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Neurosyphilis – Still a Diagnostic and Therapeutic Challenge

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Abstract

Neurosyphilis results from an infection of the brain, meninges and/or the spinal cord and may develop in persons in whom a manifest syphilis has passed untreated. The clinical manifestations are often diverse and may present as a psychiatric disorder. This article reports two cases with neurosyphilis who were followed for 33 and 21 years respectively. In one of these cases neuropathological findings are presented. Retrospective evaluations of all medical records were performed to characterize psychiatric and other clinical features, laboratory and brain imaging findings. Both patients presented a variety of psychiatric manifestations and were initially misdiagnosed. The diagnosis was based on positive serology, cerebrospinal fluid, and neuropsychiatric symptoms and supported by brain imaging. There was a marked improvement in both patients after penicillin therapy. In the case with autopsy mixed brain pathology with atrophy of the frontotemporal areas and advanced vascular pathology was seen. These cases emphasize the importance of screening for syphilis, especially in patients with unexplained psychiatric and neurological symptoms and signs.

Keywords: Neurosyphilis; Psychiatric Symptoms; Frontotemporal Syndrome; Language Disturbances; Cerebrovascular Pathology

Introduction

The first description of paralysie générale (general paralysis of the insane) was published in 1822 [1]. However, the infectious aetiology of the disease was not described until 1913 [2] and a potential cure, fever therapy was introduced by Wagner-Jauregg in 1917 [3]. Consequently neurosyphilis became an important "paradigm-disease," and a model for other mental diseases. It became possible for the disease to be diagnosed with reasonable certainty, albeit easily misinterpreted and misdiagnosed. Neurosyphilis has been described as "the great imitator" presenting with a wide spectrum of clinical manifestations [4].

Traditionally syphilis is divided into primary, secondary, latent and tertiary stages. The primary stage classically presents with local skin ulceration at the site of inoculation, secondary syphilis with generalized skin lesions (a rush frequently seen on palms of hands and/or soles of the feet), latent stage with little or no symptoms (can last up to 30 years) and the tertiary stage with lesions such as gummas, neurological or cardiac symptoms. Neurosyphilis is often referred as tertiary syphilis,

but can occur at any time in the course of syphilis [5, 6].

Neurosyphilis, along with the cardiovascular form of syphilis, is known as tertiary syphilis. In the central nervous system (CNS), it may involve the meninges, the brain and spinal cord parenchyma and the ependymal zone, appearing in the form of either meningovascular or parenchymatous neurosyphilis (or both). There is always a component of vascular engagement, the most prominent form referred to as Heubner arteritis [7]. The variety of structural changes that appear within the CNS underlies the spectrum of clinical manifestations that may make diagnosis of neurosyphilis difficult to reach. The vascular affection is specifically pertinent in this report.

Recognized as a sexually transmitted disease, syphilis appeared in Sweden in the late 15th century and ravaged the country in the following centuries, [8]. Seventy years ago a comparatively large proportion of beds at the mental hospital in Lund were occupied by patients with syphilis, and about 10 % of all deaths at the hospital were caused by the disease from 1930 to 1949. A malignant course was predominant, often resulting in death within three months to two years after admission. The diagnosis has become relatively unusual in Sweden and tertiary manifestations are rare. In 2010 the Swedish Institute of Infectious Disease Control (SBL) reported 199 new cases of syphilis, in 75 % of these the detection was based on both clinical and laboratory diagnostics. Primary syphilis was found in 62 cases (31 %), secondary in 27 cases (14 %) and in 46 cases (33 %) an early or late latent phase of syphilis was found. The remaining 64 cases (32 %) were diagnosed as an unspecified stage of the disease. The incidence of syphilis in Sweden was 2, 0 /100 000 in 2011, with a marked increase since 2000. In 2013, 275 new cases were reported, an increase of 37 % compared with the year 2012 [9].

Our aim of this paper was to report two middle-aged male patients suffering from tertiary syphilis who were referred to the Psychiatric and the Psychogeriatric departments in Lund, Sweden, for diagnosis and treatment of an unexplained mental disorder with organic traits. The patients were treated successfully with penicillin and regained full working capacity. They were followed-up clinically for 33 and 21 years respectively. The diagnosis was based on clinical symptoms and supported by positive cerebrospinal fluid (CSF), serological data and brain imaging. In one of the cases the diagnosis was also confirmed by neuropathological examination. The patients were examined according to the routine clinical care.

