Clinical case

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Longitudinal extensive transverse myelitis as the initial manifestation of the acquired immunodeficiency syndrome

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Abstract

Introduction: Longitudinal extensive transverse myelitis (LETM) is characterized by the inflammation of three or more vertebral segments. It is not a common entity, and it is even more rare as the initial manifestation of acute HIV infection.

Case presentation: A previously healthy 28-year-old male presented with progressive quadriparesis associated with spasticity and hyperreflexia. Spinal MRI showed hyperintensity of spinal levels T3 through T12, compatible with longitudinal extensive transverse myelitis; HIV serology was later found to be reactive, as well as positive polymerase chain reaction (PCR) for Epstein-Barr virus (EBV) in cerebrospinal fluid (CSF). Given that extensive workup ruled out opportunistic infections and other possible causes of longitudinal extensive transverse myelitis, the clinical manifestations were attributed to the acute HIV seroconversion.

Discussion: Acute transverse myelitis in patients with HIV is an uncommon condition that has only been described in very few case reports during seroconversion. Additionally, the positive polymerase chain reaction for Epstein-Barr virus in cerebrospinal fluid has uncertain clinical significance in patients with HIV.

Conclusion: This case highlights the importance of considering HIV as a potential underlying cause in patients presenting with neurological symptoms, even when classic symptoms of HIV/AIDS are absent. In addition, future studies should aim to explore the real importance of Epstein-Barr virus positivity in cerebrospinal fluid to improve management strategies and possible outcomes.

Keywords: Myelitis, Transverse, HIV, Acquired Immunodeficiency Syndrome, Seroconversion, Herpesvirus 4, Human, Spinal cord diseases, Cerebrospinal fluid.

Mielitis transversa longitudinalmente extensa como la manifestación inicial del síndrome de inmunodeficiencia adquirida: un reporte de caso

Resumen

Introducción: la mielitis transversa longitudinalmente extensa (MTLE) se define como la inflamación de tres o más segmentos vertebrales. No es una entidad frecuente, y es incluso más extraña como manifestación inicial de la infección aguda por VIH.

Presentación del caso: un hombre de 28 años previamente sano se presenta con una cuadriparesia progresiva asociada a espasticidad e hiperreflexia. La RMN espinal demostró una hiperintensidad de los niveles T3 hasta T12, compatible con mielitis transversa longitudinalmente extensa; la serología para VIH fue reactiva, así como la reacción en cadena de la polimerasa (PCR) del virus de Epstein-Barr en líquido cefalorraquídeo (LCR). Dado que los estudios de extensión realizados descartaron infecciones oportunistas y otras causas de mielitis transversa longitudinalmente extensa, las manifestaciones clínicas se atribuyeron a la seroconversión aguda del VIH.

Discusión: la mielitis transversa aguda en pacientes con VIH es una condición poco frecuente que sólo se ha descrito en algunos reportes de caso durante la seroconversión. Adicionalmente, el hallazgo del virus de Epstein-Barr en líquido cefalorraquídeo tiene una significancia clínica incierta en los pacientes con VIH.

Conclusión: el caso resalta la importancia de considerar al VIH como posible causa en pacientes que se presentan con síntomas neurológicos, incluso si estos no son los clásicamente descritos para el VIH/SIDA. Adicionalmente, los estudios futuros deberían tener como objetivo la determinación de la verdadera importancia de la positividad de la reacción en cadena de la polimerasa de Epstein-Barr en líquido cefalorraquídeo para mejorar las estrategias terapéuticas y los posibles desenlaces.

Palabras clave: mielitis transversa, VIH, síndrome de inmunodeficiencia adquirida, seroconversión, herpesvirus humano 4, enfermedades de la médula espinal, líquido cefalorraquídeo.

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Introduction

Longitudinal extensive transverse myelitis (LETM) is characterized by the inflammation of three or more vertebral segments. It has a broad clinical presentation, which includes paraparesis/quadriparesis, sensory impairments, and dysfunctions related to gait, bladder, bowel, and/or sexual function (1). This condition can manifest in various disease processes, mainly neuromyelitis optica (NMO), but it has also been observed in other autoimmune and inflammatory disorders affecting the central nervous system (CNS), as well as infections (2).

