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NEUROSYPHILIS PRESENTING WITH COGNITIVE DEFICITS - A REPORT OF TWO CASES

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SUMMARY

Background: *Neurosyphilis is an infection of the brain or spinal cord caused by Treponema pallidum. In the third phase of syphilis involving the central nervous system it may manifest in a widespread dysfunctions including psychiatric manifestations being often underestimated in the differential diagnosis.*

Case reports: *Two patients demonstrating rapid cognitive decline as the primary symptom for neurosyphillis are described with particular focus on the diagnostic process complexity and adequate treatment delivery.*

Conclusions: *Clinical manifestations as well as psychiatric symptoms of syphilis are diverse and often non-specific. The symptomatology of mood disorders in neurosyphilis is frequently atypical, intermittent, and pleomorphic and fails to meet DSM-5 diagnostic categories. Neurocognitive decline although could be one of the key symptoms domains in neurosyphilis. Those two cases emphasise the importance of specific differential diagnosis with rapid onset cognitive decline with spotlight to sexually transmitted diseases as syphilis.*

Key words: *neurosyphilis – cognition - neuropsychiatric symptomatology - sexually transmitted disease*

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INTRODUCTION

Neurosyphilis is an infection of the brain or spinal cord caused by Treponema pallidum. In the third phase of syphilis involving the central nervous system it may manifestin a widespread dysfunctions including psychiatric manifestations being often underestimated in the differential diagnosis. A Danish study carried out over 17 years by Danielsen et al. (2004) reported 92 patients suffering of neurosyphillis: 36% of these patients initially presented with neurological symptoms, 17% with psychiatric manifestations. A retrospective analysis of 117 patients by Flood et al. (1998) revealed a wide range of clinical courses and symptoms of neurosyphilis with 32% asymptomatic presentations. Between 1965-1984 27% of the individuals showed psychiatric manifestations while between 1985-2005 almost 86% had psychiatric symptoms.This data shows the general change in the appearance of neurosyphilis over the years (Danielsen 2004).

Although the antibiotic availability over the years decreased the complications of neurosyphilis the rate of syphilis itself increased in twenty-first centur. Due to its pleomorphic symptomsatypical forms of syphilis including psychiatric symptoms are more frequently observed nowadays.

The aim of this paper is to report on two cases of neurosyphilic patients with predominant cognitive decline demonstrating uncommon neuropsychiatric manifestation of the disease.

CASE REPORTS

Case 1

A 65-year-old Caucasian woman was admitted on to the psychiatric unit with cognitive impairment. The patient had been treated due to motor disorder accompanied by accumulating cognitive decline observed by her husband for three years and treated in outpatient setting for a year.

On admission she presented moderate dementia (MMSE 18/30; ACE-R 36/100) with generalized cognitive deficits. An in-depth elaboration of her cognitive impairment revealed dysfunction of the visual spatial memory, executive functions, operational memory, verbal memory, learning and attention processes and perception.She received memantine 20 mg/day and donepezil 10 mg/day with rapid worsening of her symptoms observed.

On neurological examination symptoms of corticobasal degeneration were observed. She was conscious, verbally responsive, however, with elements of speech disorders characterized by anomia and elements of speech apraxia. The patient presented severe bruxism. Rigidity, bradykinesia and limb apraxia were present being most severely expressed in the upper left limb. On examination involuntary dystonic phenomena occurred with her left arm involuntarily drifting gradually upwards. Brain MRI showed cortical atrophy severe in the right hemisphere of the brain predominantly in the temporal-parietal region.

Standard laboratory tests were normal. Blood serum analysis was negative for human immunodeficiency virus (HIV), Borrelia. However, syphilis on Wassermann reaction (WR) serum testing was positive being

subsequently confirmed with microhemagglutination (MHA-TP) assay. A lumbar puncture was performed and cerebrospinal fluid analysis was noted for protein level of 0.58 g/l, glucose level of 71 mg/l, normal cell count and differential, and a negative VDRL test and positive FTA -Abs treponemal antibody absorption test.

The patient was given 200 mg doxycycline orally per day for 14 days in a row withno significant improvement in her cognitive performance noticed. She was transferred to dermatology and venerology department for further treatment where intravenous procaine penicillin was provided at 24 mlnU per day for 14 days.The patient experienced functional remission and was signed out of the hospital and referred to and out-patient clinic for further consultation and diagnostics check with recommendation for intramuscular injections of 1.2 mln U per day for fourteen consecutive days.

