le; 95% CI, 1.01 to 1.04; \( P = .004 \)). The MR analysis showed that shorter TL was causally associated with a higher risk for AD (odds ratio, 1.36 per SD decrease of TL; 95% CI, 1.12 to 1.67; \( P = .002 \)).

Discussion | In the present study, for the first time to our knowledge, we used IV techniques and provided support for a causal effect of TL on the risk for AD using summary GWAS data. The MR analysis has the advantage of being independent of any measured or unmeasured confounders by using genetic variants as IVs. However, an MR study also requires a large sample size to gain sufficient statistical power. To achieve this, we took advantage of the summary GWAS data from the International Genomics of Alzheimer’s Project Consortium. Based on the original TL article,\(^4\) we roughly estimate 1 SD decrease to be equal to an attrition rate of 1226 TL base pairs in 40 to 60 years, corresponding to a 36% higher risk for AD.

Leukocyte TL, as measured in the GWAS, is correlated with TL in neurons. Thus, it should be considered a proxy of neuronal TL. We tested the MR assumption regarding the pleiotropic effects of the 7 SNPs and did not find any evidence for violations of these assumptions. Additionally, we performed sensitivity analysis by applying likelihood-based methods\(^6\) for the final MR estimate and obtained similar results.

In summary, our study provided evidence for a causal relationship between TL and AD. Further elucidation of this association could provide insights into the physiological roles of telomeres in AD pathogenesis.

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Critical revision of the manuscript for important intellectual content: All authors.  
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**OBSERVATION**

**Cryptococcal Meningoencephalitis in a Patient With Multiple Sclerosis Treated With Fingolimod**

Fingolimod, the first oral drug approved for relapsing-remitting multiple sclerosis (MS), acts primarily by blocking the outlet of lymphocytes from the lymph nodes.\(^1\) Despite the resulting lymphocytopenia, the overall incidences of infections with fingolimod were similar to those in the control groups of the pivotal studies.\(^2\) Nevertheless, since the drug's approval in 2010, few cases of serious infections have emerged under fingolimod treatment.\(^3\)

To our knowledge, we report the first case of opportunistic cryptococcal meningoencephalitis ensued in an otherwise healthy patient with MS treated with fingolimod.

**Report of a Case** | A man in his 40s presented with throbbing bilateral, retro-orbital and temporal headache (numeric rating scale score, 7/10), photophobia, and lethargy lasting for 5 days. The patient had a 3-year history of relapsing-remitting MS and had been treated with fingolimod for 2 years. Neurological examination found no nuchal rigidity or focal neurological deficits. The patient was slightly dystaric and lethargic but oriented. Laboratory test results displayed lymphocytopenia with a lymphocyte level of 400/uL (to convert to ×10\(^9\) per liter, multiply by 0.001) compatible with continuous fingolimod treatment. The white blood cell count was 7200/μL (to convert to ×10\(^9\) per liter, multiply by 0.001). Cerebrospinal fluid (CSF) findings were normal, except for mild hyperproteinorachia (Table). Brain computed tomography was unremarkable.

Despite analgesic treatment, the headache worsened (numeric rating scale score, 10/10) over the following 2 days and was complicated by vomiting and fever. Multiple nonenhanc-
ingsupratentorialandinfratentorialwhitematterlesionswere
seen on magnetic resonance imaging (Figure, A). Escalation
of pain medication resulted in headache relief on day 4, al-
though analgesics discontinuation prompted a headache re-
lapse with ataxic gait and disorientation on day 8. Repeated
magnetic resonance imaging revealed new T2-weighted hy-
perintense supratentorial and infratentorial lesions without
gadolinium enhancement (Figure, B). Lymphocytopenia wors-
ened (lymphocyte level of 90/μL), with similar reductions of
all lymphocyte subtypes (CD4, 56/μL; CD8, 24/μL; normal CD4:
CD8 ratio) and no alterations in other leukocytes. Fingolimod
was withdrawn. Cryptococcal meningoencephalitis was diag-
nosed based on antigen detection by latex agglutination in CSF
and serum, as well as positive CSF culture (Table).

Because no therapeutic recommendations for the man-
gement of cryptococcosis in patients with MS exist, we fol-
lowed the protocol for nonhuman immunodeficiency virus im-
munocompromised patients5: intravenous induction therapy
with liposomal amphotericin B (4 mg/kg per day) plus flucy-
tosine (100 mg/kg per day) for 2 weeks; oral consolidation with
fluconazole, 400 mg, per day for at least 10 weeks; and oral
maintenance with fluconazole, 200 mg, per day for at least 6
months. Elevated CSF pressure was managed by repetitive spi-
nal taps. After 14 days of antifungal therapy, the patient was
headache free. Cryptococcal antigen titer decreased, and the
CSF culture result was negative (Table). However, slurred
speech and cognitive deficits signaled clinical deterioration.
Brain magnetic resonance imaging on day 28 identified break-
down of the blood-brain barrier in the basal ganglia (Figure,
C). The condition was diagnosed as immune reconstitution
inflammatory syndrome. No specific treatment was required.
Moderate cognitive impairment persisted despite an inten-
sive neurological rehabilitation program. An MS relapse oc-
curred 9 months after fingolimod discontinuation and was
treated with intravenous steroids. Shortly thereafter, therapy
with glatiramer acetate was instituted. After normal cogni-
tive assessment and negative cryptococcal antigen titers, fun-
gal therapy was discontinued 13 months after initial presen-
tation. Six months later (ie, 19 months after the cryptococcal
meningoencephalitis), the patient was still symptom free.

