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Neurosyphilis Mimicking Herpes Simplex Encephalitis on Magnetic Resonance Imaging: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEFG 1,2 Arturs Balodis
BCDEF 1,3 Dagnija Grabovska
BDEF 4 Ramona Valante
BCD 4 Arina Novasa
DE 1,2 Uldis Raits

1 Institute of Diagnostic Radiology, Pauls Stradins Clinical University Hospital, Riga, Latvia
2 Department of Radiology, Riga Stradins University, Riga, Latvia
3 Department of Radiology, Latvian University, Riga, Latvia
4 Department of Neurology, Pauls Stradins Clinical University Hospital, Riga, Latvia

Corresponding Author: Arturs Balodis, e-mail: arturs.balodis7@gmail.com
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Patient: Male, 49-year-old
Final Diagnosis: Neurosyphilis
Symptoms: Behavioral disturbance • confusion • disorientation • hallucinations • memory loss
Medication: Penicillin G • acyclovir
Clinical Procedure: Lumbar puncture
Specialty: Infectious Diseases • Neurology • Radiology

Objective: Rare disease

Background: Neurosyphilis is a central nervous system infection caused by *Treponema pallidum*, that can develop at any time after the initial infection. The clinical signs of neurosyphilis are very variable, as well as its radiological features, and it is a diagnostic challenge. Knowledge of clinical symptoms and correct laboratory diagnostics, combined with routine radiological examination and additional diagnostic tools, such as high-resolution, three-dimensional FLAIR sequence, T2-weighted, and T1-weighted contrast-enhanced magnetic resonance imaging (MRI) are key to making an accurate diagnosis of neurosyphilis.

Case Report: We present the clinical case of a patient who presented a 1-year history of vague clinical symptoms and was misdiagnosed with herpes simplex virus (HSV) encephalitis. Initial head MRI revealed extensive cerebral white matter lesions with cortical contrast enhancement, mainly of anterior and medial parts of the left temporal lobe, as typically seen in HSV encephalitis. Empirical therapy with acyclovir was started until a diagnosis of syphilis was confirmed with laboratory findings. Later, the therapy was changed to penicillin G. The patient's condition improved after receiving targeted treatment. A control MRI scan was performed, and previously detected changes in the brain had decreased significantly.

Conclusions: MRI is the imaging of choice to support the diagnosis of neurosyphilis. Our findings suggest that neuroimaging can play an important role in indicating suspicion of syphilitic encephalitis. Enhancement of the anterior and medial parts of the temporal lobe is an atypical imaging finding, and it can simulate an infection with HSV. Early treatment is critical to a positive outcome.

Keywords: Herpes Simplex Virus (HSV) Encephalitis • Neurosyphilis • Atypical Imaging Finding • Magnetic Resonance Imaging

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/936127

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Background

Syphilis is a treatable, systemic disease caused by a bacterium called *Treponema pallidum* (a motile gram-negative spirochaete).[1] The incidence of syphilis has risen significantly in recent years, and according to the WHO systematic review and meta-analysis of global syphilis prevalence, the number of new cases of syphilis infection worldwide reached 7.1 million in 2020 [2]. The pathogenesis of syphilis is not yet fully understood and its heterogeneous clinical symptoms can sometimes make diagnosis very difficult [1]. Therefore, despite the fact that effective preventive and treatment options are available, syphilis remains a global health problem causing high morbidity.

"Neurosyphilis" refers to a central nervous system (CNS) infection caused by *Treponema pallidum* that can develop at any time after the initial infection [3]. Before antibiotics were discovered, neurosyphilis prevalence was described as approximately 25-35% among all syphilis patients. Nowadays neurosyphilis is more prevalent among patients with human immunodeficiency virus (HIV) and among individuals at high risk for HIV. Neurosyphilis is 2 times more common in men than in women, and the risk of neurosyphilis is 2-3 times higher in White than in African Americans [4].

Since neurosyphilis can present with a variety of symptoms and mimic a many neurological conditions, it is crucial to be highly suspicious of this diagnosis. Knowledge of clinical symptoms and correct laboratory diagnostics combined with the radiological examination is key to making an accurate diagnosis of neurosyphilis.