Case 2

A 49-year-old Caucasian male with no prior psychiatric history developed cognitive decline accompanied by dysphoria two month prior to admission to the psychiatric unit for the diagnosis of dementia. Being a qualified active baker's confectioner he had lost professional abilities to perform his regular duties associated with complex food preparation processes. Although his co-workers noticed those problems he had not been aware of the decline and argued in dysphoric manner when the mistakes at work had been addressed. Having been referred to the occupational medicine physician and psychiatrist cognitive deficits had been found.

He scored 26/30 in MMSE with limited insight, jesting, difficulties with word recall and no criticism. Physical examination and laboratory tests were normal. The result of a neurological examination was noted to be nonfocal. Magnetic resonance imaging (MRI) of the brain revealed moderate hyperintensive abnormalities of angiogenic origin but was negative for other pathologic findings. Standard laboratory tests were normal. Blood serum analysis was negative for human immunodeficiency virus (HIV), Borrelia. Syphilis on Wassermann reaction (WR) serum testing was positive being subsequently confirmed with microhemagglutination (MHA-TP) assay. The cerebrospinal fluid analysis as noted for pleocytosis (25/ul) and increased global protein count in cerebrospinal fluid (0.66 G/l) with a positive VDRL test and positive FTA -Abs treponemal antibody absorption test. The patient reported a year-long history of sight loss. Ophthalmologist consultation revealed possible right eye optic nerve neuropathy with hypertensive angiopathy (2^{nd} degree in both eyes) being possibly linked to neurosyphilis.

The patient was treated with 200 mg doxycycline per day, orally, for 14 days in a row. No significant improvement in his cognitive performamance was noticed. He was transferred to dermatology and venerology department for further treatment where intravenous procaine penicillin was provided at the dose of 24 mln U per day for 14 days. The patient experienced notable improvementand was signed out of the hospital and referred to and out-patient clinic for further consultation and diagnostics check with recommendation for intramuscular injections of 1.2 mln U per day for sixteen consecutive days.

DISCUSSION

These two cases demonstrate cognitive decline as the primary symptom for neurosyphillis, complicating the diagnostic process and treatment delivery for the patients. Due to the pleomorphic symptomatology of syphilis its diagnosis is complex.

All symptoms of the secondary stage of the disease resolve with or without treatment and the patient enters the asymptomatic latent period in which an infection that can be detected only by laboratory tests. Two thirds of these patients remain asymptomatic. If left untreated, years to decades after primary infection, up to 30% of the affected individuals may develop tertiary syphilis. Tertiary syphilis can manifest as benign gummas, as cardiovascular disease (e.g. aneurysm of the ascending aorta), or as neurosyphilis (Workowski 2006). However, the central nervous system may be involved already in the secondary stage. In this context the authors would like to refer to psychiatric manifestations of syphilitic arteritis with secondary thrombosis (Rozwens 2003, Wöhrl 2007).

Clinical manifestations of neurosyphilis can be divided into different subtypes. Few and inconsistent data on the prevalence of psychiatric manifestations of neurosyphilis can be found. In a retrospective analysis Timmermans et al. (2004) reported that approximately 51% of 161 patients diagnosed with neurosyphilis presented neuropsychiatric symptoms. A Danish study carried out over 17 years (Danielsen, 2004) reported of 92 patients suffering of neurosyphilis: 36% of these patients initially presented with neurological symptoms, 17% with psychiatric manifestations. Clinical manifestations of neurosyphilis are protean as stated above. A retrospective analysis of 117 patients by Flood et al. (1998) shows a wide range of courses and symptoms. Of patients with neurosyphilis: 32% were asymptomatic, 33% presented personality changes, 28% of the patients had ataxia, 23% had a stroke, and 17% had ocular symptoms. 17 % of the patients reported bladder disturbance, whilst 10% had typical shooting pains due to tabesdorsalis. Headache, dizziness, or hearing loss was observed in 10% of the patients, 7% of the patients had cerebral seizures. Mitsonis et al. (2008) examined medical records of 81 patients suffering from neurosyphilis. Between 1965-1984 27% of the individuals showed psychiatric manifestations, while between 1985-2005 almost 86% had psychiatric symptoms. The reason for this difference has not been explained (Wöhrl, 2007; Friedrich, 2011).

Clinical manifestations as well as psychiatric symptoms of syphilis are diverse and have to be considered as non-specific (Rozwens, 2003). A great number of publications focus on dementional syndromes. Goeman et al. reported in their survey on the occurrence of dementia symptoms in a 15-year-old boy with congenital syphilis (Goeman, 1996). The contemporary literature however lacks extensive epidemiological data on the incidence of numerous psychiatric presentations of neurosyphilis. About 27% of patients with primary psychiatric manifestation of neurosyphilis present with depression characterized by psychomotor retardation, melancholia, suicidal ideation, decreased sleep, energy and apetite, or cognitive impairment (Rozwens 2003, Cubała 2008).

