International Journal of Infectious Diseases 76 (2018) 1–3

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Case Report

Neurosyphilis: The shape of a rising threat

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ARTICLE INFO

Article history:
Received 23 May 2018
Received in revised form 26 July 2018
Accepted 27 July 2018
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Neurosyphilis
CSF pleocytosis
Immunocompetence
Dural thickening

ABSTRACT

This report describes a case of neurosyphilis presenting with memory disturbances, attention deficit, and acute psychotic decompensation in an immunocompetent man. Despite the known connection of neurosyphilis with psychiatric symptoms, this cause often remains unrecognized. This report emphasizes the importance of maintaining a suspicion for the disease in patients with vague symptoms and describes the diagnostic difficulties.

Introduction

A whole range of diseases can affect patients through neuropsychiatric manifestations. Identifying the medical disease at an early stage can be crucial because many conditions can be reversible with appropriate and timely treatment. Processes causing neuropsychiatric symptoms include autoimmune, infectious, endocrine, metabolic, and neoplastic diseases (Isaac and Larson, 2014).

The term neurosyphilis refers to an infection of the central nervous system caused by the spirochete *Treponema pallidum* resulting in an insidious chronic meningeal inflammation. Despite the increasing incidence of the tertiary form of syphilis associated with the increasing prevalence of HIV infection, neurosyphilis remains uncommon in immunocompetent patients (Rodrigues et al., 2012). However, the number of infected patients is increasing in Eastern European countries (Brinar and Habek, 2006). The rapid and accurate diagnosis of neurosyphilis is challenging (Rodrigues et al., 2012); however, there are certain clinical signs and findings that may arouse suspicion.

The aim of this report is to emphasize the importance of increased protein levels in the cerebrospinal fluid (CSF) and dura thickening in patients with rapidly emerging neuropsychiatric symptoms and/or dementia. These findings should raise the suspicion of neurosyphilis and lead to further serology and CSF analysis.

Case report

A 47-year-old man presented with a 5-month history of progressively worsening neurological symptoms that had started as memory disturbances (especially short-term memory disturbances) and attention deficit. A month after the onset of symptoms, the patient had experienced acute psychotic decompensation and hallucinatory-paranoid events. The patient was initially misdiagnosed with a schizoaffective disorder and treated with antipsychotic drugs. Psychological tests revealed deviations in terms of short-term memory and graphomotor skill. Cognitive impairment was without daily fluctuations and was slightly more evident while the patient was being treated with antipsychotic therapy. His speech was not affected and he could successfully perform daily activities. Occasionally he was depressed without anxiety or aggression.

Eight months after symptom onset, magnetic resonance imaging (MRI) and computed tomography (CT) of the brain revealed age-inappropriate and premature atrophic changes of the brain parenchyma, with wide CSF spaces infra- and supratentorially. MRI also showed thickening of the dura and bilateral subdural hygromas (Figure 1). Neurocognitive testing indicated

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https://doi.org/10.1016/j.ijid.2018.07.022

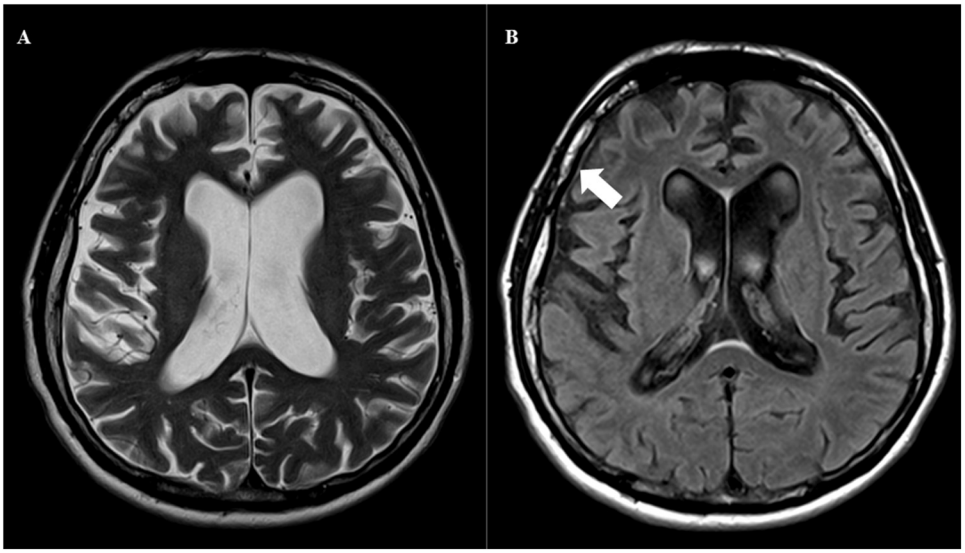

Figure 1. MRI axial T2-weighted (A) and FLAIR (B) images demonstrating diffuse atrophy, bilateral lamellar subdural hygromas, and dural thickening (arrow).

cognitive impairment in verbal and non-verbal domains of non-associative memory, and less severe disturbances of attention and executive functions. Values of thyroid hormones, vitamin B12, and folic acid were within the normal range.