In the present article, we describe the case of a patient who initially presented with non-specific clinical symptoms and eventually was diagnosed with neurosyphilis. The initial head magnetic resonance imaging (MRI) revealed radiographic features of acute encephalitis, which are indistinguishable from herpes simplex encephalitis. Initial diagnosis and treatment were imprecise until a definitive laboratory diagnosis of syphilis was confirmed. This case report demonstrates the path for diagnosing neurosyphilis, emphasizes the importance of a multidisciplinary approach to patient care, and discusses radiological features in patients with the condition.

Case Report

A 49-year-old man presented with a 1-year history of behavioral changes. The patient's family noted progressive memory loss and confusion. Last month there was a progression of symptoms and the patient became more disoriented and had hallucinations, so he was referred to the hospital. There

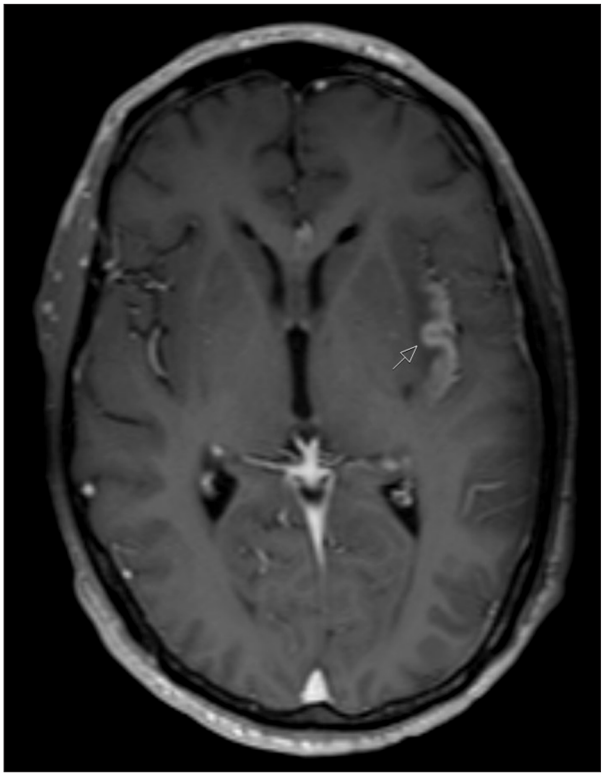

Figure 1. First axial contrast-enhanced T1-weighted magnetic resonance imaging (MRI), showing enhancement along the left insular lobe, particularly of the insular cortex (arrow).

was no relevant past medical history and no recent travel. It is known that the patient had an alcohol addiction and he regularly consumed alcohol. A blood test was unremarkable on admission. The patient was disoriented in time and space. A neurological examination revealed light motor and sensory aphasia, but the rest of the neurological examination was unremarkable. Lumbar puncture showed pleocytosis – 12 uL (ref.int. 0-5 cells) 25% granulocytes and 75% lymphocytes, and there was a high protein level (1.737g/L) in CSF.

Initial head computed tomography (CT) scan showed a possible tumor mass in the left temporal lobe. Head magnetic resonance imaging (MRI) was indicated for further investigation.

The first MRI scan on contrast-enhanced T1-weighted sequence axial showed enhancement along the left insular lobe, particularly of the insular cortex (**Figure 1**) and hyperintense signal areas diffusely in the white matter in the left temporal lobe, with cortical contrast enhancement along with the lateral and anterior-medial-basal parts of the left temporal lobe (**Figure 2**). Similar, but less prominent changes, were seen in the right temporal lobe.

