CASE REPORT

NEUROSYPHILIS MIMICKING AUTOIMMUNE ENCEPHALITIS: A CASE REPORT AND REVIEW OF THE LITERATURE

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Abstract

Neurosyphilis may imitate a wide range of neurological and psychiatric diseases, including autoimmune encephalitis. To avoid further cognitive decline and morbidity, early recognition and adequate treatment are of particular importance in both neurosyphilis and autoimmune encephalitis. In case of a strong clinical suspicion of a diagnosis of autoimmune encephalitis, guidelines recommend initiating immunotherapy even in the absence of immunological confirmation. Here, a case of neurosyphilis is reported in which the potential overlap in clinical presentation of autoimmune encephalitis and parenchymatous neurosyphilis is discussed.

The here reported data suggest that, in cases presenting with new onset focal epilepsy, slowing of electroencephalographic activity over the temporal regions and magnetic resonance imaging suggestive of swelling of the amygdala, neurosyphilis should be excluded prior to initiation of immunotherapy for suspected autoimmune encephalitis.

Key words: epilepsy; neurosyphilis; autoimmune encephalitis

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Introduction

Neurosyphilis refers to invasion of the central nervous system (CNS) by Treponema pallidum subspecies pallidum, the causative agent of syphilis. Syphilis is a mainly sexually transmitted multistage and multi-organ infectious disease, with a long and variable course. Neurosyphilis is a potentially invalidating but curable disease. However, advanced disease may be irreversible, which warrants early detection and treatment. Epileptic seizures and status epilepticus are rare presentations of neurosyphilis (Drago et al., 2016). Although the epidemiology of modern neurosyphilis is not well defined due to the paucity of population-based data (Ghanem, 2010), the prevalence of neurosyphilis seems to increase (Drago et al., 2016).

Historically, infectious diseases are the most frequently identified causes of acute encephalitis (Venkatesan & Probasco, 2018). However, the results of a recent study suggest that, at a population level, autoimmune encephalitis (AE) is as common as infectious encephalitis (Dubey et al., 2018). Moreover, the detection of AE is increasing over time since more antibody biomarkers are discovered (Dubey et al., 2018). In AE, IgG autoantibodies attack parts of nerve cells as "foreign" and this triggers an immune response, followed by inflammation and disruption of normal nerve function. Seizures in AE are most often associated with antibodies directed to N-methyl-d-aspartate receptor (NMDAR), leucine-rich glioma inactivated protein 1 (LGI1) and contactin-associated protein-2 (Caspr2) (formerly known as voltage-gated potassium channel (VGKC) complex antibodies), and antibodies directed to intracellular synaptic proteins including glutamic acid decarboxylase (GAD) (Bien & Holtkamp, 2017).

Epilepsy in AE associated with antibodies directed to cell-surface proteins may be very difficult to control with anti-seizure medications. However, in contrast to seizures in encephalitis associated with classic, paraneoplastic antibodies, seizures in AE frequently respond well to combined treatment with immunotherapy and anti-seizure medication (Leypoldt, Armangue, & Dalmau, 2015; Geis, Planagumà, Carreño, Graus, & Dalmau, 2019). Early initiation of immunotherapy is associated with improved outcome (Graus et al.,

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2016). Therefore, in case of a strong clinical suspicion of a diagnosis of AE, guidelines recommend to start immunotherapy, even in the absence of immunological confirmation (Venkatesan & Benavides, 2015; Graus et al., 2016).

Both neurosyphilis and several categories of AE associated with antibodies directed to cell-surface proteins may present with a constellation of new onset seizures, mesiotemporal Magnetic Resonance Imaging (MRI) hyperintensities and intermittent temporal slowing on Electroencephalogram (EEG) (Scheid, Voltz, Vetter, Sabri & von Cramon, 2005; Budhram, Silverman, & Burneo, 2017; Marra 2017; Serrano-Cardenas, Sánchez-Rodríguez, Pozueta, Pelayo & Riancho, 2018). In this paper we first discuss neurosyphilis and autoimmune encephalitis. Then, to emphasize the importance of considering neurosyphilis in patients suspected of AE, a patient with neurosyphilis mimicking AE is described.