The human immunodeficiency virus (HIV) has emerged as a significant public health concern on a global scale. As of the end of 2023, approximately 39.9 million individuals were living with HIV worldwide, of which 38.6 million were aged 15 years and older. Additionally, there were 630,000 deaths related to HIV-associated illnesses globally in that same year (3).

Neurological compromise in HIV-infected individuals can occur because of the direct effect of the virus, opportunistic infections, cancer, antiretroviral drug therapy initiation, or vascular events (4). It is worth noticing, however, that in most cases, neurological compromise is evidenced as HIV infection progresses and AIDS develops. More specifically, around 40-70% of people with HIV will develop a neurological issue of clinical interest (5). The most prevalent neurological complication is subacute encephalitis, followed by aseptic meningitis, myelitis, neuropathies, vacuolar myelopathy, cranial nerve involvement, and malignancies (6). Acute transverse myelitis (ATM) in individuals with HIV is a rare condition, with only a limited number of case reports documenting its occurrence during primary infection (7).

In this article, we present a case report of a previously healthy 28-year-old male, who presented with right lower extremity paresis and was then diagnosed with LETM secondary to HIV-AIDS.

Case report

A 28-year-old male with no relevant past medical history was admitted to the emergency department (ED) complaining about right lower extremity paresis, paresthesia, gait limitation, and occasional headaches with blurry vision over the past week. His initial physical exam (PE) showed hemodynamic stability, muscle strength of 3/5 in right hip flexion and ankle plantar flexion, and 4/5 in other segments of the right lower limb, with ipsilateral hypoesthesia. Symmetrical muscle tone was intact, and myotendinous reflexes were 3+/5+.

A non-contrast head CT identified hypodensity in the right corona radiata. An HIV fourth-generation ELISA test was reactive, and his CD4+ cell count was 199 cells/µl. Consequently, he was diagnosed with HIV/AIDS.

By the next day's neurology evaluation, he had progressed to quadriparesis with symmetrical spasticity and hyperreflexia (+++) in the lower limbs, without Babinski sign or sphincter dysfunction. A contrasted MRI of the spine was ordered, and ophthalmology noted bilateral non-granulomatous panuveitis, linked to the HIV de novo infection. Treatment with prednisolone and tropicamide was initiated, improving his visual acuity.

The spine MRI demonstrated extensive hyperintensity from T3 to T12, consistent with transverse myelitis (TM), as well as enhancement of cervical, dorsal, and lumbar roots, multiple cervical nodes, and marked prominence of the soft tissues of the nasopharynx (Figures 1 and 2). Given the diagnosis of LETM and polyradiculitis in an AIDS patient, opportunistic infections and lymphoproliferative syndrome needed to be ruled out. Lumbar puncture revealed lymphocytosis, hypoglycorrhachia, hyperproteinorrachia, and a positive PCR for Epstein Barr virus.

On day 16, he developed a fever, cough, and hepatomegaly. Contrast-enhanced chest and abdominal CT revealed cervical, axillary, mediastinal, and pelvic lymphadenopathy; miliary-pattern micronodules in both lungs; and hepatosplenomegaly. A cervical lymph node biopsy demonstrated reactive follicular and paracortical hyperplasia, with negative immunohistochemistry stains.

Extensive testing ruled out tuberculosis (TB) infection, bacterial pneumonia, and other opportunistic infections. These included sputum acid-fast bacilli smears and mycobacterial cultures from bronchoalveolar lavage (BAL) and cerebrospinal fluid (CSF), as well as bacterial and mycobacterial cultures in CSF, sputum, and cervical ganglionic tissue, all negative for TB. However, BAL culture was positive for Haemophilus influenzae, prompting initiation of amoxicillin 500 mg every 8 hours PO for 7 days, resulting

