Neurosyphilis: The Reemergence of an Historical Disease

Ronit Gilad MD[1], Yair Lampl MD[1], Gershon Blumstein[3] and Michael Dan MD[2]

[1]Department of Neurology and [2]Unit of Infectious Diseases, Wolfson Medical Center, Holon, Israel
Affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[3]National Reference Center for Syphilis, Public Health Laboratories, Tel Aviv, Israel

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Syphilis, "the great imitator," used to be part of the standard differential diagnosis of neuropsychiatric disease. With the advent of penicillin, the incidence of tertiary syphilis has greatly declined. The disease is now considered unusual in the developed countries, except in the context of human immunodeficiency virus infection. In a recent review of syphilis the authors stated that "late neurosyphilis is extremely rare in the antibiotic era" [1]. Non-HIV-related neurosyphilis became uncommon enough for the American Academy of Neurology to drop lumbar puncture from its suggested list of tests for dementia [2]. More recently a new focus of disease resurgence has emerged: there has been an up to 50-fold increase in the incidence of syphilis in the Russian Federation and other newly independent states of the former Soviet Union [3] since the early 1990s. Other than the local significance of this new trend, it may have repercussions beyond the borders of the former Soviet Union. An estimated 2 million citizens from the former USSR have moved since the Soviet collapse in 1989, mostly to North America, western Europe, and Israel. Another immigrant population with a high prevalence of positive treponemal serology (3–12%) is that arriving from Ethiopia. Physicians providing care to immigrants from the former Soviet Union and Ethiopia should be aware of the potential role of syphilis in the etiology of acute and subacute neuropsychiatric diseases in these patients, and should consider the entity in the differential diagnosis, when appropriate. We report the cases of two recent immigrants from the former USSR who were diagnosed with neurosyphilis, and take the occasion to remind the medical community of this forgotten entity.

HIV = human immunodeficiency virus

Patient Descriptions

Patient 1

A 47 year old woman was hospitalized in a psychiatric hospital in June 2005 with sudden onset of psychotic symptoms for the first time in her life. Her medical history was unremarkable; she denied alcohol abuse or drug use and her family history for neurologic and psychiatric disorders was negative. The woman was married for 22 years; she had been a teacher in Georgia before arriving in Israel in February 2005. On admission she was oriented only to self, experienced intermittent agitation, expressed bizarre ideas, reported hearing hallucinatory voices, and had delusional thoughts. Her thought progression was illogical and often tangential, and her judgment was poor. She was alert, but made errors during recall, serial thinking and subtraction from 100, with short-term memory showing a moderate cognitive decline; the Mini-Mental State Examination score was 22 out of 30. Other components of the neurologic examination were normal, including cranial nerves, motor and sensory functions, cerebellar function, reflexes and gait, except for bilateral brisk reflexes. Neuro-ophthalmologic examination revealed normal pupils in size and shape, reactive to light and near vision. Fundi were normal, and no optic atrophy or afferent pupil defect was found. The rest of the physical examination was unremarkable.

Laboratory studies, including blood cell count and chemistry panel, were normal. HIV, hepatitis B and C virus serology, toxicology screen, thyroid and liver functions, vitamin B12, folate, and erythrocyte sedimentation rate were unremarkable. However, the Serum Venereal Disease Research Laboratory (VDRL) test was positive at a titer of 1:16; serum *Treponema pallidum* hemagglutination, and fluorescent treponemal antibody absorption test were also positive. Cerebrospinal fluid analysis revealed 62 white blood cells/mm^3 (80% lymphocytes), total protein level 117 mg/dl, and glucose level 65 mg/dl (100 mg/dl in blood). CSF serology was positive for VDRL (1:4), TPHA and FTA-Abs tests. Brain computerized tomography was normal and magnetic resonance imaging showed mild to moderate cerebral atrophy. Electroencephalogram showed diffuse slowing.

Because of her cognitive state and cultural barriers, a reliable sexual history could not be obtained. However, her husband's syphilis serology was also positive: VDRL was weakly positive, and TPHA and FTA-Abs tests were positive. He declined further investigation and treatment, declaring that he was in perfect health. The patient received crystalline penicillin G, 4 million units intravenously every 4 hours for 14 days. Her psychotic symptoms mildly improved, but there was no change in her cognitive decline. Mini-Mental State Examination score was 22 out of 30. On follow-up 6 months later, there was no substantial change in her clinical condition; repeat CSF examination revealed 4 cells, protein 65, and positive VDRL with a 1:2 titer.

