

# Psychological/Cognitive Aspects in Untreated Neurosyphilis and Treatment with Penicillin G (A Case Study)

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Received: February 25, 2012

Accepted: April 9, 2012

Published: June 1, 2012

doi:10.5539/ijps.v4n2p210

URL: <http://dx.doi.org/10.5539/ijps.v4n2p210>

## Abstract

Active neurosyphilis is uncommon after the introduction of penicillin. We evaluated the pathology of a case of untreated neurosyphilis that was diagnosed as a manic episode. Examinations were performed before and after high-dose penicillin G treatment. Evaluations included the Mini-Mental State Examination (MMSE), the Neurobehavioral Cognitive Status Examination (Cognistat), the Bender Gestalt Test, an electroencephalogram, and brain magnetic resonance imaging/angiography. The most obvious improvements after treatment with penicillin G were the constructive ability and the ability to draw two- and three-dimensional designs. A paradoxical deterioration in several items on the Cognistat after treatment suggested an impairment in working memory. The clinical and psychological abnormalities observed in this case were speculated to be due to disturbed visual cognition related to encephalitis and impaired working memory related to temporofrontal lobe pathology. Current diagnostic tools were useful for precisely diagnosing and assessing the prognosis of older patients with late-onset mania

**Keywords:** neurosyphilis, cognition, penicillin G, mania, psychological tests

## 1. Introduction

It is uncommon to find active neurosyphilis after the introduction of penicillin treatment (Musher, 1991). Several studies have indicated abnormalities in psychological aspects of patients with neurosyphilis (Friedrich, Geusau, Greisenegger, Ossege, & Aigner, 2009; Hirasawa et al., 1994; Luo et al., 2008; Roberts & Emsley, 1995; Spiegel & Qureshi, 2010); however, the effects of penicillin treatment have not been readily assessed with recent psychological evaluation tools. We studied an untreated case of neurosyphilis that presented with a manic episode. We treated the case with high-dose penicillin G (an effective antibiotic in neurosyphilis). We evaluated psychological aspects before and after penicillin G therapy with the Mini-Mental State Examination (MMSE), the Neurobehavioral Cognitive Status Examination (Cognistat) (Kiernan, Mueller, Langston, & Van Dyke, 1987), and the Bender Gestalt Test; the original version that consists of nine figures (Bender, 1938) with scoring based on accuracy and other characteristics. In addition, we performed physiological measurements with an electroencephalogram (EEG) recording and brain magnetic resonance (MRI) imaging to examine functional and morphological abnormality in the brain, respectively.

## 2. Case Presentation

The case was a 65-year-old, right-handed male with 9 years of primary and junior high school education. He worked in a supermarket until he was 60 years old. He had not married. He had no past history of neurologic or psychiatric diseases. Prior to admission to the hospital, at midnight, the patient refused to pay his taxi fee and struck the taxi driver. When accosted by the police, the patient did not provide a reason for this behavior and presented with manic delusions (he started the company; he was a friend of the prime minister, etc). As a result of an interview with psychiatrists, the patient was temporarily diagnosed with mania, because his behavior fit several diagnostic criteria for a manic episode based on the International Classification of Disease version 10 (ICD-10). These symptoms included an irritable mood, grandiosity, extreme talkativeness, and psychomotor agitation. Therefore, mania was considered, despite of uncertainty in the duration of these abnormal symptoms and the inability to exclude involvement of an organic disease. Pharmacological therapy was started with 600

mg/d valproic acid, 3 mg/d risperidone, and 50 mg/d zotepine for mood stabilization, and benzodiazepines with an anti-histaminergic agent for sleep disturbance. Five days after the initial treatment, the patient was transferred to a psychiatric ward in the psychiatric hospital for further treatment. In this report, the day of admission to the ward was designated as day one. The patient showed periodic aggression or somnolence and grandiose delusion, despite continuation of the pharmacological treatment. The patient also exhibited amnesia for the several days prior to the incident with the taxi driver, and he did not have a clear memory of the day of the event; his explanation seemed to be confabulation. The patient's facial expression appeared to lose muscle tone and both eyes showed slight ptosis. Both pupils were round, but constricted with light. The examination schedule is illustrated in Figure 1.