Methodes

For this study, the literature on neurosyphilis presenting as an autoimmune encephalitis is investigated, primarily to illustrate the necessity to consider both neurosyphilis and AE in the diagnostic work-up of patients presenting with focal seizures, focal temporal EEG slowing and swelling of the amygdala.

Results

Neurosyphilis

Neurosyphilis is often referred to as a tertiary or late effect of syphilitic infection. However, involvement of the CNS may occur at any stage of infection. The initial stage of syphilis is characterized by the appearance of a "chancre" (a soft, non-painful, non-tender, indurated ulcer without exudate) that appears at the site of inoculation approximately 10-90 days after acquisition of the infection. Classically, secondary syphilis manifests with skin rash, mucosal ulceration and lymphadenopathy. Inflammation of the optic nerve, uveitis luetica, interstitial keratitis and otitis luetica are the most common complications at this stage of infection. Syphilitic meningitis, meningovascular syphilis, hepatitis, nephritis, gastritis and joint inflammation may also occur (Kent & Romanelli, 2008). Tertiary, non-transmissible, syphilis may manifest approximately 3 to 15 years after the initial infection in one third of infected patients without treatment and can be divided into three categories: gummatous syphilis (50%), cardiovascular syphilis (33%) and late parenchymatous neurosyphilis (15%) (Bhatti, 2007; Kent & Romanelli, 2008).

Although curative modern antibiotics and public health measures were responsible for the dramatic decline in the prevalence of syphilis from the middle of the last century (Berger, 2011), a worldwide increase in the incidence of syphilitic infections is reported since the turn of the millennium (Fenton et al., 2008). Many European countries observed a sharp increase up to 50% in the rates of reported syphilis infections in the period 2010 and 2015 (ECDC, 2017). In 29 Member States of the European Union and European Economic Areas, 28,701 syphilis cases (6.0 per 100,000) were reported in 2015, mostly in patients older than 25 years of age (ECDC, 2017). A recent nationwide study on neurosyphilis in the Netherlands demonstrated a mean annual incidence of 0.47 per 100,000 adults, with predominantly male subjects (Daey Ouwens et al., 2014). Host-associated factors that drive the re-emergence and spread of syphilis include high-risk sexual activity, migration and travel, economic and social conditions that limit access to health care (Fenton et al., 2008; Stamm, 2016) and substance abuse (Fenton et al., 2008). The majority of cases are reported in Human Immunodeficiency Virus (HIV) infected patients (Marra, 2009).

Decreasing reports of late neurosyphilis have been encountered with increasing reports of early neurologic involvement (Ghanem, 2010). In a recent survey of the literature of the last five years, 286 patients diagnosed with neurosyphilis were identified (Drago et al., 2016). General Paralysis of the Insane was the most common form of neurosyphilis (49%), followed by syphilitic meningitis in 22%, whereas both meningovascular and tabetic forms were found in 12% of cases. Gummatous and epileptic manifestations were rare. Focal, generalized, tonic-clonic, clonic and "jerky" seizures were reported, and in several cases the terms "epilepsy" and "seizures" were not further specified (Drago et al., 2016). The reported frequency of seizures in neurosyphilis, especially in the meningovascular form and General Paralysis of Insane, varies from 3% to 60% (Sinha et al., 2008; Daey Ouwens et al., 2019). Rarely, patients with neurosyphilis present with status epilepticus (Ances et al., 2004; Sinha et al., 2008; Kumari et al., 2015). However, most of these studies involve a small number of patients. In a recent relatively large series of 120 neurosyphilis patients, seizures were present in 25% of patients (Sinha et al., 2008). Generalized seizures were reported in half of the patients, several patients presented with focal seizures and a few patients with status epilepticus. EEGs were recorded in nearly half of the patients and revealed slowing of background activity, epileptiform discharges and / or periodic lateralized epileptiform discharges (PLEDs). Brain Computerized Tomography and MRI-findings included medial temporal lobe changes, diffuse atrophy, ischemic changes, hydrocephalus, cerebellar atrophy and meningeal enhancement.

