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Letter to the Editor

Neurosyphilis as a Rare Cause of Mild Cognitive Impairment and Depression: Two Case Reports and Literature Review

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Syphilis infection caused by *Treponema pallidum* is also referred to as the 'great imposter' due to its varied manifestations. Neurosyphilis is tertiary syphilis that involves the brain. 'General paresis' is a later manifestation of neurosyphilis.[1-3] With the widespread clinical use of penicillin, neurosyphilis has become rare and is not typically considered by clinicians. However, because neurosyphilis can be a cause of treatable dementia, there is a need to consider neurosyphilis as a possible cause of mild cognitive impairment (MCI). We present two cases that initially presented with cognitive decline, depression, and gait instability and were later diagnosed with general paresis.

Case 1: A 50-year-old male patient with arthritis presented with progressive cognitive decline, gait instability, and tremors for 2–3 months. He also complained of depressed moods and insomnia. Brain magnetic resonance imaging (MRI) findings were unremarkable except for diffuse cortical atrophy. Neurological examination including posterior column involvement signs did not reveal any focal signs. He showed intentional tremors in both hands. Detailed neuropsychological tests showed impairments in language, visuospatial, memory recall, and frontal executive functions. He was diagnosed with amnestic multiple domain MCI. Blood tests showed normal vitamin-B12 and folate levels, normal thyroid function, and negative human immunodeficiency virus (HIV) test. However, a rapid plasma reagin (RPR) level was elevated to 8.4 RPR unit (RU). Further, treponemal tests were positive. Follow-up brain MRIs six months later showed multifocal non-enhancing hyperintensities in FLAIR imaging (**Fig. 1**). Cerebrospinal fluid (CSF) showed pleocytosis, elevated protein, and reactivities to treponemal tests confirming general paresis (**Table 1**). His arthritis was diagnosed as syphilitic arthritis. The patient was treated with intravenous ceftriaxone for two weeks. On follow-up tests, his cognitive function was slightly improved (Korean version of Mini-Mental State Examination [K-MMSE] 30, clinical dementia rating [CDR] 0.5 (sum of boxes [SOB]: 1.5), global deterioration scale [GDS] 3). He reported improvements in the tremor, cognition, and insomnia at three months post-treatment.

Case 2: A 63-year-old male without any comorbidities present at the hospital with memory decline and gait instability for 3–4 months. There was no focal neurologic symptom except bilateral sway while turning around. Brain MRI showed diffuse cortical atrophy especially in the fronto-temporal cortex and hyperintensities in the splenium. He was diagnosed with amnestic multiple domain MCI showing visuospatial, memory encoding, and frontal executive dysfunctions. Blood tests including chemistry, vitamin-B12, folate