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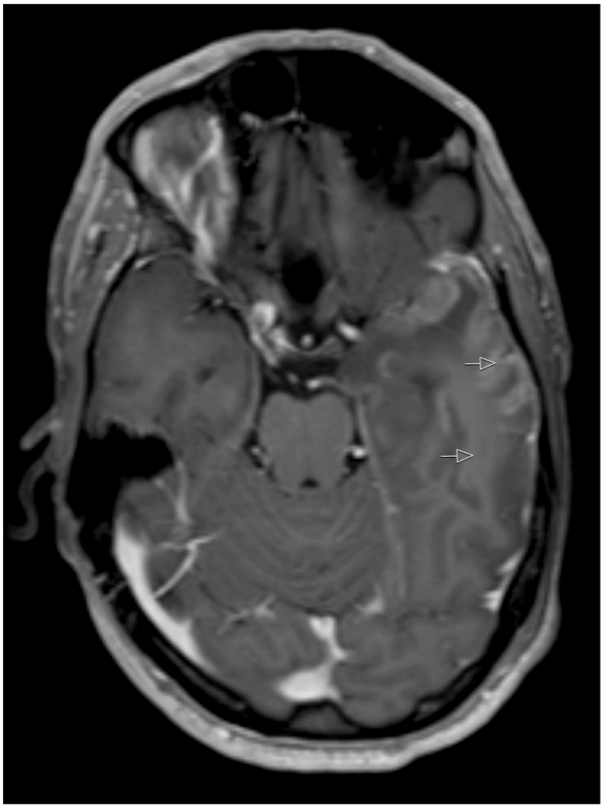

Figure 2. First axial contrast-enhanced T1-weighted MRI, showing hyperintense signal areas diffusely in the white matter in the left temporal lobe, with cortical contrast enhancement along the lateral and anterior-medial-basal parts of the left temporal lobe (arrows). Similar but less prominent changes are seen in the right temporal lobe. The interruption of the anatomical continuity of the lateral aspect of the right temporal lobe is an artifact.

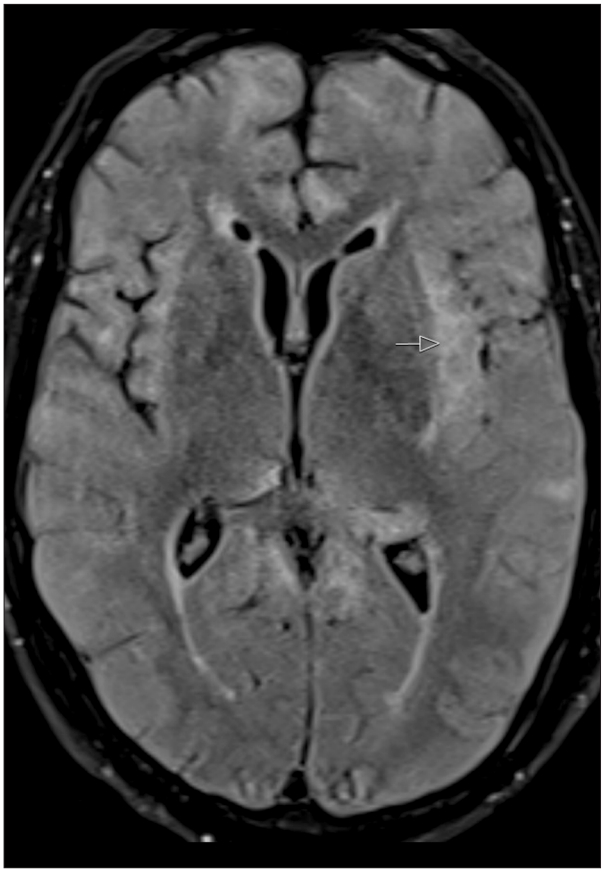

Figure 3. First axial FLAIR-weighted MRI showing hyperintense signal areas along the left insular lobe (arrow). Similar but less prominent changes are seen in the right insular lobe. A hyperintense signal is seen in the cingulate gyrus, bilaterally, as well as in frontal poles, more intense on the right.

On FLAIR-weighted sequence, axial hyperintense signal areas were detected along the left insular lobe. Similar, but less prominent, changes were seen in the right insular lobe. Hyperintense signal areas also were detected in the cingulate gyrus, bilaterally, and in the right frontal pole (**Figure 3**). Hyperintense signal areas also were seen diffusely in the white matter and cerebral cortex in the medial and anterior-basal parts of the left temporal lobe. There was a mass effect with compression of the temporal horn of the lateral ventricle and deformation of the cerebral peduncle to the left. Similar, but less prominent changes were seen in the right temporal lobe (**Figure 4**).