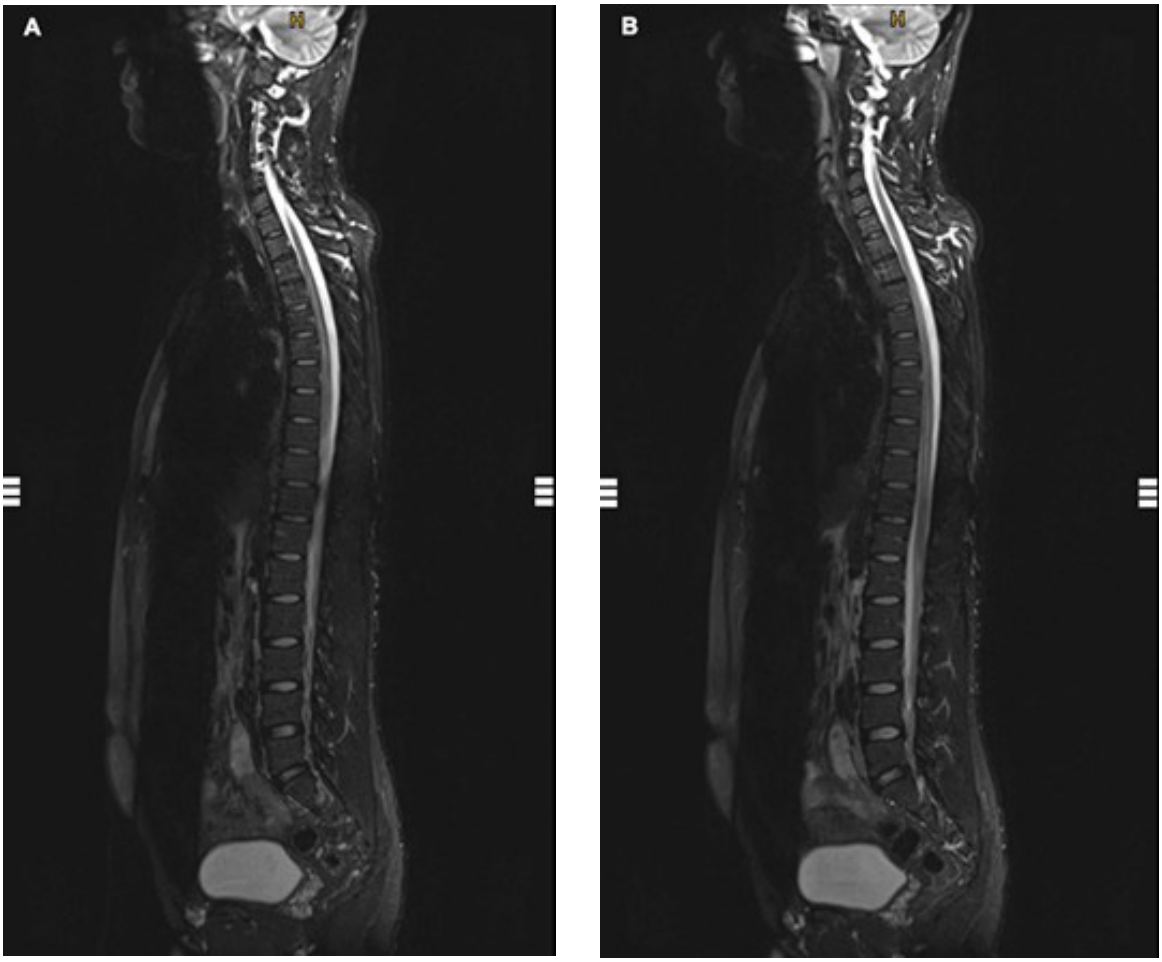

Figure 1. (A) and (B) show sagittal images in T2 STIR with intrasubstance hyperintensity of the spinal cord that extends from T3 to T12

Source: Obtained from the patient's medical history with prior informed consent.

in resolution of respiratory symptoms. Additional testing, including treponemal test and toxoplasma IgM on serum; Cryptococcus neoformans antigen in serum; and multiple CSF analyses (including Cryptococcus neoformans antigen, cytomegalovirus viral load, herpes simplex virus 1 and 2 PCR, fungal cultures, India ink, FilmArray, and potassium hydroxide microscopy) were negative.

As no contraindications were identified, highly active antiretroviral therapy (HAART) was initiated using tenofovir disoproxil fumarate 25 mg/emtricitabine 200 mg q.d. and dolutegravir 50 mg BID PO. Prophylaxis for Pneumocystis jiroveccii with daily double-strength trimethoprim/sulfamethoxazole was also started.

