Gummations neurosyphilis
Cerebral form
Spinal form

Long-term longitudinal studies performed earlier in this century revealed that out of 953 persons with primary or secondary syphilis, 6.5 percent subsequently developed CNS involvement (8,9). The most common forms of nervous system involvement were asymptomatic neurosyphilis (31%) and tabes 30%. The incidence of paresis was most likely underrated since such patients were more probable to have been treated in psychiatric rather than general hospitals.

General Paresis

General paresis is a meningoencephalitics associated with true invasion of the cerebrum by T. Pallidum. The clinical illness is a chronic process that may present in middle or late adult life. The course is progressively downhill, in untreated patients. This form of late Syphilis develops 15 to 20 years after initial infection. Patients with this disease made up to 5 to 10 percent of all first admissions of psychotic patients to psychiatric hospitals prior to World War II. (9,10).

Symptoms and Signs
The clinical picture is an aggregation of neurologic findings and psychiatric symptoms. It can imitate nearly any type of psychiatric or neurological disorder. It is usually insidious in onset. The early characteristics are normally of psychiatric kind, and the trend of illness is that of a dementing process. Initial manifestations embody progressive memory loss, worsening of intellectual function and personality changes which was the case in our patient. Other symptoms include defects in judgement, emotional lability, delusions, and inappropriate social or moral behavior, in our case there were no delusional symptoms. Depression in some studies has been reported as the predominant presenting feature and the most common initial diagnosis in patients with paresis (11). The patient was clinically depressed, with a GDS of 14/30.

In patients with paresis of apparently sudden clinical onset, the earliest indication of the disease may be seizures, transient ischemic attacks, or an apparent stroke with loss of consciousness (apoplectiform attack), followed by hemiparesis, monoplegia, or aphasia. Pupillary abnormalities are among the most common neurologic findings in general paresis (Table 3 - next page). Speech gets continuously thicker, and the issue may be complicated by the development of global aphasia. A true Argyll Robertson pupil is not common in early paresis; at this stage the pupil may be large (rather than miotic), unequal, and sluggishly reactive to light and accomodation. Gradually, normal pupils can turn to Argyll Robertson type that was present in this patient, characterised by:

(1) The retina is sensitive (i.e., eye is not blind);
(2) Pupils are small, fixed and do not react to strong light;
(3) Pupils react normally to convergence-accommodation;
(4) Mydriatics (atropine) fail to dilate pupil fully;
(5) Pupils do not dilate on painful stimuli.

Apathy, hypotonia, unsteadiness, dementia, and physical deterioration become the major elements in the clinical picture, as the disease advances. Recurrent focal or generalized seizures accompany progressive deterioration resulting in bedridden, paralyzed, incontinent state. The term Lisauer's dementia paralytica describes a small group of atypical cases of paresis which showed focal neurological signs and on autopsy exposed impressive atrophy of certain cerebral convolution (9), especially in the frontal and temporal lobes. Such patients formerly had focal seizures followed by hemiparesis, hemianopia, or aphasia which thereafter cleared.

The duration of untreated paresis, from the onset of detectable mental symptoms till death, has ranged from a few months, in cases of sudden onset, to 4 or 5 years (9). Spontaneous remissions in mental symptomatology have happened infrequently, but have not changed the ultimate course of the disease. In the pre-penicillin era, treatment of paresis with malaria plus arsenicals benefited 33 to 50 percent of cases by arresting progression of the disease and allowing some type of occupational activity. The shorter the duration, and the milder the symptoms at the institution of therapy, the better the prognosis. In this lady treatment started late and no amelioration of symptoms was noted after treatment.

A few cases of general paresis, despite treatment with large doses of penicillin, have communicating hydrocephalus as a complication. This leads to either lack of clinical amelioration or gradual worsening. These patients develop gait apraxia, akinetic mutism, incontinence and pyramidal tract signs along with severe dementia (12). CSF shunting causes prompt amelioration in several cases. Diminished CSF absorption by chronic meningitis and meningeal fibrosis in general paresis seems to be the cause for this process.

Laboratory Findings

The blood nontreponemal serology has been reported positive in 95 to 100 percent of cases of paresis (9,12). In another study, only 48.5 percent of patients with a diagnosis of neurosyphilis had a positive nontreponemal serology (13). However, 56.3 percent of patients had a history of earlier treatment of syphilis. Thus, this series may not be as conflicting with other studies as it seems, since earlier treatment may have been adequate to cause seroconversion (without preventing the subsequent development of neurosyphilis). The serum FTA-ABS test is uniformly positive in patients with paresis. In our case both VDRL and FTA were positive.