Based on the MR scan imaging and cerebrospinal fluid (CSF) exam results, there was a high suspicion of herpetic encephalitis and the patient received empiric treatment with acyclovir, but his condition did not improve on acyclovir therapy. Cerebrospinal fluid was sent for serological testing, where herpes simplex virus (HSV) 1 and 2, Epstein-Barr virus, and cytomegalovirus were negative. A blood test showed a negative HIV antibody, but there was a positive *Treponema pallidum* test. The results of the serum rapid plasma reagent (RPR) and serum *Treponema pallidum* hemagglutination (THPA) tests were positive. Serum TPHA titer was 1: 5120. CSF RPR test was 3+ and TPHA test was 4+. The positive CSF *Treponema pallidum* tests established the diagnosis of neurosyphilis, and other infection (HSV, EBV, CMV) or autoimmune encephalitis were ruled out. Therapy with acyclovir was canceled and penicillin G (18 million units/day) was started. After a few days of receiving penicillin G, the patient's symptoms improved. The patient becomes orientated in time, space, and person, with no aphasia. He received penicillin for 14 days, but continued to experience psychotic symptoms, for which he was referred to a psychiatrist. The patient could not specify the source of infection. The patient's wife's blood test for *Treponema pallidum* was negative.

A control axial contrast-enhanced T1-weighted MRI scan was performed 15 days later and, compared to the previous scan, a positive change was seen. Previously observed changes had

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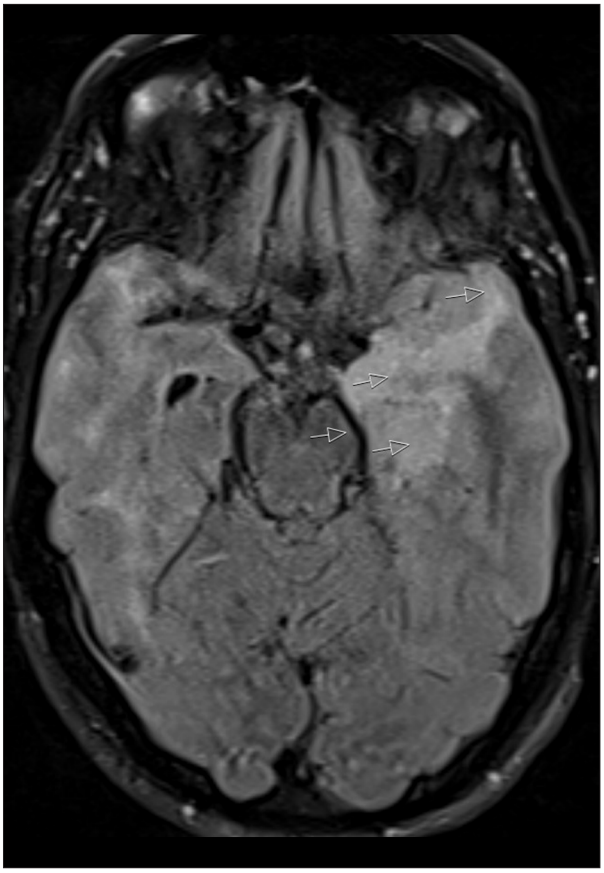

Figure 4. First axial FLAIR-weighted MRI showing hyperintense signal areas diffusely in the white matter and cerebral cortex in the medial and anterior-basal parts of the left temporal lobe (arrows). There is a mass effect with compression of the temporal horn of the lateral ventricle and deformation of the cerebral peduncle to the left (arrow). Similar but less prominent changes are seen in the right temporal lobe.

decreased significantly (**Figure 5A, 5B**). A hypointense signal remained on the medial surface of the frontal cortex, bilaterally (**Figure 5A**).

The patient received recommendations to continue antipsychotic drugs, with psychiatrist consultation if needed. It was recommended to repeat the brain MR scan and lumbar puncture after 6 months.

Discussion

While all the world's research community's efforts in the last few years have been focused on fighting the COVID-19 pandemic, the threat of other diseases is quietly growing in its shadow. Sexually transmitted infections, such as syphilis, remain one of the most common global health problems [1].