Case 1

A 38-year old man, with no prior diagnosis or treatment of mental illness sought help from his local general practitioner (GP). There was no heredity for dementia or other neuropsychiatric disease. He had slight dyslexia and had suffered a single epileptic seizure of unknown cause at the age of 6. At the age of 23 he suffered a brain concussion related to a traffic accident. In all other aspects he had been a healthy person, working full-time with no sick leave for the last 15 years. Previously a rather shy and quiet person, at the age of 38 his behaviour slowly changed and he started to talk loudly to himself when he was alone. He was aware of his strange behaviour but unable to control the voluble flow of words and associations. When the condition worsened he contacted his GP, who referred him to the general hospital. The preliminary diagnosis at the acute medical ward was mania with psychotic symptoms and the patient was referred to the Psychiatric department. At admittance he seemed exhausted; he talked incessantly both day and night, was sometimes incoherent and pleaded for help to calm down and to "shut off his over-talking". He was lucid and fully oriented but restless with a slight increase of mood tone. No major neurological abnormalities were observed but there was a slight dysarthria with a nasal twang. His mimic movements were sparse, with episodic paramimic twitchings (uncontrolled muscle movements in the face). His hand movements were fumbling and his handwriting unsteady. The preliminary diagnosis was "manic-like organic mental syndrome" and the diagnostic process leant towards an infectious cause (rabies was suggested), a metabolic disease, an inflammatory or a tumorous process. Electroencephalogram (EEG) showed a general non-focalized slowing without focal abnormalities. The body temperature fluctuated between 37 and 38 centigrades. A computerized tomography (CT) could not be completed because of severe agitation. CSF analysis showed monocytic pleocytosis and a slightly increased protein level. The IgG-index was 1, 00 with multiple bands in the gamma region. There were no indications of metabolic or toxic factors involved. On the fifth day a positive Wasserman reaction (WR) was noted, later confirmed with a positive fluorescent treponemal antibody absorption test (FTA-ABS) in blood. Repeated CSF analyses supported the diagnosis of tertiary neurosyphilis and additional clinical information indicated that the primary infection had occurred 8-10 years earlier.

He was treated with procaine benzylpenicillin for three weeks (intramuscular, 600.000 IE daily) after premedication with prednisolone. This resulted in an exacerbation of the clinical somatic symptoms, interpreted as a severe Jarish-Herxheimer reaction [10]. The patient showed ataxia, astasia, left-sided ptosis, urinary retention, fever and headache for several weeks. The patient slowly improved and was discharged after five months of hospital care. At a follow-up one year later he reported good physical and mental health, and was almost back to his premorbid condition. He was fully oriented with a fairly normal speed of speech and demonstrated full working capacity. The positive report was confirmed by the patient's close relatives. The patient was followed up with CSF analysis and measurements of regional cerebral blood flow (CBF with two-dimensional 133-Xenon-inhalation technique) on several occasions [11].The results showed a global blood flow level

within the lower part of the normal zone with slight regional reductions frontally. A Single Photon Emission Computerized Tomography (SPECT) eleven years after the antibiotic therapy showed moderate focal reductions within right frontal and left temporal cortical areas (Figure 1).

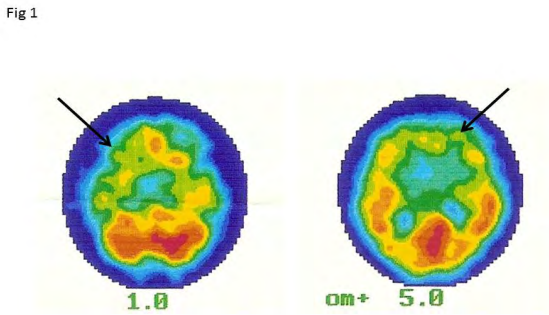

Figure 1. Tomographic rCBF measurement (Ceretec-SPECT) eleven years after diagnosis, showed moderate focal reductions within left temporal (left arrow) and right frontal cortical (right arrow) areas.

The patient worked full-time in his profession, which was the same as prior to the disease, and he retired at the age of 63 years. At this age he was still living at home with normal daily abilities and social contacts. Three years later a slowly progressive mental deterioration was observed and he moved to a home for the aged. At the age of 69 he was fully oriented, but with a slight memory failure for recent events. He showed a slight dysarthria, logorrhea and hyperorality. Hypomimia and echolalia, components of the PEMA syndrome (palilalia, echolalia, mutism and amimia) were also noted. Both the PEMA syndrome and hyperorality can be seen in patients with Frontotemporal dementia (FTD) [12,13]. His gait gradually became slow and staggering, with need for support. The emotional contact with his nearest remained relatively well preserved. He died at the age of 71 years, 33 years after the established diagnosis of neurosyphilis and subsequent treatment.

