CASE REPORT

Changes in psychiatric symptoms and neuroimaging due to Jarisch-Herxheimer reaction after penicillin therapy for neurosyphilis: A case report

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Abstract

BACKGROUND: Based on the limited amount of published evidence, patients with symptomatic Jarisch-Herxheimer reaction may experience a worsening of neuropsychiatric symptoms, but in this case study, we reported a specific patient with dementia and neurosyphilis who was treated with penicillin and suddenly developed psychotic symptoms and Jarisch-Herxheimer reaction along with irreversible damage to the central nervous system.
CASE PRESENTATION: A 51-year-old Han male was hospitalized at our hospital with dementia, where he was also diagnosed with neurosyphilis based on intracranial magnetic resonance imaging and cerebrospinal fluid analysis. Prior to the diagnosis of neurosyphilis, the patient had never received penicillin or other medication for syphilis. Three days after intravenous penicillin treatment, the patient became disoriented, was no longer able to recognize his family members, and had psychotic symptoms that were similar with Jarisch-Herxheimer reaction secondary to encephalopathy. With continued penicillin (6 million units/day) and prednisone treatment, patient's psychotic symptoms were controlled and cognitive symptoms were remained. Repeat intracranial MRI revealed irreversible damage of patient's central nervous system.
CONCLUSIONS: This case indicates that patient with dementia may also have neurosyphilis. Patient with dementia and neurosyphilis may have specific JHR during intravenous penicillin treatment. It is crucial to avoid permanent neurological damage for patient with dementia and neurosyphilis using penicillin and prednisone treatment.

Introduction

Syphilis is a bacterial infection caused by the spirochete Treponema pallidum (Hook 2017; Kojima&Klausner 2018). According to the World Health Organization, an annual over 11 million new cases of syphilis worldwide and more than 90% of cases occur in developing countries (Rowley *et al.* 2019). In recent years, the incidence of syphilis in China is increasing gradually. The incidence of neurosyphilis has increased from 0.21 /100,000 in 2009 to 0.31 /100,000 in 2014. From 2014 to 2019, the incidence of syphilis reported in China increased from 30.93/10 million to 38.37/10 million, with an average annual growth rate of 4.41% (Vos *et al.* 2016; Wang *et al.* 2016; Zhang *et al.* 2016).

A regimented schedule of antibiotics is the usual treatment for syphilis, such as penicillin, cephalosporins and macrolide antibiotics. After initiation of treatment, a transient immune response known as the Jarisch-Herxheimer reaction (JHR) maybe occurs in patients (Rissardo Jamir *et al.* 2019). JHR symptomology differs from that seen in primary and secondary syphilis and may be divided into two types that occur alone or consecutively: the asymptomatic JHR manifests as systemic changes during the first 24 h after treatment initiation, while the symptomatic JHR manifests as exacerbation of mental symptoms or other neurological signs during the first days after treatment initiation (Zifko *et al.* 1994). Based on the limited amount of published evidence, patients with symptomatic JHR may experience a worsening of neuropsychiatric symptoms.

In this case study, we reported a specific patient with dementia and neurosyphilis who was treated with penicillin and suddenly developed psychotic symptoms and JHR along with irreversible damage to the central nervous system.

Case presentation

A 51-year-old Han man was hospitalized at our hospital with memory loss, anhedonia, significant personality changes, delayed reactions, and increased irritability. His memory loss had reduced his daily autonomy as he could not remember simple things such as items on his grocery list or whether he had taken his medication. His clinical symptoms occurred three months before he came to our hospital, and during that time, he had been diagnosed at a local hospital with dementia syndrome, scoring 10 of 30 on the Montreal Cognitive Assessment. The patient had a history of diabetes.

At our hospital, the results of patient's complete blood counts and routine serum analysis were normal, although the hematocrit (0.37) was slightly below the normal range (0.40-0.50). Patient's intracranial magnetic resonance imaging (MRI) showed microhemorrhages in the left parietal lobe and hypoperfusion in the bilateral temporal lobe with no areas of high signal detected (Figure 1). His syphilis serum test: TPPA (+), TRUST (+), no explanation of unclean sexual life history and smelting tour history. Cerebrospinal fluid contained high levels of microprotein (1.17 g/L; normal range, 0.15-0.45 g/L), glucose (8.46 mmol/L; normal range, 2.5-4.4 mmol/L), and nucleated cells (59×10^6 /L; normal range, 0-10×10^6 /L).

Based on these findings, the patient's diagnoses were revised to neurosyphilis, and he was given penicillin (6 million units/day) intravenously for 14 consecutive days. The patient reported never being given penicillin before. The patient showed no remarkable changes for the first 48 h. On the third day of treatment, the patient suddenly became disoriented and reported being unclear about where he was; he also experienced hallucinations and delusions, e.g. he reported fears that his son was going to be deformed, the police were going to arrest him, and someone was going to hurt him. The patient refused to eat or take his oral medication (Acarbose) and exhibited impulsive behavior (e.g., attack his son and medical staff). Penicillin treatment was suspended, but these psychotic symptoms still existed.

After consultation with and examination by infectious disease specialists, neurologists and psychiatrists, the patient might have JHR. Specialists suggested to continuously use penicillin (6 million units/day) treatment and oral prednisone was added for 5 consecutive days: 15 mg on day 1, 20 mg on day 2 and 60 mg on days 3-5. On day 5 of oral prednisone treatment, the patient was able to recognize himself and his family, and recall partly what had happened to him during the previous days. However, the patient still suffered memory loss.