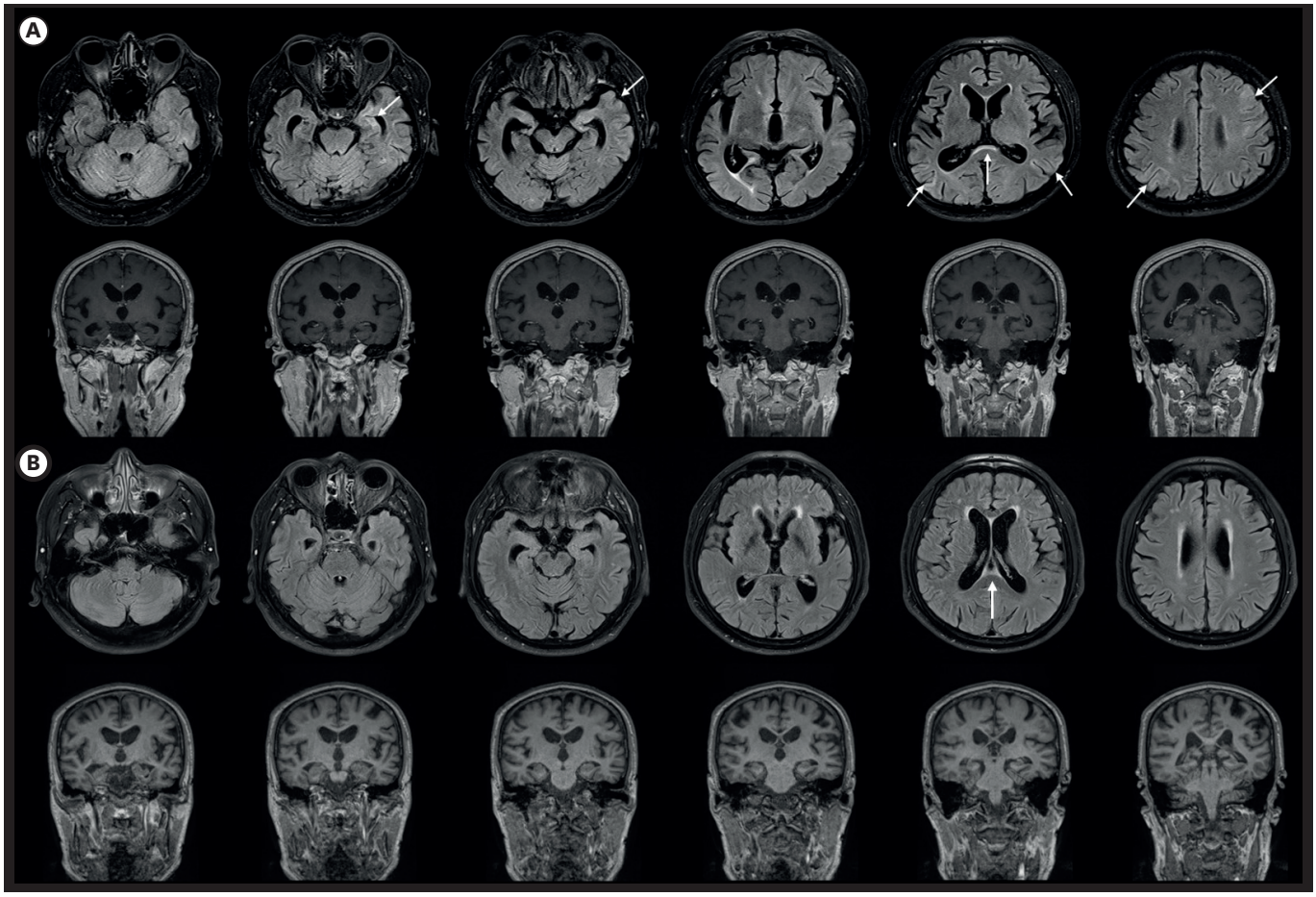

Fig. 1. Patients' brain MRI. (A) Case 1: MRI shows diffuse cortical atrophy and multifocal hyperintensities in the splenium, left temporal, both the parietal and frontal cortices; (B) Case 2: MRI shows diffuse cortical atrophy and hyperintensity in the splenium.
MRI: magnetic resonance imaging.

levels, thyroid function, and the HIV test were normal. The serum RPR levels increased (6.1 RU). All the other treponemal tests were positive. CSF revealed pleocytosis, increased protein, and positive treponemal tests (**Table 1**). The spine MRIs done to assess posterior column involvement were normal. He was treated with ceftriaxone and discharged in stable condition. Cognitive tests on a follow up two weeks later showed little change (K-MMSE 26, CDR 0.5 [SOB: 3.0], GDS: 3); however the CDR-SOB score was slightly improved.

Neurosyphilis is known to occur in 5%–30% of people infected with syphilis.[4] Symptoms of general paresis include neurological deficits, such as cognitive impairments, Argyll Robertson pupils, sensory changes, and neuropsychiatric symptoms, such as personality changes, delusions, and hallucination, which are caused by meningoencephalitis with neurodegenerations.[1,2,4] In patients with positive syphilis screening tests (non-treponemal tests, RPR), treponemal tests, treponema pallidum hemagglutination assay (TPHA) and fluorescent treponemal antibody absorption test (FTA-ABS), should be assessed.[5] If neurologic signs of meningitis or stroke are observed, CSF examinations should be performed before treatment.[5] Based on the guidelines, no single test can be confirmative; diagnosis of neurosyphilis depends on a combination of CSF test results including pleocytosis, increased protein, or reactive CSF-Venereal Disease Research Laboratory (VDRL)