Rapid plasma regain (RPR) titer and Treponema pallidum hemagglutination assay (TPHA) were performed on the patient's serum and cerebrospinal fluid (CSF) to evaluate current or past infection of syphilis (Table 1). Total protein concentration and cell count were elevated in the CSF. The Nonne-Apelt and Pandy reactions (traditional tests used for neurosyphilis) in the CSF were positive. There was no other abnormality in laboratory data except slightly low serum protein levels. The patient was diagnosed with neurosyphilis from these results. Treatment with intravenous penicillin G (4 million units every 4 h) was administered for 2 weeks, from day 16 through day 30 (Figure 1). After this treatment, the patient's aggression and somnolence diminished gradually, but the peculiar facial expression and ptosis did not change. The grandiose content of speech also declined, and the patient began to speak in realistic terms. In examinations, the RPR and TPHA test values were reduced in both the serum and CSF; protein levels and cell numbers were normalized, and the Nonne-Apelt reaction, but not Pandy reaction, became negative for the CSF (Table 1). The patient was discharged on day 100 after admission.

An EEG performed before the penicillin G treatment showed slow waves, but not epileptic discharges (Figure 2A). After treatment, the EEG changed to a normal pattern of mixed alfa-waves and fast waves (Figure 2B). On day 44, MRI and magnetic resonance angiography (MRA) were performed. MRI showed atrophy in the temporal lobe, including the hippocampus (Figure 3A). But no space-occupying lesion, like neurosyphilitic gumma was noted. MRA indicated a narrowing of cerebral arteries (Figure 3B). Cognitive changes that followed the penicillin G treatment were evaluated with MMSE, the Cognistat, and Bender Gestalt Test. The MMSE score was elevated from 16/30 to 21/30. Results in the Bender Gestalt Test were improved after the penicillin G treatment; 84 to 51 in total scores. Although the Cognistat scores generally improved, changes in individual items were profound (Figure 4). The most obvious improvement was the constructive ability. Results in drawing tests indicated improvements in performing copies of two-dimensional and three-dimensional perspective designs (Figure 5).

Table 1. Results in blood and serum examinations before and after penicillin G treatment

		RPR test	TPHA test		Protein (mg/dl)	Glucose (mg/dl)	Chloride (mEq/l)	Lymphocytes (mm <sup>3</sup> )	Neutrophil (mm <sup>3</sup> )	Nonne -Apelt reaction	Pandy reaction
Normal ranges	Serum	< 1	< 80								
	CRF	< 1	< 10	CRF	15 - 45	45 - 80	120 - 130	< 5	0	(-)	(-)
Day 9 of admission	Serum	< 128	< 20480								
	CRF	< 2	< 5120	CRF	79	65	122	12	1	(+)	(+)
Day 44 of admission	Serum	< 64	< 10240								
	CRF	1	< 2560	CRF	57	66	120	3	1	(-)	(+)

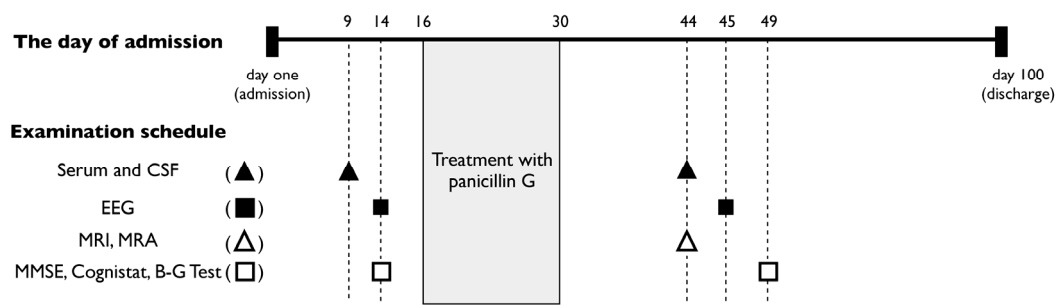


Figure 1. Illustration of the timing of the penicillin G treatment and examinations performed after admission to the hospital. B-G Test, the Bender Gestalt Test