After 4 days of HAART, the patient reported marked improvement, particularly in ambulation. Neurological symptoms were attributed to acute HIV seroconversion. He was evaluated by physiatry and physical therapy during his hospitalization, leading to further strength and mobility improvement after a month. He was discharged with outpatient follow-up in neurology, physiatry, and physical therapy but was ultimately lost to follow-up.

Discussion

We describe a patient with progressive quadriparesis, spasticity, and hyperreflexia ultimately diagnosed with de novo HIV/AIDS infection. Spine MRI revealed LETM, attributed to HIV infection.

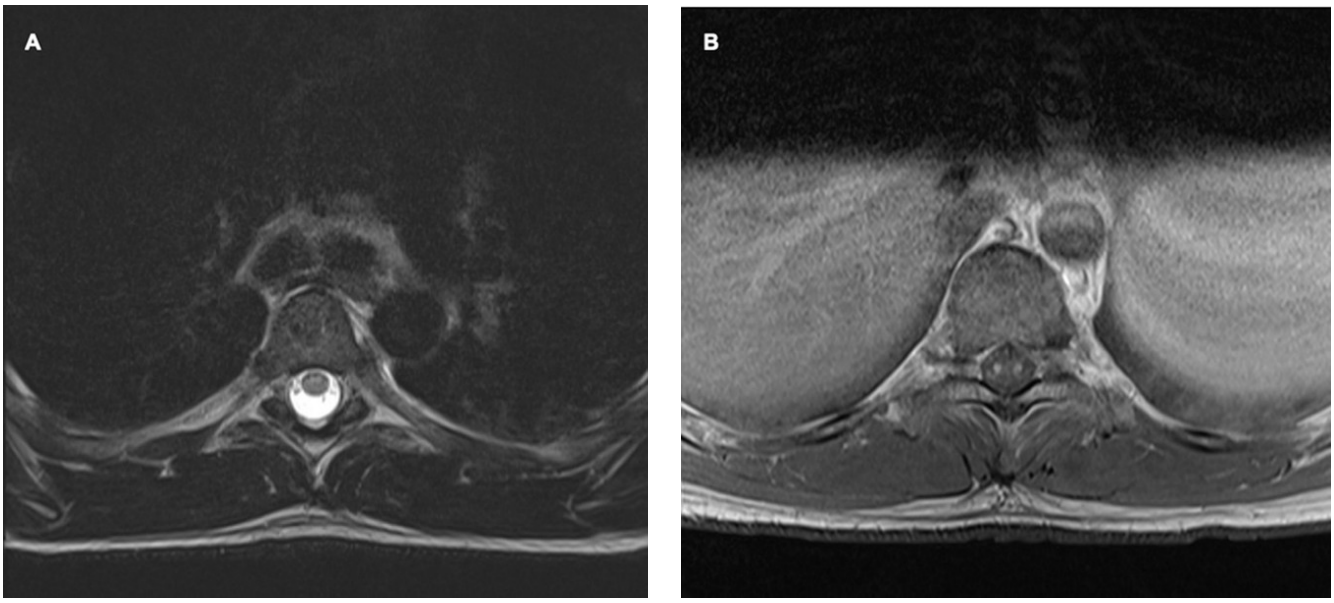

Figure 2. (A) Dorsal axial image in T2 with diffuse intrasubstance hyperintensity. (B) Post-contrast T1 dorsal axial image with increased signal intensity of the descending tracts

Source: Obtained from the patient's medical history with prior informed consent.

LETM is radiologically defined as T2 hyperintensity affecting three or more contiguous segments of the spinal cord. Clinical presentation varies by spinal level and may include paraparesis/quadriparesis, sensory deficits, sphincter dysfunction, and, in severe cases, respiratory failure and even death. Symptoms typically develop acutely and, if untreated, may lead to permanent and significant disability (1). A recent case series by Dhakal et al. (8) in Nepal reported quadriparesis as the most common presentation (75%), followed by sensory changes, paraparesis, and bladder dysfunction. Etiologies included NMO spectrum disorders (NMOSD) in 50% of cases, while the remaining cases had unknown causes.