Ten months after symptom onset, CSF analysis showed an increased number of lymphocytes (67/3 × 10^6/l; normal range 15/3 × 10^6/l) and elevated protein values (68 mg/dl; normal range 17–37 mg/dl). The value of Tau protein in the CSF was 257 pg/ml and the value of pTau - phosphorylated tau protein was 18 pg/ml. The level of beta-amyloid was 762 pg/ml. Creatine kinase in the blood was also increased (1014 U/l; normal range 0–177 U/l). Due to the increased number of lymphocytes and elevated protein values in the CSF with the presence of dura thickening, a serological and neuroimmunological evaluation was performed, which revealed neurosyphilis. The following tests were reactive: Venereal Disease Research Laboratory/Rapid Plasma Reagin (VDRL/RPR; serum 1:128, CSF 1:4), *Treponema pallidum* hemagglutination (TPHA; serum 1:20 480, CSF 1:2560), and fluorescent treponemal antibody absorption (IgG-FTA-ABS; serum 1:40, CSF poor reactive). HIV infection was also suspected, but the patient was seronegative. Therapy was started with a course of intravenous procaine benzylpenicillin. The diagnosis was established 10 months after the onset of symptoms.

The patient was hospitalized again after 3 and 11 months. CSF analysis after 11 months revealed a decrease in lymphocyte count (2/3 × 10^6/l) and protein values (40 mg/dl). A repeated MRI examination after 3 months did not show the previously visible subdural hygroma, and dural thickening was less prominent; however, atrophy of the brain parenchyma was more evident, particularly in the hippocampus. The cognitive impairment was still present, but there had been a significant improvement following antibiotic therapy. There was an evident reduction in RPR titer, indicating a good response to therapy (initial: serum 1:128, CSF 1:4; after 3 months: serum 1:32, CSF 1:2; after 11 months: serum 1:8).

Discussion

This case stresses the need to include neurosyphilis in the differential diagnosis for subjects presenting with neuropsychiatric manifestations. There has recently been a drastic increase in the incidence of syphilis (Mattei et al., 2012). Although still uncommon in immunocompetent patients (Rodrigues et al., 2012), this fact should be a warning to clinicians to enhance their level of suspicion, especially within the HIV-positive population.

Neurosyphilis has diverse presentations and may occur at any stage of the disease (Mattei et al., 2012). If symptoms occur at the beginning of the disease, the spirochete usually affects the CSF, meninges, and blood vessels. The late variant is manifested by the involvement of the parenchyma of the brain and spinal cord. CSF examination is required in patients with syphilis and neurological symptoms, as well as in patients with clinically and serologically determined treatment failure (Mattei et al., 2012).

The non-specific clinical presentations and unclear significance of supportive laboratory tests make the rapid and accurate diagnosis challenging. There are several current criteria based on CSF antibody tests, positive serum RPR, the *Treponema pallidum* particle agglutination (TPPA) test, and white blood cell count. Neurosyphilis is suspected when the CSF white blood cell count is higher than 20 × 10^6 cells/l or a CSF VDRL test result is reactive (Zhang et al., 2015). Although an elevation of the CSF protein concentration is consistent with neurosyphilis, it may be less specific than CSF pleocytosis (Marra et al., 2008; Tso et al., 2008). In patients with suspected neurosyphilis, a CSF lymphocyte count >5 × 10^6 cells/l or a protein concentration >45 mg/dl is consistent with the diagnosis of neurosyphilis (Tso et al., 2008). In patients with HIV infection and syphilis, establishing a diagnosis of neurosyphilis is particularly difficult because HIV itself causes mild CSF pleocytosis and a mild elevation of the CSF protein concentration (Marra et al., 2008). If the initial examination of CSF shows pleocytosis like in the patient presented herein, CSF analysis should be repeated every 6 months until the number of cells decreases to a normal value. The RPR titer can be linked to disease activity, and a four times reduction in titer could be used as proof of successful therapy (Saunderson and Chan, 2012), which was also the case in the patient reported here.

There is an increasing role of neuroimaging methods in the diagnosis of unclear dementia and psychoses. Dural thickening is a rare disorder of diverse etiology, associated with rheumatoid arthritis, syphilis, Wegener's granulomatosis, tuberculosis, and cancer (Kupersmith et al., 2004). A connection between dementia and dural thickening has recently been established. One study observed dural thickening on MRI in one-third of patients with mild cognitive impairment or Alzheimer's disease (Qureshi et al., 2015). Neurosyphilis should also be considered as a possible

differential diagnosis because it can affect the meninges resulting in dural thickening (Rosa Júnior et al., 2016).

In conclusion, in the event of a relatively sudden appearance of psychiatric and cognitive symptoms, all possible secondary causes, including syphilis, should be excluded. This case demonstrates the need for greater clinical and epidemiological vigilance to reduce the morbidity and mortality associated with syphilis, especially in patients with various neurocognitive symptoms, and also the need to shorten the often lengthy diagnosis time.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethical approval

All procedures were performed with the full cooperation of the patient, with adequate understanding. Therefore they were performed in accordance with the ethical standards of the Declaration of Helsinki.

Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Study concept and design: Borovečki, Bilić. Acquisition of data: Blažeković, Ozretić, Habek, Bilić, Borovečki. Analysis and interpretation of data: Blažeković, Ozretić, Habek, Borovečki. Drafting of the manuscript: Blažeković. Critical revision of the manuscript for important intellectual content: Blažeković, Ozretić, Habek, Bilić, Borovečki. Administrative, technical, and material support: Blažeković, Ozretić, Habek, Borovečki.

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