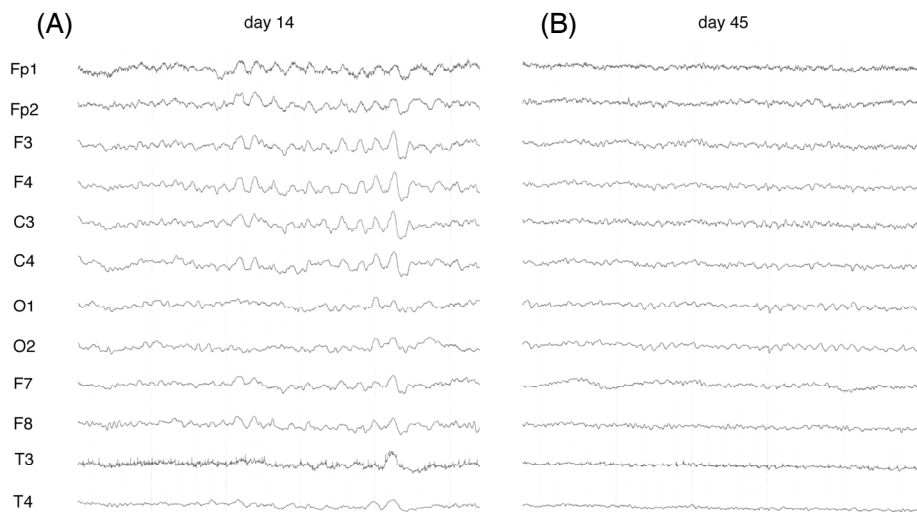


Figure 2. EEG patterns on day 14 (A) and day 45 (B)

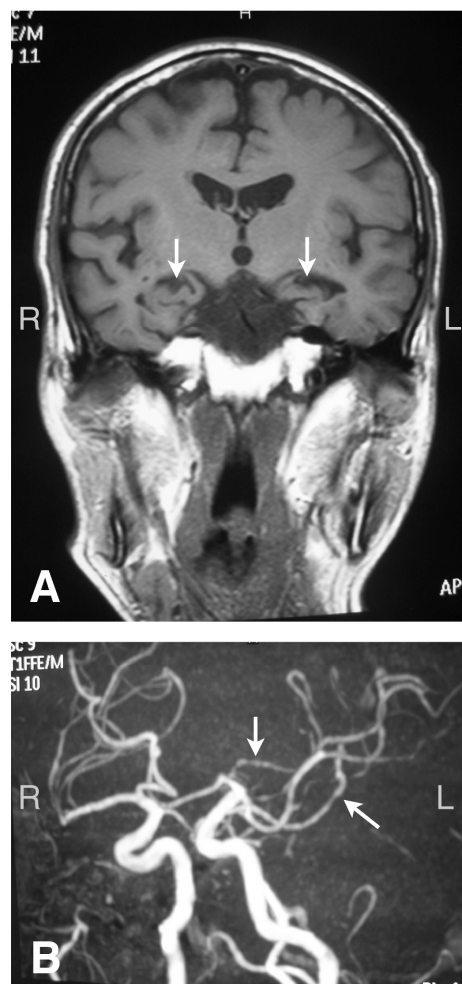


Figure 3. Images show a coronal section (A) of T1-weighted MRI, and MRA (B). Arrows indicate the hippocampal atrophy (A) and the narrowing of arteries (B)