The differential diagnosis of LETM is extensive, encompassing inflammatory conditions, autoimmune diseases, paraneoplastic syndromes, neoplasms, metabolic disorders, vascular abnormalities, and infections (Table 1). NMOSD, characterized by autoantibodies targeting aquaporin-4 (AQP-4), is classically associated with LETM and typically presents with episodes of optic neuritis, myelitis, and brainstem encephalitis (9). Although AQP-4 antibodies were not assessed in this patient due to the initial focus on an infectious etiology related to HIV, this test could have been useful to rule out NMOSD and should be considered in similar cases in the future. Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) has also emerged as a distinct etiology, particularly in patients with recurrent optic neuritis, myelitis, or acute disseminated encephalomyelitis (ADEM), and often presents with a distinct clinical and serological profile compared to that of NMOSD (10,11).

Among non-inflammatory causes of LETM, vascular myelopathies represent a key differential. These can arise from vascular abnormalities affecting the spinal cord, including arterial ischemia, venous congestion, and arteriovenous malformations, among others. While both LETM and vascular myelopathies can present with motor, sensory, and/or autonomic dysfunction, vascular etiologies typically have a hyperacute or acute onset, in contrast to the more subacute course seen in LETM (12-14).

A United States national retrospective study conducted from 1999 to 2015 reported a point prevalence of 7.86 TM cases per 100,000 individuals, with 24.3% classified as LETM. Around 57% of patients had an idiopathic etiology, while 17% had multiple sclerosis, 8.3% had NMOSD, and 5.8% had infectious or parainfectious causes (15).

Table 1. Etiology and differential diagnosis of LETM (2)

Diagnosis	
Inflammatory conditions	
- Acute disseminated encephalomyelitis	
- Multiple sclerosis	
- Neuro-Behçet's	
- Neurosarcoidosis	
Autoimmune diseases	
- Neuromyelitis optica	
- Systemic lupus erythematosus	
- Sjögren syndrome	
- Antiphospholipid syndrome	
- Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disease (MOGAD)	
Neoplasms	
- Paraneoplastic disorders	
- Ependymoma	
- Astrocytoma	
- B-cell lymphoma	
- Intramedullary metastases	
Metabolic disorders	
- Vitamin B12 deficiency	
- Copper deficiency	
Vascular deficiencies	
- Spinal cord infarction/ischemia	
- Dural arteriovenous fistula	
Infections	
Virus	- Herpes virus: Epstein Barr virus, cytomegalovirus, herpes simplex virus, varicella zoster virus
	- Human Immunodeficiency Virus (HIV)
	- Human T cell lymphotropic virus (HTLV-1)
Bacteria	- Treponema pallidum
	- Mycobacterium tuberculosis and Mycobacterium bovis
	- Borrelia burgdorferi
	- Mycoplasma
Parasites	- Toxocara canis
	- Ascaris suum
	- Schistosomiasis
Other	
- Radiotherapy	
- Spinal cord contusion	

Source: Adapted from (2).

Comprehensive evaluation, including contrast-enhanced cranial and spinal MRI, CSF analysis, and blood work, is essential for accurate diagnosis and guiding appropriate treatment and prognosis, as they will vary according to the underlying etiology (16).

HIV infection can present with many neurological syndromes. Between 40 to 70% of patients experience neurological symptoms at some stage of the disease, secondary to either direct CNS involvement or opportunistic infections. Approximately 70% of patients will be symptomatic at the time of HIV seroconversion, with neurological manifestations present in 10%. Common presentations include aseptic meningitis (25%), fulminant encephalopathy, ADEM, bradykinesia, optic neuropathy, Bell's palsy, symmetric distal sensory polyneuropathy, and Guillain-Barré syndrome (GBS) (5,17).

LETM has been reported during the initiation of HAART as a manifestation of the immune reconstitution inflammatory syndrome (IRIS), especially in individuals with profoundly immunosuppressed states, such as those with CD4+ T-cell counts below 50 cells/mm³ and/or high HIV viral loads (>5.5 $\log_{10}$ copies/mL). The underlying pathophysiology involves a dysregulated immune response triggered by the rapid restoration of immune function, particularly the rebound of the CD4+ T-cell population. This reconstitution may provoke an excessive inflammatory response, characterized by infiltration of CD8+ T-cells into the spinal cord, resulting in significant injury. Although the true incidence of LETM as part of IRIS remains unclear due to its rarity, a study conducted in Canada reported neurologic IRIS, including LETM, in approximately 0.9% of patients initiating HAART over an eight-year period (18-21).