Patient's intracranial MRI at the end of the entire course of treatment showed multiple patchy slightly long T1 features, slightly long T2 signal shadows in the bilateral frontal parietal temporal lobes, and high signal in bilateral medial temporal lobe (Figure 2). Repeat analysis of cerebrospinal fluid did not detect nucleated cells, while levels of microprotein (0.85 g/L) and glucose (5.26 mmol/L) were substantially lower than that at admission. High-throughput genetic assays of cerebrospinal fluid failed to detect the presence of microbes.

Discussion and conclusions

Previous studies have shown that symptoms of neurosyphilis can be similar with psychiatric disorders. Indeed, in many cases, psychotic disorders (e.g., dementia) might be comorbidity with an underlying diagnosis of neurosyphilis (David Spelber&Sheila Lahijani 2020). The patient in this study began to show signs of cognitive impairment three months before admission to our hospital. Subacute yet rapidly progressive cognitive impairment lasting weeks to months is the most frequent manifestation of systemic palsy in neurosyphilis, involving disorientation and deficits in memory,

Fig. 1. T2W MRI. On admission indicating microhemorrhages in the left parietal lobe and hypoperfusion in the bilateral temporal lobe with no areas of high signal detected

speech and judgment (Stefani *et al.* 2013). It is possible that the patient's syphilis was already fairly advanced by the time he was correctly diagnosed at our hospital. It is important that dementia may be comorbidity with syphilis.

After taking penicillin for a few days, the patient developed psychiatric symptoms. Multidisciplinary consultation suggested that the psychiatric symptoms were due to the nonspecific inflammatory response in JHR. Tests of cerebrospinal fluid ruled out other microbial infections. Comparison of MRI scans before and after penicillin treatment showed extensive damage to the patient's central nervous system. The results of this case show that penicillin treatment for patient with dementia and syphilis may have JHR and cause severe damage of the central nervous system.

Few cases of secondary JHR due to antibiotics in patients with neurosyphilis have been reported. A 52-year-old Caucasian man with neurosyphilis (originally misdiagnosed as cellulitis) experienced hallu-

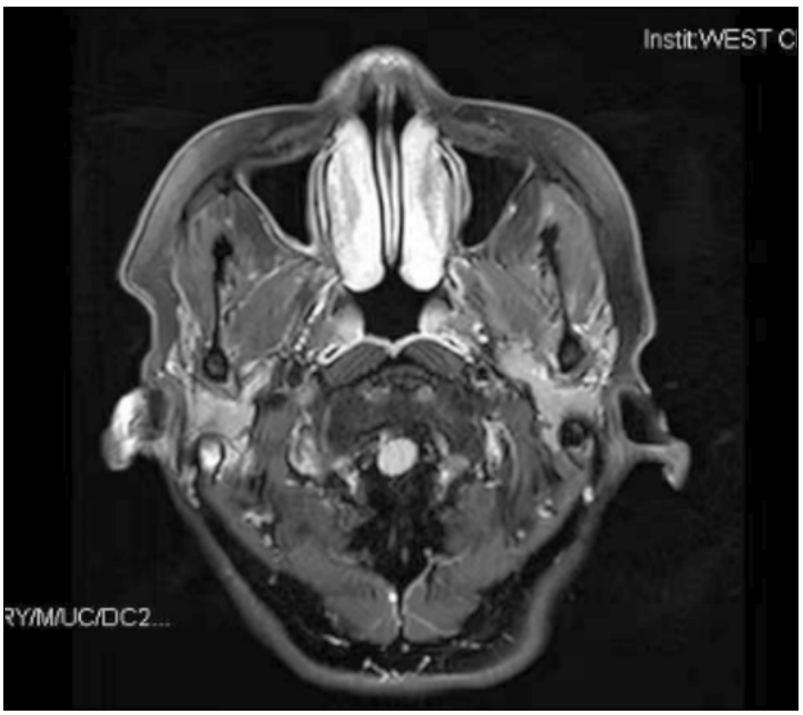

Fig. 2. T2W MRI. After the entire course of treatment, indicating bilateral medial temporal lobe showed high signal

cinations and delusions (e.g., direct communication with God) after taking antibiotics for one week (David Spelber&Sheila Lahijani 2020). A 23-year-old Caucasian man with neurosyphilis developed generalized convulsive epilepsy as part of the JHR after receiving penicillin (Rissardo Jamir *et al.* 2019). A 52-year-old patient with neurosyphilis showed a central nervous system damage by MRI within 7 days of starting penicillin therapy, after concomitant use of penicillin and dexamethasone, the MRI abnormalities recovered quickly (Zhang *et al.* 2008). In contrast to the above cases, the case in this study suggests that penicillin treatment with neurosyphilis can induce JHR, and may even cause irreversible damage to the central nervous system.

The pathogenesis of JHR remains poorly understood but is thought to be related to the massive release of non-endotoxin heatogens and spirochete lipoproteins after initial penicillin treatment (Belum *et al.* 2013; Davis *et al.* 2013). Based on the symptoms displayed during a suspected case of JHR, patients may be treated by several anti-inflammatory regimens, such as intravenous methylprednisolone (1 g/day) and oral prednisone (60 mg/day) (Kojan *et al.* 2000). Prednisone and other glucocorticoids have anti-shock, anti-inflammatory and immunosuppressive effects, which can dampen allergic reactions (Wu *et al.* 2013). Administering prednisone to the patient in this study while he was receiving penicillin reduced the psychiatric symptoms and partially restored the cognitive deficit that appeared after he began taking the antibiotic. Nevertheless, the patient continued to suffer memory deficit and his mental status was not effectively restored, which may be related to irreversible damage to the central nervous system as a result of penicillin-induced JHR.

This case illustrates that initial penicillin treatment of patients with both dementia and neurosyphilis may cause JHR and rapid worsening of psychiatric symptoms and irreversible damage to the central nervous system. It is crucial to prevent or mitigate adverse reactions to medication in patients with syphilis, particularly those who have never received penicillin before.

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