Clinical manifestations of neurosyphilis can be divided into different subtypes, as stated below.The asymptomatic form is characterized by the presence of a CNS infection as indicated by CSF abnormalities in the absence of psychiatric or other symptoms. Further, neurosyphilis may be divided in a meningeal, a meningovascular, a parenchymatous, and a gummatous subform. This classification seems useful and is widely used (Friedrich 2011) (Table 1).

Table 1. Neurosyphillis classification (modified from: Friedrich & Aigner 2011; Rozwens et al. 2003)

I. Asymptomatic		
II. Meningeal	Acute meningitis	with basiliar involvement with hydrocephalus with vertex involvement
	Spinal pachymeningitis	
III. Meningovascular	Cerebral	
	Spinal	Meningomyelitis Acute transverse meningitis
IV. Parenchymatous	General paresis Tabesdorsalis Optic atrophy	
V. Gummatous	Cerebral compression symptoms Spinal compression symptoms	

Although there is no gold standard test to diagnose neurosyphilis, serum analysis for syphilis with non-specific lipoidal tests (RPR and VDRL) and treponemal-specific tests (FTA-ABS) should be considered routine in patients presenting with and hospitalized for mental disorders. A CSF analysis for VDRL is used to define a “confirmed” case of neurosyphilis although this test has been found to be non-reactive in 43% of cases. the CSF RPR test is currently not recommended and studies have found it to be less specific. In summary, the CSF VDRL test is considered the test of choice in diagnosis of neurosyphilis and although a positive vDRl establishes a diagnosis, a negative VDRL does not exclude it.[8] The appropriate screening for syphilis in serum by Treponema antibody tests, such as the Treponema Pallidum Particle Agglutination Test (TPPA), is necessary to reveal a tertiary syphilis. These tests are, in particular for asymptomatic patients in the stage of late latency, the only reference to an infection with Treponema pallidum [3]. A CSF analysis for VDRL is used to define a “confirmed” case of neurosyphilis although this test has been found to be non-reactive in 43% of cases.

Computer tomography and MRI used to evaluate series of patients with neurosyphilis most commonly found generalized cerebral atrophy and foci of increased signal intensity, but to date, there are no pathognomonic radiographic findings suggesting a diagnosis of neurosyphilis.According to literature, the most common changes observed in the MRI are symmetrical subcortical and cortical atrophy (37%), stroke (25%) and non-specific vascular changes in the white matter of the brain (20%) and psychiatrists should take neurosyphilis into consideration when facing the differential diagnosis in central vascular disorders (Czarnowska-Cubała, 2013).

TREATMENT

The expert consensus recommendation for dementia symptoms accompanying syphilis is a symptomatic treatment with acetylocholinesterase inhibitors and/or memantine. Furthermore, various national Alzheimer societies recommend syphilis serologic testing as part of routing medical investigation of a demential syndrome (Wöhrl, 2007). Penicillin remains the mainstay of therapy to treat neurosyphilis. This treatment regimen has been found to quickly resolve symptoms in patients with early meningeal neurosyphilis, but for late disease with parenchymal involvement, resolution of symptoms may not occur (Patel, 2011).

There is substantial evidence that in certain subgroups of patient including HIV-positive patients there is room for doxycycline as a treatment of choice for neurosyphillis with some evidence in literature. Patients who do not respond to doxycycline, penicillin remains the golden standard although intravenous regimen is required.Clinicians should be aware that an extended course of high-dose, oral doxycycline may be an effective and safe alternative regimen to intravenous or intramuscular penicillin, without requiring hospitalization or home health care, for the treatment of neurosyphilis in HIV-infected patients. Prospective trials are needed to assess the long-term efficacy oral doxycycline for neurosyphilis (Kang-Birken 2010; Gordon 1994).

CONCLUSION

The neuropsychiatric symptomatology tertiary syphilis is often atypical, intermittent, and pleomorphic and fails to meet DSM-5 diagnostic categories. There is no consensus and guideline on how to deal with psychiatric manifestations in association with neurosyphilis (Friedrich 2011). Neurocognitive decline although, could be one of the key symptoms domains in neurosyphilis.

These case series emphesises importance of differential diagnosis with rapid onset cognitive declinewith regards to sexually transmitted diseases as syphilis.

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