Autoimmune encephalitis

Already in the 1960s, autoimmune mechanisms were considered to be involved in the pathogenesis of limbic encephalitis in patients with carcinoma (Corsellis, Goldberg, & Norton, 1968). The hypothesis of an autoimmune-mediated pathogenesis of paraneoplastic limbic encephalitis resulted in the discovery of specific neuronal antibodies targeting neuronal nuclear or cytoplasmic proteins, such as Hu, Yo and MA2, and intracellular synaptic proteins such as GAD65. More recently, encephalitis associated with antibodies that target cell-surface or synaptic proteins are recognized (Lancaster & Dalmau, 2012). Typical clinical presentations include seizures, memory loss, cognitive impairment, psychiatric symptoms and movement disorders. Seizures manifest frequently in the acute, inflammatory-provoked phase of many types of antibody-mediated encephalitis, ranging from 33% to 100%, depending on the antigen (Geis et al., 2019). Nearly 75% of patients with anti–NMDAR encephalitis, the most frequent AE, develop seizures (Geis et al., 2019). Temporal lobe seizures are common across all types of antibodies, while γ-aminobutyric acid receptor A and B (GABAa and GABAb) AE often present with new-onset status epilepticus and LGI1 AE with faciobrachial dystonic seizures (Bien, 2017; Spatola & Dalmau, 2017; Geis et al., 2019). Autonomic

seizures and hyponatremia also typically occur in LGI1 antibody associated encephalitis (Geis et al., 2019).

Although diffuse and focal EEG slowing are common in all forms of AE, "extreme delta brush" may serve as a specific marker for anti-NMDAR AE (Graus et al., 2016). Extreme delta brush is characterized by rhythmic delta activity at 1−3 Hz with superimposed bursts of rhythmic 20–30 Hz beta frequency activity "riding" on each delta wave (Schmitt et al., 2012). However, this pattern is only noted in a minority of patients (11%–30% of adults and 6% of children) and is associated with more severe symptoms (Van Sonderen et al., 2018). Increased signal in medial temporal lobes are the most reported MRI finding in Fluid-attenuated inversion recovery (FLAIR) and T2 Weighted Image (T2WI) sequences, but nonspecific changes are also reported. In LGI1 AE with isolated faciobrachial dystonic seizures MRI T1WI and T2WI may demonstrate basal ganglia hyperintensity. In 70% of cases with anti-NMDAR AE no abnormalities are detected. (Geis et al., 2019).

A diagnosis of definite AE can be made if T2WI MRI findings of bilateral brain abnormalities highly restricted to the medial temporal lobes are present or specific antibodies in serum or cerebrospinal fluid (CSF) are detected (Graus et al., 2016). However, antibody testing is not always readily accessible and test results can take several weeks to return. Moreover, test results cannot serve as a gold standard since absence of known antibodies does not exclude AE and positive tests do not always imply an accurate diagnosis (Graus et al., 2016). Therefore, in the initial assessment of suspected AE, thorough neurological evaluation and standard diagnostic tests (EEG, MRI-brain and CSF studies) should prevail, since early initiation of immunotherapy in AE may improve prognosis (Venkatesan & Benavides, 2015; Graus et al., 2016). Diagnostic criteria for possible AE are defined as a subacute onset of neuropsychiatric symptoms (working memory deficits, altered mental status or psychiatric symptoms) and at least one of the following: new focal CNS findings, seizures not explained by a previously known seizure disorder, CSF pleocytosis and MRI features suggestive of encephalitis (Graus et al., 2016). Alternative causes should be excluded.