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Table 1. Patient's characteristics

Variables	Case 1	Case 2
Age (yr)	50	63
Gender	Male	Male
Education (yr)	14	9
Comorbidity	Arthritis for 4 years	None
APOE genotype	E3/3	E3/4
Symptom duration (mon)	2–3	3–4
Neuropsychological test results (SNSB II)		
K-MMSE	28	26
CDR (SOB)	0.5 (2.0)	0.5 (3.5)
K-IADL	0.2	0.4
Geriatric depression scale	8/15	14/15
Digit span forward (%ile)	41.99	51.59
K-BNT (%ile)	0.01	54.87
RCFT (%ile)	0.01	0.28
SVLT, immediate recall (%ile)	1.75	0.10
SVLT, delayed recall (%ile)	0.31	1.85
SVLT, recognition (%ile)	25.26	28.39
RCFT, immediate recall (%ile)	0.17	2.07
RCFT, delayed recall (%ile)	0.06	3.55
RCFT, recognition (%ile)	32.70	13.79
COWAT, phonemic (%ile)	8.91	11.39
Stroop, color reading (%ile)	4.87	0.02
Brain MRI findings		
Lacune (No.)	0	0
White matter hyperintensities	P1/D1, minimal	P1/D1, minimal
Microbleed (No.)	0	0
Hippocampal atrophy, grade	G2/2	G1/1
Syphilis work ups		
Serum	RPR, quan: reactive (1:128) TPHA: reactive FTA-ABS, IgM: negative FTA-ABS, IgG: positive HIV Ag/Ab: negative	RPR, quan: reactive (1:128) TPHA: reactive FTA-ABS, IgM: positive FTA-ABS, IgG: positive HIV Ag/Ab: negative
CSF	WBC: 71 (Lymphocytes 83%), RBC: 0 Protein: 65.8 mg/dL Glucose: 58 mg/dL	WBC: 83 (Lymphocytes 95.2%), RBC: 20 Protein: 74.6 mg/dL Glucose: 43 mg/dL
CSF syphilis markers	RPR, quan: reactive (1:16) TPHA: reactive FTA-ABS, IgM: weakly positive FTA-ABS, IgG: positive	RPR, quan: reactive (1:16) TPHA: reactive FTA-ABS, IgM: negative FTA-ABS, IgG: positive

APOE: apolipoprotein, K-MMSE: Korean version of the Mini-Mental State Examination, CDR: clinical dementia rating, SOB: sum of boxes, K-IADL: Korean version of instrumental activities of daily living, K-BNT: Korean version of Boston naming test, RCFT: Rey complex figure test, SVLT: Seoul verbal learning test, COWAT: Controlled Oral Word Association Test, MRI: magnetic resonance imaging, P: periventricular, D: deep white matter, RPR: rapid plasma reagin, TPHA: Treponema pallidum hemagglutination assay, FTA-ABS: fluorescent treponemal antibody absorption test, HIV: human immunodeficiency virus, CSF: cerebrospinal fluid, WBC: white blood cell, RBC: red blood cell.

and serologic tests with neurologic signs.[5] Since CSF-VDRL is highly specific but insensitive, a negative CSF-VDRL test despite reactive serology and CSF pleocytosis, should be confirmed with a CSF FTA-ABS, which is less specific but highly sensitive.[5] After confirmation, intravenous aqueous crystalline penicillin G for 10-14 days is recommended as the first-line treatment. However, ceftriaxone is an alternative regimen in case of penicillin allergy.[5]

Overall, the patients did not have any remarkable findings in the first brain MRIs, neurological examinations, and blood results, but showed positive syphilis screening tests results. Intriguingly, Case 1 showed multifocal hyperintensities representing encephalopathy

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and neuroinflammation due to neurosyphilis on follow-up MRIs. Neurosyphilis connection with MCI often remains unrecognized; most MCI cases are treated based on the clinical impression of Alzheimer's disease. Because neurosyphilis is rare and usually does not present with focal neurologic signs, clinicians should be more vigilant when evaluating syphilis screening tests and consider neurosyphilis as a differential diagnosis of MCI to optimize treatment for elderly patients.

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