CSF abnormalities are present in practically all cases of untreated paresis (9). The characteristic CSF findings, include the following:

(1) Normal or, occasionally, slightly increased pressure;
(2) Lymphocytic pleocytosis (usually 8 to 100 lymphocytes per cubic millimeter);
(3) Increased protein concentration usually 50 to 100 mg/dl)
(4) Increased globulin concentration;
(5) Positive colloidal gold reaction, when performed
(6) Normal or occasionally, mildly reduced glucose; and
(7) Reactive nontreponemal test.

The CSF nontreponemal tests show a very high specificity, and false positive VDRL test is remarkably exceptional. Thus, a positive CSF VDRL test is a powerful indication for a diagnosis of neurosyphilis. However, CSF nontreponemal tests may have

Table 3. Symptoms and Signs of General Paresis

Symptoms	Signs
Irritability	Pupillary abnormalities
	Argyl II
	Robertson Pupils
Personality Changes	
Failure of Memory	Tremor (tongue, hands)
Poor Concentration	Dysarthria
Careless in appearance	Lack of facial expression (masked face)
Intellectual deterioration	Pyramidal signs
Decreasing efficiency	Convulsions
Defective Judgement	Incontinence of urine and feces
Insomnia	
Changes in mood (euphoria, depression, agitation)	
Delusions	
Hallucinations	
Seizures	
Confusion and disorientation	

a sensitivity of less than 100 percent. In some patients with clinically diagnosed neurosyphilis (14), CSF Wassermann reactions have been reported negative. This can happen in a patient whose neurosyphilis process has been confined by treatment leaving steady mental changes.

In a few clinically characteristic cases of neurosyphilis (15) CSF VDRL may be negative, and the entire CSF analysis may be normal. Although abnormalities occur in the CSF of 25 to 40 percent of patients with untreated secondary syphilis (16), designating early association of nervous system, treatment with penicillin usually prevents any progression to symptomatic neurosyphilis. CSF FTA-ABS may be reactive as a product of diffusion of serum syphilis, therefore there are problems with the specificity of this test (17). False positive reactions occur in 0.5 to 4.5 percent. In addition, a reactive CSF FTA-ABS result may not indicate active neurosyphilis, since the reactivity may be produced by diffusion of serum immunoglobulins into the CSF (18). Also contamination of a CSF specimen with very small amounts of FTA-positive blood can produce a false positive CSF FTA test (19). For these reasons the interpretation of a

positive CSF FTA test is unclear (20). At present, a positive CSF FTA test alone in a patient with neurologic findings of uncertain nature does not establish a diagnosis of neurosyphilis.

In patients with paresis EEG is abnormal in 80 percent of cases. Recently CT scan has been utilized to assess cerebral syphilis (21). Findings on CT scan range from extensive regions of decreased attenuation of the cerebral white matter, particularly in the frontal lobes and paraventricular areas of parietal lobes to enlargement of cortical sulci and associated ventricular dilation (21). These findings resemble the CT scan pattern observed in demyelinating disorders. Other CT findings include cortical atrophy and multiple areas of hypodensity in both cerebellar hemispheres and in the brain stem (these findings are consistent with infarctions) (21). Godt et al (22) found both enhancing lesions (gummas) and generalized cortical and subcortical atrophy in several patients with neurosyphilis. Chest roentgenograms may show widening of the aorta, consistent with syphilitic aortitis, which occasionally coexists with parenchymatous neurosyphilis.

Diagnosis and Differential Diagnosis

The clinical picture, is easily distinguishable in its full-blown form, however is more hard to ascertain when atypical or incomplete. Spinal fluid alterations usually help in the diagnosis. The CSF is abnormal in all untreated cases of general paresis, but the same alterations can happen in the middle of other neurosyphilis. Hence, the association of preexisting CSF alterations of asymptomatic syphilitic meningitis with a diversity of organic brain syndromes can be misdiagnosed as general paresis. These include cerebral tumor, subdural hematoma, cerebral arteriosclerosis, Alzheimer's disease, multiple sclerosis, senile dementia, and chronic alcoholism. CT scan findings, the presence of pupillary changes, and a history of drug or alcohol abuse are useful in accurate diagnosis. Hallucinations are important in delirium tremens but are unusual in general paresis. However alcoholic worsening and Korsakoff's psychosis can present a picture of memory loss, unsuitable conduct, mood swings, and faulty opinion that is hard to differentiate from paresis.