The immediate cause of death was a massive aspiration. The autopsy with detailed neuropathological examination showed bilateral atrophy of the frontal poles and atrophy of the frontal and temporal lobes. Due to the finding of gliosis and reduction of nerve cells in many cortical areas, along with a lack of detectable specific protein pathology, the morphological alterations were judged to be associated with the known previous syphilis, and thus of post-infectious type [7]. The parietal and occipital lobes were preserved as were the substantia nigra and locus coeruleus. The neuropathological investigation also showed a particular advanced atheromatosis and arteriosclerosis of the basal vessels most marked in the posterior circulation i.e. the vertebral and basilar vessels. Even more prominent was a stenosing arteriosclerosis of intracerebral vessels of extraordinary type, judged to be the late effects of an endarteritis of the primary infectious disease. Bilateral lacunar infarctions were found within the striatum, topographically related to the site where the most severely stenosed parenchymal vessels were found (Figure 2).

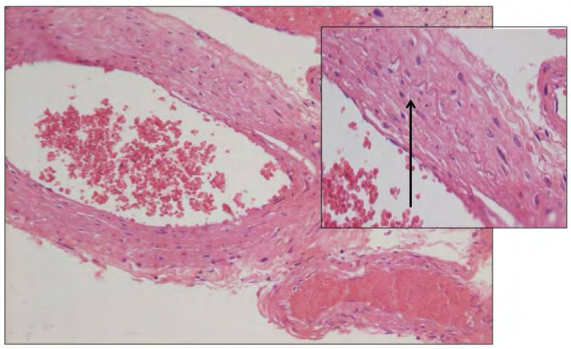

Figure 2. Microphotograph of a small meningeal artery exhibiting the same characteristic traits as does numerous vessels within the brain of case 1. As a result of a previous endarteritis, the intima and media is thickened by a proliferation of fibroblasts, collagen and smooth muscle cells (enlarged in inset photo), while there is no current inflammation. Hematoxylin-eosin staining.

This patient thus presented a rather dramatic organic brain syndrome eight to ten years after the primary infection. The clinical diagnosis was confirmed by traditional analyses of CSF and blood. The treatment with penicillin was successful, with almost full recovery after one year. This normalization was followed by thirty years of normal mental and physical health until a second period of mental deterioration started, three years before death.

Case 2

Accompanied by a colleague, a 44 year old academic teacher contacted his GP. The patient suffered hepatitis type B fifteen years earlier, but was otherwise in good physical health. There was no heredity for dementia or other neuropsychiatric disease. The premorbid personality was described as normal with a pleasant, warm and empathic attitude towards his family and other people.

During the four months prior to seeking help his personality and behaviour were gradually changing. He became emotionally apathetic and detached. A general psychomotor retardation, increased fatigue, memory failure and irritability were also seen. Alcohol problems and drug addiction were denied. The physical examination was described as normal, although the neurological investigation showed suspected lively tendon reflexes bilaterally. An organic brain disease was suspected and the patient was referred to the Psychogeriatric department. A laboratory screening was performed including WR. CT scan and MRI showed a slight dilatation of the lateral and third ventricles and EEG showed a general diffuse slowing without focal or epileptogenic changes. A second MRI, two weeks later, showed a widened fissure Sylvii and ventricles and T2 hyper-

intensities indicating a previous inflammatory process. An initial CBF-examination (two- dimensional 133-Xenon-inhalation technique) showed a moderately subnormal flow level and slight to moderate flow reductions in multiple regions including right frontotemporal and parietal regions and the left dorsal parietal region (Figure 3).

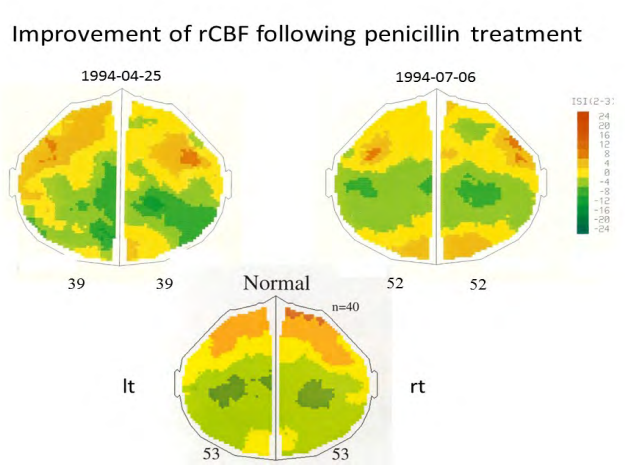

Figure 3. Vertex projections of the cortical blood flow distribution using the 2-D 133-Xenon inhalation technique [11]. The two upper panels show the results from the patient. As a comparison the lower picture shows data from a normal reference group. The mean hemispheric cortical blood flow values (ISI 2-3-parameter) are shown in the lower part of each panel. The regional values are shown as color coded percentages of the hemispheric mean.