Case report

A 62-year-old right handed man was referred to the department of neurology because of episodes of transient loss of consciousness for one year. His wife reported that attacks typically started with a moaning sound "resembling a baby's crying", followed by stiffening of the right arm, unresponsiveness, stiffening of the whole body and shaking during several minutes. Afterwards he spoke in his mother tongue, a language not familiar to his wife. Generally, full recovery took fifteen minutes. These episodes were often preceded by anger and followed by a slightly euphoric feeling.

His medical history mentioned 40 pack years of smoking. The patient reported therapy for gambling addiction and prior antibiotic treatment for syphilis, albeit that he could not provide details on these issues. Due to dilated cardiomyopathy and severe aortic and mitral regurgitation, he was initially treated with mitral valve and aortic valve surgical repair, followed by aortic valve prosthesis replacement with a mechanical prosthesis. Henceforward his left ventricular function recovered to normal. Cardiological workup, including implantation of an internal loop recorder, did not reveal any tachy- or bradyarrhythmias during the episodes described above. He received oral anticoagulation with a vitamin K antagonist. His personal and family history were negative with regard to seizures and febrile convulsions. Somatic and neurological physical examination did not reveal any abnormalities. Interictal EEGs showed intermittent temporal slowing, more on the left than on the right side, but no specific epileptic discharges (**figure 1**).

FLAIR and T2WI cranial MRI sequences demonstrated an increased volume of the left amygdala as well as a marked atrophy in the parietal regions (**figure 2**).

Figure 1. *Interictal EEG displaying intermittent bilateral temporal slowing, left more than right*

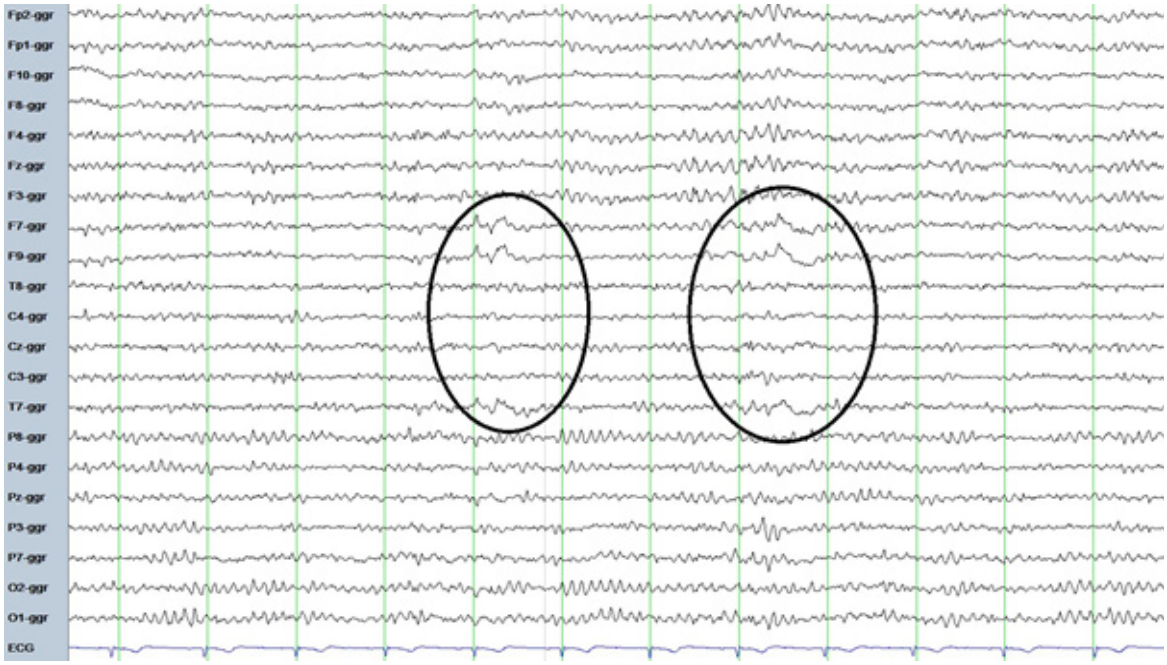
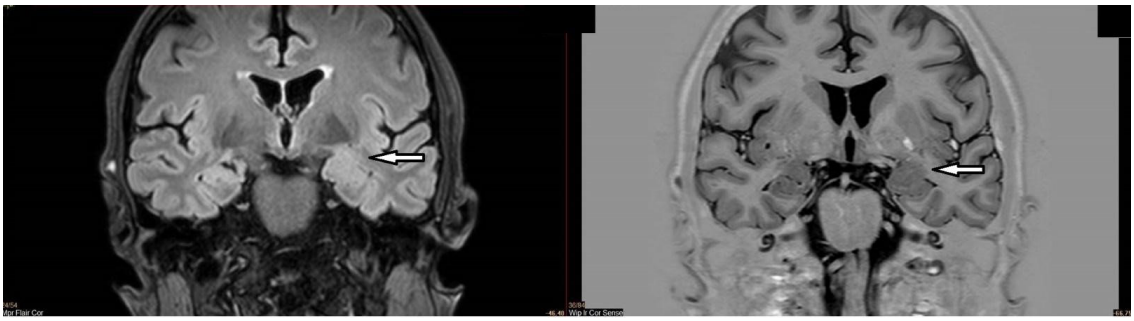