Even though neurosyphilis in the penicillin era is a relatively rare diagnosis, it occurs in most patients with syphilis, due to the high ability of *Treponema pallidum* to penetrate to the CNS. Diagnosis of neurosyphilis is often challenging, and it is usually confirmed by a combination of CSF analysis and clinical findings. Neuroimaging findings mostly are non-specific, but they can be helpful in diagnosis and management [4].

In the early stages, neurosyphilis can be asymptomatic with no radiographic features. The most common MRI diagnostic features in the early stages are brain white matter lesions, meningeal and parenchymal enhancement presenting as acute syphilitic meningitis, cranial nerve (CN VII, VIII) enhancement, and syphilitic gummas. Early neurosyphilis can also manifest as meningovascular syphilis with the same radiographic features as syphilitic meningitis (leptomeningeal enhancement and presence of syphilitic gummas), focal segmental vascular narrowing of any caliber vessels on angiographic studies, and cortical or subcortical infarction regions in any vascular territory. In late stages, neurosyphilis can present with cerebral atrophy or tabes dorsalis, mimicking the radiographic appearance of subacute combined degeneration of the cord [5,6].

Our findings suggest that in patients with non-specific neurological symptoms and psychotic disorders, neuroimaging can play an important role in indicating suspicion of encephalitis [7]. Enhancement of anterior parts of the temporal lobe is an atypical imaging finding, which can simulate an infection with herpes simplex virus, which is also the most common differential diagnosis of syphilitic encephalitis [8]. Typical findings of neurosyphilis and herpes simplex virus encephalitis can be indistinguishable on MRI and include unilateral or bilateral MRI hyperintensities in the mesiotemporal lobes on T2-weighted imaging or FLAIR imaging. In this case, to ensure a precise diagnosis, the laboratory diagnosis was crucial, as there were no other characteristic signs of neurosyphilis in the imaging studies. Consequently, neurosyphilis patients are frequently misdiagnosed with HSV encephalitis, preventing them from receiving appropriate treatment and often causing greater neurologic damage [9].

The clinical features that may help differentiate neurosyphilis from HSV encephalitis are that the onset of neurosyphilis is generally subacute or chronic and is characterized by slow progression and a long course, unlike the more common presentation of viral encephalitis with a rapidly progressive course. On imaging features, neurosyphilis usually presents with atrophy of the mesiotemporal lobes. Atrophy is related to the indolent nature of neurosyphilis, which is very different from the rapid and intense onset of viral encephalitis. Furthermore, gyral enhancement, signs of hemorrhage, and areas of restricted diffusion are frequently described in viral encephalitis, but are generally absent in neurosyphilis. Imaging of viral encephalitis