Patient 2

A 44 year old heterosexual man was investigated in February 2006 for an acute

CSF = cerebrospinal fluid
TPHA = *Treponema pallidum* hemagglutination
FTA=Abs = fluorescent treponemal antibody absorption

transient event consisting of headache, numbness of right arm, difficulties in concentrating and slurred speech that lasted for less than 24 hours. He was born in Turkemenistan from where he emigrated to Israel in 2001. He smoked heavily, but was otherwise healthy and did not have a personal or family history of atherosclerotic vascular disease. Cerebral CT, carotid duplex scanning, and transesophageal echocardiography did not show abnormalities. The investigation included syphilis serology, which was positive with a serum VDRL titer of 1:8, positive FTA-Abs and TPHA tests, and weakly positive immunoglobulin M. CSF analysis revealed 42 WBC/mm^3 (80% lymphocytes), total protein level 65.10 mg/dl, and glucose level 65 mg/dl (99 mg/dl in blood). CSF serology was positive for VDRL (1:2), TPHA and FTA-Abs. HIV serology was negative. The patient did not recall signs suggestive of primary or secondary syphilis in the past. He reported, however, having urethritis previously. Treatment with crystalline penicillin, 24 million units per day, was administered intravenously for 10 days. The patient has not experienced any neurologic events since.

Comment

The manifestations of central nervous system syphilis, readily recognized by physicians practicing up to five decades ago, are unfamiliar to many contemporary clinicians because of the rarity of the condition. The CNS can be involved during any stage of the disease. At the early phase of syphilis up to 40% of untreated patients will have evidence of CNS involvement, which is most often asymptomatic (i.e., inflammatory and/or serologic findings in the CSF without neurologic symptoms). In the majority of untreated patients the early neurosyphilis will resolve spontaneously, and 10 years after the acquisition of the infection late asymptomatic syphilis will be present in about 6% of cases. According to some estimates, late symptomatic neurosyphilis will develop in about 90% of these individuals [4].

Late symptomatic disease can present as either meningovascular or parenchymatous neurosyphilis. Meningovascular neurosyphilis is an inflammatory process that results from the development of typical endarteritis obliterans in the small blood vessels of the meninges, brain and spinal cord and leads to multiple small areas of infarction. Hemiparesis, aphasia, and either focal or generalized seizures may occur. Parenchymatous neurosyphilis is a degenerative condition characterized by widespread destruction of nerve cells, principally in the cerebral cortex. It represents a combination of psychiatric manifestations and neurologic findings, and includes general paresis (cortical involvement) and tabes dorsalis (spinal cord involvement). Cognitive dysfunction and dementia are the hallmarks of general paresis; behavioral changes are present in up to 50% of affected people, and simple dementia occurs in 35% of patients. Spinal cord damage involves principally demyelinization of the posterior column, dorsal roots, and dorsal root ganglia, manifesting with sensory ataxia, lancinating pain and bowel and bladder dysfunction (tabes dorsalis). Meningovascular syphilis usually occurs 5–10 years after the onset of disease, general paresis 15–20 years after, and tabes dorsalis 25–30 years after.

The patients presented here exemplify the two forms of late symptomatic neurosyphilis, namely parenchymatous neurosyphilis (patient 1), and meningovascular syphilis (patient 2). The role of syphilis in the neurologic and psychiatric manifestations in these patients was supported by the positive serum and CSF serology, and the inflammatory findings in the CSF. According to the Centers of Disease Control guidelines, definite neurosyphilis is defined as a positive CSF VDRL test (specific, but only 30–70% sensitive), while probable neurosyphilis means CSF pleocytosis (> 5 WBC/mm^3) or elevated protein in the context of syphilis exposure (evidenced by a positive serum treponemal antibody response) without a better explanation [5].

The response to penicillin therapy is inconsistent: meningovascular disease responds more favorably, while response is usually poor in parenchymatous syphilis although some patients may improve [4]. Penicillin remains the drug of choice and should be administered intravenously or intramuscularly for 10 to 14 days. If CSF pleocytosis is present initially, a CSF examination should be repeated every 6 months until the cell count is normal. Changes in the VDRL-CSF or CSF protein after therapy are slower, and persistence of abnormal results may be less significant. If the cell count has not decreased after 6 months, or if the CSF is not normal after 2 years, retreatment should be considered [4].

Both our patients originated in highly endemic countries and presented with new-onset psychiatric and neurologic symptoms with no other previously known predisposing factors. Indeed, neurosyphilis should be suspected when a new episode of psychosis or neurologic deficit occurs in a middle-aged individual, particularly if risk factors are present. Clinicians, including internists and neurologists, and especially psychiatrists, need to have a high index of suspicion of neurosyphilis, which may have an exclusively psychiatric presentation rather than medical or neurologic symptoms. Alertness should be particularly high with patients at increased risk for contracting T. *pallidum* infection, such as immigrants from endemic areas.

WBC = white blood cells
CNS = central nervous system

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Correspondence: Dr. M. Dan, Unit of Infectious Diseases, Wolfson Medical Center, Holon 58100, Israel.
Phone: (972-3) 502-8729
Fax: (972-3) 501-6126
email: midan@post.tau.ac.il