An adult-onset seizure disorder can be a presentation of paresis or of an exceptional form of neurosyphilis. Paresis may be ruled out when CSF irregularities are lacking. When CSF alterations of neurosyphilis are present, the inquest change to whether the seizures symbolize epilepsy in a patient with asymptomatic neurosyphilis or whether they are the presentations of syphilitic brain injury. The presence of focal neurologic findings in patients with neurosyphilis-produced seizures aids in answering the question.

Management

ANTIBIOTIC THERAPY

The management of neurosyphilis and outcome has markedly improved since the introduction of penicillin. In a multicenter study including treatment of over 1000 patients with paresis, a total penicillin dosage of six million units was judged to be satisfactory (23). Patients who required re-treatment to arrest the infection had received less than six million units of penicillin initially. In the past decade it has been recognized that the treatment with 7.2 million units of benzathine penicillin G (2.4 million units intramuscularly weekly for 3 doses) is sufficient treatment for all kinds of neurosyphilis. The most recent recommendations of the Centers of Disease Control (24) involve the use of either intraveneous aqueous penicillin G for 10 days, intramuscular procaine penicillin G for 10 days, or weekly injections of benzathine penicillin G for 3 doses (Table 4) (24). Intravenous penicillin G for 10 to 15 days is the most reasonable therapy to employ for symptomatic or asymptomatic neurosyphilis. This assures penicillin concentrations in CSF which are continuously at least several fold above the minimally treponimicidal concentration of 0.018 microgram per milliliter during therapy (25, 26). Alternatively, daily aqueous procaine penicillin G (plus probenecid) for 10 to 14 days would be preferable to benzathine penicillin G, that is no longer recommended by the World Health Organization.

FOLLOW-UP AND RE-TREATMENT

The CSF data are normally a reliable index of the activity of neurosyphilis and furnish a gauge of the efficacy of the antibiotic therapy. When initial penicillin therapy has stopped the infection, repeat CSF examination at 3 to 6 months reveals normal cell count and, if initially elevated, a decline in concentration of protein (27).

Table 4. Drug Regimens for Treatment of neurosyphilis

1. *Aqueous crystalliine penicilline* G: 12 to 24 million units intravenously daily (2 to 4 million units every 4 h) for 10 days, followed by benzathine penicillin G 2.4 million units intramuscularly weekly for 3 doses

2. *Aqueous procaine penicillin* G: 2.4 million units intramuscularly daily plus probenecid 500 mg orally 4 times daily, both for 10 days followed by benzathine penicillin G 2.4 million units intramuscularly weekly for 3 doses

3. *Benzathine penicillin* G: 2.4 million units by intramuscular injection weekly for three doses

4. *Tetracycline hydrochloride:** 500 mg orally 4 times daily for 30 days

* For patients who are allergic to penicillin.

One year after treatment CSF examination reveals a persistent fall in the protein level and a decrease in the titer of the nontreponemal serologic test. However, the latter may not become completely negative for several years or longer and is not an indication of active neurosyphilis under these circumstances. In three to six months if the CSF cell count does not return to normal or if, having returned to normal, the count rises again in relapse, then re-treatment is indicated. If relapse has not occurred during a period of 2 years after adequate penicillin therapy, it is unlikely to occur. Subsequently, reexamination should be done annually for several years. Blood serologic testing should be performed at 6 and 12 months and afterwards at yearly intervals for at least 3 years (28).

PROGNOSIS

The natural history of the disease is progressive, and the result is ultimately deadly. The span of life from the beginning of tangible mental symptoms to death normally extends from a few months to 4 or 5 years, but an infrequent treated patient with so-called stationary paresis has survived for 10 years (9). Recent studies involving longer term follow-up indicate the development of new neurosyphilis signs in 39 percent of patients treated with penicillin (29). Advancement of the disease can happen indeed in the absence of reactive CSF tests. It is equivocal whether the evolution of new signs in patients with paresis treated with what has been determined adequate penicillin dosage is due to persistence of treponemes in the CSF, to the need for spirochetocidal concentrations of penicillin in the CSF (30, 31), or to an increased susceptibility to other neurologic processes. More study of these treatment failures is required.

Conclusion

Syphilis is still prevalent, especially in particular sectors of the population. Late complications can be somewhat less of an issue than the preantibiotic era, however vigilance to the probability of late Syphilis and appreciation of clinical manifestations of late Syphilis are crucial if these forms of disease are to be diagnosed and treated adequately. The main consideration must be vigilance in finding, treating, and preventing early Syphilis. Since all forms of Syphilis, especially certain types of late Syphilis, are less common than the glory days of Syphilis as a clinical specialty, it is important to educate others and to remind ourselves of the multiple faces of the great actor, lues venerea.

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