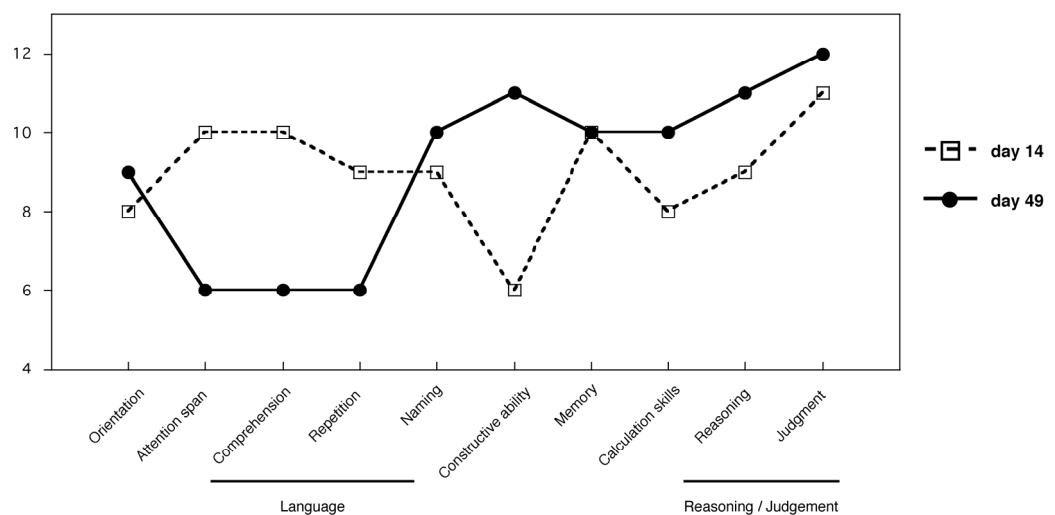


Figure 4. Cognistat results before (day 14, open bars) and after penicillin G treatment (day 49, hatched bars). Score indications: > 9, normal function; 8, mild impairment; 7, moderate impairment; 6, severe impairment

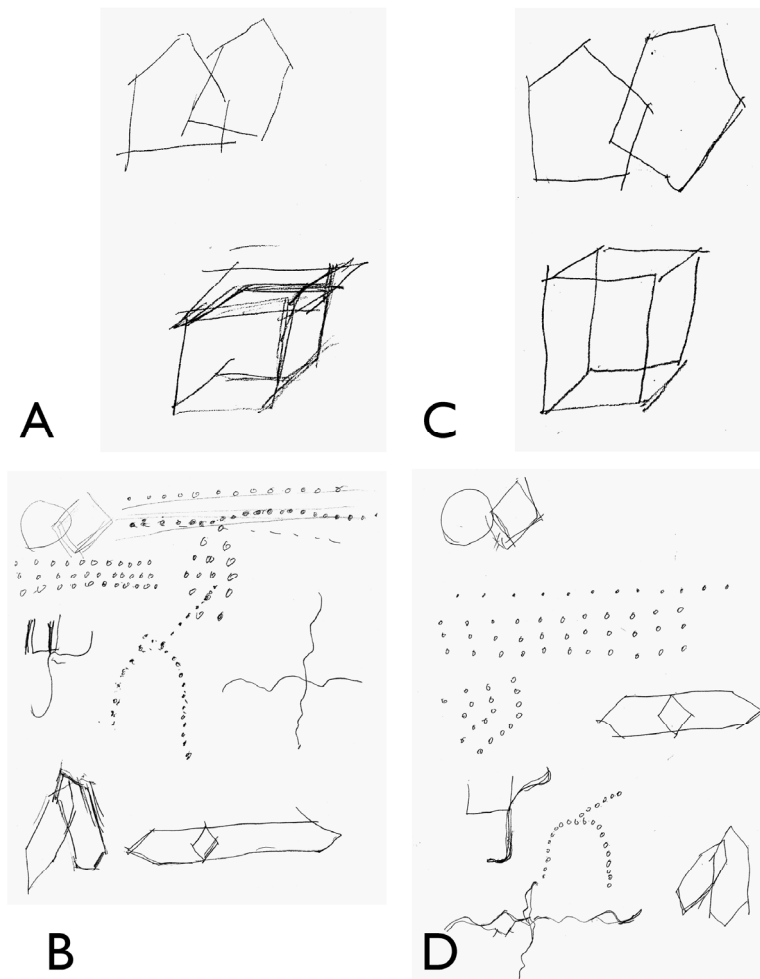


Figure 5. Results of the MMSE drawing tests (A, C) and Bender Gestalt Tests (B, D). A and B were obtained before penicillin G treatment (day14), and C and D were obtained after penicillin G treatment (day 49)

### 3. Discussion

The patient had not been treated for syphilis until the present treatment, and the duration of infection was unknown. However, the syphilis infection appeared to involve the CNS, based on the late-onset psychiatric aberration without previous history, abnormal neurological signs, such as the facial expression and ptosis, suggestive of cranial nerve palsy, and positive syphilic reactions in the CSF. From a clinical and pathophysiological perspective, this case is considered late-onset mania due to parenchymatous neurosyphilis. It can be diagnosed as the organic manic disorder in ICD-10.