Discussion | Opportunistic cryptococcosis is common among im-
munocompromised individuals with human immunodefi-
ciency virus and leukemic or immunosuppressed transplant

Table. CSF Findings on Repeated Examinations

<table>
<thead>
<tr>
<th>CSF Parameters (Normal Range)</th>
<th>Day 1</th>
<th>Day 8</th>
<th>Day 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening pressure (5-18 cm H2O)</td>
<td>9</td>
<td>38</td>
<td>NT</td>
</tr>
<tr>
<td>WBC count (&lt;5/μL)</td>
<td>3</td>
<td>20</td>
<td>67</td>
</tr>
<tr>
<td>Mononuclear (% of WBC count)</td>
<td>NA</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Protein (0.01-0.04 g/dL)</td>
<td>0.09</td>
<td>0.07</td>
<td>0.07</td>
</tr>
<tr>
<td>Lactate (5.41-19.82 mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (39.64-73.87 mg/dL)</td>
<td>50.45</td>
<td>26.67</td>
<td>35.86</td>
</tr>
<tr>
<td>Cryptococcal antigen (negative)</td>
<td>NT</td>
<td>1:2048</td>
<td>1:1024</td>
</tr>
<tr>
<td>Cryptococcal culture</td>
<td>NT</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>PCR for HSV, VZV, and Mycobacterium tuberculosis</td>
<td>Negative</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Mycobacterial culture</td>
<td>Negative</td>
<td>Negative</td>
<td>NT</td>
</tr>
</tbody>
</table>

Abbreviations: CSF, cerebrospinal fluid; HSV, herpes simplex virus;
NA, not applicable; NT, not tested; PCR, polymerase chain reaction;
VZV, varicella-zoster virus; WBC, white blood cell.

Figure. Magnetic Resonance Imaging (MRI) Findings on Repeated Examinations

A, On day 2, axial T2-weighted MRI shows multiple nonenhancing supratentorial and infratentorial (not shown) lesions (arrowheads). B, On day 8, new T2-weighted MRI lesions in the basal ganglia, again without gadolinium enhancement (arrowheads). Similar lesions were also identified in the pons and the mesencephalon (not shown). C, On day 28, gadolinium enhancement in the basal ganglia on T1-weighted MRI (arrowheads).
Idiopathic Inflammatory Myopathy Treated With High-Dose Immunoablative Cyclophosphamide—A Long-term Follow-up Study

To our knowledge, this is the first report of the use of high-dose immunoablative cyclophosphamide (HiCy) therapy in the absence of stem cell rescue in patients with idiopathic inflammatory myopathy.

Report of a Case | The clinical presentation of the patient has been described elsewhere (case number 8 in the article by Valiyel et al^2). Briefly, the patient was a woman in her 30s who presented with a 5-month history of progressive proximal muscle weakness, low-grade fevers, and weight loss. Initial workup revealed an elevated creatine kinase (CK) level (8495 U/L; to convert to microkatal per liter, multiply by 0.0167), an irritable myopathy on electromyography, and a necrotizing myopathy on muscle biopsy. Before presentation to our center, she was treated with oral prednisone, 60 mg per day for 2 months, with minimal improvement in muscle strength. At presentation, neurological examination demonstrated symmetrically reduced arm abduction (4/5), hip flexion (4−/5), knee flexion (4/5), and neck flexion (3/5) muscle strength. The serum test result for autoantibodies to signal recognition particles 72, 54, and 19 was positive. Suspecting potential concomitant steroid-induced myopathy, prednisone was tapered down to 30 mg per day and azathioprine was started at 100 mg per day and titrated up to 150 mg per day for 3 months. Subsequently, owing to rising muscle enzymes, azathioprine was replaced with methotrexate at 20 mg per week and continued for 3 months along with prednisone. Again, she continued to worsen clinically and was switched to intravenous immunoglobulin.

A 6-month course of intravenous immunoglobulin at 2 g/kg per month failed to halt her progression, and she developed further weakness. At this time, magnetic resonance imaging of the thighs showed bilateral 2−3+ edema with 1+ atrophy throughout hip rotators and medial and posterior compartments of the thigh (Figure, A). Afterward, she was treated with rituximab...