Moreover, the EBV is highly prevalent, and around 85% of adults worldwide have been infected with it. Its most common manifestation is infectious mononucleosis (IM). CNS involvement is rare (1-5%), mostly seen in immunocompromised hosts, typically manifesting as aseptic meningitis, meningoencephalitis, ADEM, cerebellitis, GBS, and cranial and peripheral nerve neuropathies; however, myelitis is not as common (22,23). In fact, it is the rarest of the neurological complications and occurs more often in children (24). In a cohort of 89 children with EBV-related CNS infection, encephalitis and meningoencephalitis were the most common presentations (72%), followed by GBS (17%), ADEM (3.4%), and acute myelitis (2.2%) (25).

The precise prevalence of TM in adults with EBV infection is not well-defined, though it is considered rare (26). EBV primarily targets B cells and epithelial cells, including those within neural tissue, and possesses the capability to establish latency by evading immune detection. Subsequently, it can reactivate, resulting in inflammation and demyelination, predominantly mediated by CD8+ cytotoxic T lymphocytes, as well as through molecular mimicry between viral antigens and self-antigens present in the spinal cord (27-29).

Our patient was found to have EBV DNA in the CSF. Nevertheless, its significance in individuals with HIV remains unclear, specifically in patients without primary cerebral lymphoma (PCL). In a study of adults with HIV in Zambia, EBV DNA was detected in the CSF of 28.9% of patients presenting neurological symptoms. Three possible explanations have been proposed: 1) active CNS infection, 2) reactivation due to another CNS pathogen, and 3) the presence of quiescent virus. However, this finding did not correlate with increased mortality, advanced immunosuppression, or other specific neurological diagnoses.

The above highlights the uncertainty of CSF positivity in terms of severe outcomes and the need for complete clinical evaluation when found; thus, all symptoms and findings in this patient were attributed solely to the HIV/AIDS syndrome (30,31). To explore this attribution, we considered the Bradford Hill criteria for causality. The dose-response relationship aligns with the patient's favorable response to HAART. Biologically, this association is plausible, as HIV can induce direct CNS inflammation through the activation of proinflammatory cytokines and blood-brain barrier disruption, potentially leading to myelitis (32).

Additionally, the association of LETM as an initial manifestation of HIV infection, although seldom, has already been hypothesized by prior case reports, with only three documented cases to our knowledge: a 35-year-old male with urinary retention and acute paraparesis in 2014; a 30-year-old male with urinary retention, hypoesthesia, and hypoalgesia in the lower limbs in 2011; and a 29-year-old male with paraparesis and hyperreflexia in the arms in 1987 (7,33,34). However, establishing a definitive causal relationship between HIV seroconversion and LETM is beyond the scope of this article. We proposed this association as a working hypothesis to document this unusual presentation and encourage further research (35).

Conclusion

We report a case of a 28-year-old male whose LETM was the initial manifestation of HIV infection. This case highlights the importance of considering HIV as a potential underlying cause in patients presenting with neurological symptoms, even when classic symptoms of HIV/AIDS are absent. Early recognition and initiation of HAART not only addressed the neurological deficits but also emphasized the need for increased clinician awareness of atypical HIV presentations. Additionally, this case highlights the importance of doing a very judicious work-up in individuals with HIV who present with positive PCR for EBV in CSF, as it is a common finding in this type of patients but with unclear clinical significance; therefore, it must not be assumed to be the culprit of all symptoms without first ruling out any other causes. Future research should aim to explore the real importance of EBV positivity in CSF to improve management strategies and possible outcomes.

Authors' contribution. Ana María Jiménez: Conceptualization, investigation, project administration, supervision, visualization, writing (original draft, review, and editing); Sofía Escobar: Investigation, writing (original draft); Jose Miguel Gloria: Conceptualization, visualization, writing (original draft, review, andediting).

Ethical implications. Informed consent was obtained from the patient prior to the initiation of this case report, ensuring that he understood the nature of the documentation and provided permission for the use of their medical information. We also used the CARE checklist when writing our report. The authors declare no further ethical implications.

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Conflict of interest. The authors declare no conflicts of interest.

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