The high-dose intravenous penicillin G therapy effectively alleviated the patient's abnormal psychiatric symptoms, and it improved the RPR titer and TPHA results from serology and lumbar puncture. This observation was consistent with a previous finding that serum antibody tests for cardiolipin, like the RPR titer (Musher, 2008) or the Venereal Disease Research Laboratory (VDRL) test (Roberts & Emsley, 1995), could indicate *treponema pallidum* activity. The slow wave activity identified by EEG before treatment was consistent with previous findings in active neurosyphilis (Luo et al., 2008). An alleviation of encephalitis with penicillin G treatment was suggested by reduced protein concentrations and lymphocyte numbers in the CSF and by the normalization of EEG patterns.

Cerebral atrophy has frequently been found in neurosyphilis (Brightbill, Ihmeidan, Post, Berger, & Katz, 1995; Holland, Perrett, & Mills, 1986; Kodama et al., 2000; Luo et al., 2008; Peng et al., 2008; Yu et al., 2010; Zifko et al., 1996). Our finding of temporal lobe atrophy was also consistent with previous findings (Kodama et al., 2000;

Yu et al., 2010). The MRA showed mild vascular pathology, including stenosis of cerebral arteries; this may be another pathology of neurosyphilis; infarction or arteritis (Brightbill et al., 1995; Holland et al., 1986; Luo et al., 2008; Peng et al., 2008; Smith & Anderson, 2000).

The general improvement we noted in psychological tests, including the MMSE, agreed with previous reports (Friedrich et al., 2009; Hirasawa et al., 1994; Luo et al., 2008). However, results in the Cognistat appeared to reflect profound changes in cognitive function. The majority of Cognistat items improved after penicillin G treatment. In particular, scores in constructive ability were markedly elevated. Results in drawing tests also supported an improvement of visual cognition and a normalization of the stereognostic sense. The drawing tests of MMSE showed an improvement of perspective drawing of a cube. The Bender Gestalt Test measures perceptual motor skills that indicate neurological intactness or brain damage. The present result of the Bender Gestalt Test showed a decrement of errors in performance, i.e., in arrangement of dots or positioning of figures. We interpreted this to indicate that the improved function was induced by the alleviation of encephalitis. Aberrant neuroinflammation is a candidate cause of brain pathology in bipolar disorders (Rapoport, Basselin, Kim, & Rao, 2009). Evidence of encephalitis or vascularitis in MRA images implied that abnormal neuroinflammation may have been involved in producing the manic state in this neurosyphilis case. In contrast, high scores in the Cognistat memory item indicated intact delayed recall and normal scores in naming implied no anterograde amnesia or aphasia.

In contrast to the other improvements, scores were reduced in attention span, based on a digit span task, word comprehension, and word repetition. This deterioration suggested an impairment of short-term memory or working memory, rather than long-term memory. The MRI findings of atrophy in the temporal lobe suggested pathological conditions in this region. Both temporal lobe pathology and frontal lobe dysfunction has been proposed to be involved in working memory deficit (Faraco et al., 2011). Hence, invasion of syphilis or augmented affects during penicillin therapy might have caused substantial temporal damage or temporofrontal dysfunction that resulted in the cognitive dysfunction observed after the alleviation of encephalitis. Interestingly, accumulating evidence has shown that cognitive dysfunction, including impaired working memory, has persisted in patients with manic bipolar patients after remission (Bora, Yucel, & Pantelis, 2009).

In summary, we reported a case of late-onset mania that emerged in a patient with untreated neurosyphilis, and treatment with penicillin G. The successful clinical outcome supported the premise that abnormal mental states in neurosyphilis were treatable with antibiotics. However, psychological examinations performed with the treatment revealed both anticipated and paradoxical changes in cognitive function. These findings indicated a remarkable improvement of visual cognition, an intact long-term memory, and a deterioration in working memory. These results might imply that a reversal of functional or organic brain pathology occurred during penicillin therapy. The improved cognition appeared to be related to alleviated encephalitis that accompanied a normalization of the EEG. The deteriorated cognition might be related to temporofrontal dysfunction caused by neurosyphilis, as suggested in the MRI. Hence, we speculated that abnormal neuroinflammation and temporofrontal dysfunction were both involved in this neurosyphilis case. These symptoms may be applicable to the pathology of non-organic bipolar disorders. Finally, this case investigation demonstrated that current diagnostic tools were useful for precisely diagnosing and assessing the prognosis of late-onset psychosis.

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