Figure 2. *Cranial MRI displaying increased volume of the left amygdala*



A specific focus of temporal lobe epilepsy was not found. Anti-neuronal antibodies, including NMDA-R, VGKC-complex, Hu, Yo, Ri, Tr, amphiphysin, CV2, Ma1/2 were not detected. Syphilis screening test was positive and the Venereal Disease Research Laboratory (VDRL) test was 1:16, demonstrating active syphilis infection. HIV-testing was not performed. CSF revealed normal cell count, protein and glucose concentration; Treponema blot: positive; Treponema pallidum haemagglutination assay: positive (1:1024) and rapid plasma reagin: positive (< 1.1).

Finally, a diagnosis of parenchymatous neurosyphilis was established, presenting with encephalitis of the mesial temporal lobe of the language dominant hemisphere and characterized by focal to bilateral tonic-clonic seizures. Treatment with intravenous penicillin 12 million units/d for 10 days and lamotrigine up to 75 mg twice daily was initiated. Two months later the patient was seizure free and at that time a second MRI showed a still hyper-voluminous left amygdala. The patient remained seizure free and, after two years, lamotrigine was tapered off. The patient was lost for follow-up serological examination and died several years later of an unrelated disease.

Discussion

In the here presented case, a history of new onset focal epilepsy, intermittent temporal slowing on interictal EEG and swelling of the left amygdala were all suggestive of a diagnosis of possible AE. In such cases, CSF analysis may be helpful in differentiating infectious and autoimmune encephalitis. A moderate lymphocytic pleocytosis (>= 5WBC/mL) is suggestive of AE (Venkatesan & Probasco, 2018), while a high number of mononuclear cells in CSF is supportive of a diagnosis of neurosyphilis (Janier et al., 2014). In both neurosyphilis and AE, CSF glucose is expected to be normal whereas protein count may be slightly elevated, and intrathecal oligoclonal bands as well as an elevated serum / CSF IgG index may be present (Janier et al., 2014; Bien & Holtkamp, 2017). However, in late parenchymatous neurosyphilis cell count and protein count may be normal (Janier et al., 2014). With respect to MRI findings of increased FLAIR / T2WI signal with highly selective medial temporal lobe involvement, it has to be stressed that these are not only associated with both AE and neurosyphilis, but also with other diseases such as Sjögren's syndrome, human herpesvirus 6 infection and rare cases of lupus (Leypoldt et al., 2015).