The initial examination (1994-04-25) showed a slightly subnormal flow level and slight to moderate focal reductions in right frontotemporal and parietal regions and in left dorsal parietal areas. A follow up examination eight weeks after treatment (1994-07-06) showed an evident normalization of both the general blood flow level (34 % increase) and the regional pathology. Only a slight blood flow reduction in a right prefrontal area persists.

The patient was referred to the Neurologic department. He showed a lack of focus and was slightly disoriented as to the date and day of the week. The examination showed lively palmomental reflexes, lively tendon reflexes, pouting, an undecided Babinski sign but normal muscular tension and sensibility. CSF showed an increased number of mononuclear cells strongly indicating an infectious disease. The patient was sometimes agitated, lacking insight and repeatedly left the hospital in a state of confusion. Compulsory care was motivated for a short period and the patient was referred to the psychiatric department for further examination and treatment. During the following week his gait was slow and staggering. His answers were terse and he stared with an intense gaze which was sometimes accompanied by an inadequate, disinhibited smile. He partly lacked insight, but admitted that his memory had deteriorated during the last six months. His memory was fragmented and fluctuating, he showed lack of concentration and was irritable. The tentative aetiology was an infectious or inflammatory brain disease. Three weeks after the first referral, syphilis serology presented a positive TPHA-test and WR resulting in treatment with benzylpenicillin. The patient soon reacted with fever and exanthema and prednisolone was added against the expected Herxheimer reaction [14]. The patient gradually improved but showed signs of marked depression. Ten days after the treatment was initiated, an exanthema appeared on the chest and the penicillin was replaced with broad spectrum antibiotics. The patient readily agreed to stay in hospital. He often lay on his bed, smoking carelessly and stubbing his cigarettes out on the bedside table. This regressive behaviour was less pronounced when he visited his family at home. Eventually his behaviour and memory improved, as did the serological parameters. After eight weeks of penicillin treatment a follow up CBF examination, showed a clear normalization with less pronounced focal pathology and a normal general blood flow level (Figure 3).

The patient was discharged three and a half months after his first referral. His wife antedated the clinical onset of the disease to about ten months earlier, reporting tiredness, emotional changes and memory failure as being the initial symptoms. At discharge the patient showed a normal emotional contact. He was lucid, fully oriented with insight and self-critical comments on his previous behaviour and was able to resume his previous profession.

He was followed-up every second year for ten years with blood and CSF examinations. MR three years after admission, showed ventricles with normal width, and no other brain pathology.

At a follow up after ten years the patient, still working full time in his previous profession, described himself as somewhat tired but otherwise fully recovered. At the age of 62 the patient retired, but was still in good health. At a recent follow-up, 21 years after the first referral, the patient remained in good physical and mental health.

Discussion

These two case reports illustrate the importance of considering the diagnosis of neurosyphilis in patients with mental illness, especially when presenting a clinical picture with atypical and unexpected organic features. Several alternative diagnoses were suggested before neurosyphilis was considered. In the first diagnostic round mania, bipolar affective disorder, delirium, schizophrenia-like psychosis, cerebrovascular disease, FTD and even rabies were suggested. In our experience, patients with neurosyphilis may present a large variety of clinical features, including psychiatric symptoms and neurological signs and may therefore remain undiagnosed, thus delaying the treatment that has been available since the introduction of

pyrexia therapy in 1917 and penicillin and other antibiotics in the mid forties' [15].

The outcome depends on early diagnosis and efficient treatment. The clinical follow-up has to consider aggravation with the possibility of a severe Herxheimer reaction in spite of the protective umbrella based on the combination of antibiotics and corticosteroids.

Neurosyphilis remains a diagnostic and therapeutic challenge. The aim of this paper was to elucidate the clinical outcome of neurosyphilis in a long time perspective. A particular feature, demonstrated in case 1, is that of severe and widespread vascular sclerotic pathology, judged to be a sequel of the syphilitic endarteritis [16].

It is important that each new generation of psychiatrists takes on the challenge of diagnosis and treatment of paralysie générale, although there are a limited number of recent publications on these clinical issues. Our conclusion is that the recognition of neuropsychiatric features and the use of routine screening tests for syphilis are necessary in this process. The good news is that even patients with a dramatic cognitive deterioration and deranged behaviour may well respond to traditional antibiotic treatment with a remarkable and lasting physical and mental recovery.

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