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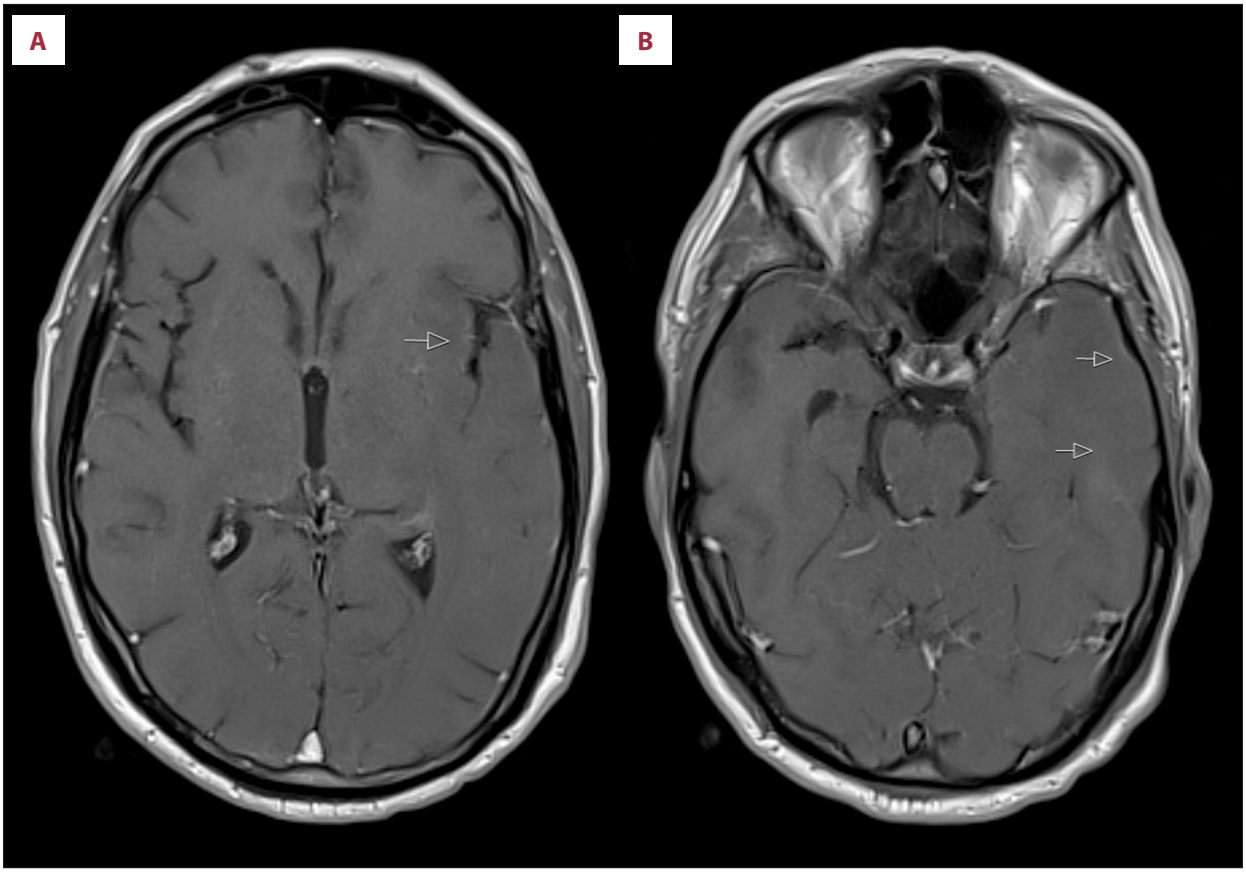

Figure 5. (**A, B**) **Second axial contrast-enhanced T1-weighted MRI** showing a marked decrease in the previously observed changes (arrows). In addition, a hypointense signal is observed in the medial surface of the frontal cortex, bilaterally (**A**).

often shows clear boundaries between the lesions and the outer edge of the lenticular nucleus. These delimitations have been described as 'knife' signs and can be an important distinguishing characteristic [9]. In our patient, the consequences of CNS infection will be assessed after 6 months, when the control MRI will be performed.

In the literature, it has been described that the spinal fluid examination establishes the diagnosis of neurosyphilis, with diagnostic sensitivity of 67-72% [3]. Magnetic resonance imaging is the imaging of choice to support the diagnosis of meningovascular syphilis and to detect changes in cerebral vessels due to increased sensitivity (sensitivity is close to 100%); however, its specificity is considerably lower [6].

Recent studies indicate that syphilis is a top candidate for the development of a successful vaccine in the near future [10]. But until then, we have to use the available tools to prevent, accurately diagnose, and treat appropriately one of the oldest diseases in the world, which is still spreading.

Conclusions

Neurosyphilis is a potentially life-threatening disease that can cause irreversible neurological damages, including dementia, permanent paralysis, and death. The prognosis of patients with neurosyphilis mostly depends on early detection of the disease. Diagnosis is confirmed by a combination of clinical symptoms, CSF analysis, and neuroimaging findings. The most common MRI findings in neurosyphilis are a parenchymal and meningeal enhancement, cerebral vasculitis with focal segmental vascular narrowing of any caliber vessels, cortical or subcortical infarction regions in any vascular territory, and syphilitic gummas, but normal findings are just as common. In some cases, as the present case report has demonstrated, neuroimaging findings in neurosyphilis mimic the imaging features of HSV encephalitis [6,9]. To reduce the risk of potentially irreversible complications, treatment should be initiated immediately, and the drug of choice is penicillin G.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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