Syphilis, also known as "the great imitator", and neurosyphilis are both widely known to share clinical features with many diseases. Neurosyphilis mimicking AE has recently been reported in at least 24 patients (AbdeleRahma, Santamaria & Rakocevic, 2012; Budhram et al., 2017; Serrano-Cardenas et al., 2018). Nearly all patients with this condition were males with a median age of 50 years (range: 30-73 years), thus, younger than that of the presented patient. The most common clinical manifestations at admission were cognitive impairment (71%), seizures (54%) and psychiatric disorders (50%). Typical EEG findings were focal slow waves, as in our case, and periodic lateralized epileptiform discharges (Serrano-Cardenas, 2017). Currently, the pathogenic background of mesial temporal hyperintensity on brain T2WI in neurosyphilis is unknown. It has been postulated that parenchymal neurosyphilis is a more likely etiology than meningovascular neurosyphilis, since imaging abnormalities did not reflect a vascular territory and, neuropathologically, arteritis in neurosyphilis is usually seen in large and medium-sized blood vessels (Scheid et al., 2005). Unfortunately, no studies comparing MRI findings with pathological data have been performed as yet (Hama, Ishiguchi, Tuji, Miwa & Kondo, 2008).

Recently, two patients have been published with serologically confirmed neurosyphilis accompanied with positive NMDAR antibody tests in serum and CSF (Qin et al., 2017) and another patient was reported with neurosyphilis coexistent with anti-NMDAR encephalitis (Beiruti, Abu Awad, Keigler, Ryder, Shahien, 2019). In these three cases, neurosyphilis and anti-NMDAR encephalitis may have occurred simultaneously. Alternatively, it could be hypothesized that neurosyphilis triggered a secondary immunological response of anti-NMDAR-antibody production, analogous to the observation of AE following Herpes Simplex encephalitis (Qin et al., 2017). In our patient, no serum NMDAR antibodies were detected. However, these antibodies are not always discovered in serum (Bien & Holtkamp, 2017) and, unfortunately, CSF antibody tests were not performed in our patient.

Drago et al. (2016) reported in their review of the literature of 2010 - 2014 that in 60% of 286 patients reviewed, no data regarding previous primary infection neither nor data regarding prior penicillin treatment were found and in 38% of the publications information was lacking on past medical (sexual) history and treatment. Moreover, even after standard antibiotic treatment in early stage syphilis, neurosyphilis can develop in both immunocompromised and immunocompetent patients. Therefore, Drago et al. (2016) hypothesized that the number of patients who developed neurosyphilis despite an antibiotic treatment is probably underestimated. Cardiovascular syphilis was a common late manifestation of syphilis prior to the introduction of penicillin as the standard therapy for syphilis. In 1956, a diagnosis of cardiovascular syphilis was reported in 15% (202 patients) of 1,330 syphilitic patients with and without specific cardiovascular

complaints (Macfarlane, Swan & Irvine, 1956). Clinically, cardiovascular syphilis manifested with uncomplicated aortitis, aorta dilatation (124 patients), enlargement of the left ventricle (89 patients), and aorta aneurysms (31 patients), that was accompanied by aortic valve regurgitation in 15 patients. A recent autopsy case series provides evidence of the ongoing existence of cardiovascular syphilis in the antibiotic era (Roberts, Ko, & Vowels, 2009). Cardiovascular syphilis was identified as cause of death in 32% of 90 patients. At least 26% of 90 patients with cardiovascular syphilis had evidence of aortic regurgitation. It is possible that syphilis infection had resulted in dilated cardiomyopathy in the here presented patient, but the reported improvement after aortic valve replacement suggests a primary valvular disease (O'Farrell, 1987; Graciaa, Mosunjac, Workowski, Kempker, 2017). Although isolated aortic valve pathology may occur after syphilis infection, no histopathological evidence for this diagnosis was available in the here presented patient.

Conclusions

This case report reminds clinicians that neurosyphilis can share clinical and biological features with AE. In the diagnostic work-up of patients presenting with focal seizures, focal temporal EEG slowing and swelling of the amygdala, neurosyphilis should therefore always be excluded, even in those who were considered treated adequately for syphilis in the past. Further studies are required to determine which immunologic mechanisms contribute to this atypical presentation of neurosyphilis.

Ethical standards

Written informed consent was obtained from the patient's nearest relative and legal representative for publication his case history and EEG as well as MRI findings.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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