



Case Report

Acute Ischemic Stroke in a Patient with Multiple Sclerosis after Initiating Teriflunomide Treatment: A Challenging Case

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ABSTRACT

[Multiple sclerosis](#) is an autoimmune disease of the [central nervous system](#), during which vascular events, including [atherosclerosis](#), are more common and progress faster. [Teriflunomide](#) (TFN) is an oral drug that studies have indicated has low [side effects](#) alongside high efficiency. In this article, a middle-aged woman with multiple sclerosis was introduced, whose medication was changed to TFN. Thirty-five days later, she presented with focal [neurologic symptoms](#), and investigations reported a [lacunar infarction](#). Having excluded potential causes of [acute ischemic stroke](#), such as vascular and rheumatologic factors, the only identifiable factor was the introduction of a new medication. The process of conclusively attributing TFN as the causative agent requires further clarification in future studies.

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Key words

Acute ischemic stroke

Adverse effects

Multiple sclerosis

Teriflunomide

Introduction

[Multiple sclerosis](#) (MS) is a chronic [inflammatory disease](#) that, due to autoimmune mechanisms, initially causes the destruction of the [myelin sheath](#) of [central nervous system](#) axons, and subsequently, axonal dysfunction. Different [clinical courses](#) have been described for MS, with the most common being relapsing-remitting MS (RRMS). These are episodes of flare-ups separated by periods of complete or incomplete recovery and are related to approximately 80% of cases.¹

An idea accepted by most experts is vascular dysfunction in patients with MS, although its [pathophysiology](#) has not been clearly described so far. Some of the hypotheses presented for this event include arterial cerebral hypoperfusion and dysfunction of [endothelial cells](#).²

There are various treatment options for MS, including injectable drugs (interferons and glatiramer acetate) and oral agents such as [fingolimod](#) and [teriflunomide](#) (TFN). TFN reversibly inhibits the [dihydroorotate dehydrogenase](#) enzyme, which is required for the proliferation of activated lymphocytes.³ Therefore, fewer lymphocytes are available to cross the blood-brain barrier.

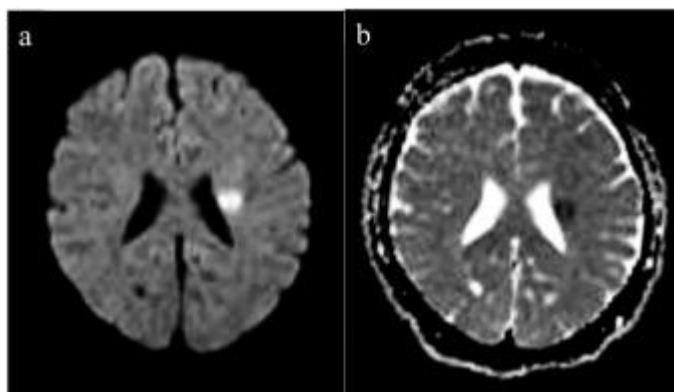
Several [side effects](#), including the elevation of [hepatic enzymes](#),⁴ [lymphopenia](#) and [neutropenia](#), hypertension, and [gastrointestinal discomfort](#), have been reported.⁵ Among the newly suspected rare complications is the increased risk of thrombosis and [vascular accidents](#) in patients with MS. However, the volume of available data still does not support this hypothesis.

In this article, we report a rare case of a middle-aged woman presenting with [acute ischemic stroke](#) (AIS) following TFN prescription.

Case Presentation

The patient is a 48-year-old woman with a 6-year history of RRMS. Her [body mass index](#) was 23.2, and she was a lifetime nonsmoker. The RRMS course started with paresthesia and inferior limb sensation loss due to acute partial [transverse myelitis](#) (Expanded Disability Status Scale score = 1.0). At that time, brain magnetic resonance imaging (MRI) findings revealed several [MS](#) plaques in the brain and 1 [cervical spine MS](#) plaque. Additionally, the [cerebrospinal fluid analysis](#) was positive for [oligoclonal bands](#) and showed an elevation in the immunoglobulins index. In her first year of the disease, due to [neuropathic pain](#) symptoms, the patient was prescribed [carbamazepine](#), which was discontinued due to drug rash with eosinophilia and systemic symptoms syndrome, manifested by [skin lesions](#), increased [eosinophils](#), and impaired [liver function test](#) results. Following the discontinuation of [carbamazepine](#), the symptoms experienced were resolved. Her [MS](#) course was controlled by [interferon](#) β 1a, with an [Expanded Disability Status Scale](#) score of 0, and she had a 6-year relapse-free period. In her last follow-up, the patient complained of flu-like symptoms, oral aphthous lesions, and [arthralgia](#) in her lower limb joints. Further workups by an expert rheumatologist showed no findings in favor of [Behçet disease](#) (according to the International Study Group), other [vasculitis](#), and rheumatologic diseases. Thus, the neurologist changed her therapy to 14 mg [TFN](#) daily due to the possible [side effect](#) of [interferon](#) β 1a. Oral aphthous and related symptoms resolved within 1 week. After 35 days, in October 2022, the patient presented to the [neurology](#) department of Rajaei Hospital with sudden right limb weakness from 6 hours ago. The patient had no history of diabetes mellitus, hypertension, [hyperlipidemia](#), or other vascular events. Her vital signs were stable (blood pressure = 138/76 mm Hg, pulse rate = 89 beats/min, respiratory rate 17 breaths/min, temperature = 37.4 °C), and her [Glasgow Coma Scale](#) score was 15 out of 15. The forces of the right extremities were reduced (lower = 1 out of 5, upper = 3 out of 5), and [National Institutes of Health Stroke Scale](#) score was 4. There was no sensory impairment in the examination. Brain MRI revealed a [lacunar infarction](#), restricted to the left [basal ganglia](#). Due to the previous [diagnosis of MS](#), a [fast MRI](#) protocol was accomplished, revealing a hyperintense area with restricted diffusion in the left basal ganglia ([Figure 1A](#)) with low intensity on the apparent diffusion coefficient map ([Figure 1B](#)). The diffusion weighted imaging/apparent diffusion coefficient map showed an intense mismatch in a

typical vascular territory, favoring [AIS](#). The electrocardiogram finding was normal, and the [ejection fraction](#) was 55% in [tissue Doppler imaging](#). [Transesophageal echocardiography](#) demonstrated no evidence in favor of thrombosis or [patent foramen ovale](#). Furthermore, [magnetic resonance venography](#), bilateral carotid and vertebral Doppler [sonography](#), as well as head and neck [computed tomography angiography](#), showed normal results. In the secondary investigation, there was no evidence of any autoimmune or genetic prothrombotic state in her family. The bilateral lower limbs [Doppler ultrasound](#) revealed normal [venous blood flow](#) in both lower extremities. Moreover, the [coronavirus](#) disease 2019 [polymerase chain reaction](#) test was negative, and there was no recent [vaccination](#) history. Laboratory tests, including complete blood count, [erythrocyte sedimentation rate](#), C-reactive protein level, [glycated hemoglobin](#) test, fasting blood sugar test, [blood urea nitrogen level](#), creatinine level, [liver function test](#), and lipid profile, were normal, and all tests for rheumatologic diseases were negative. Complementary [hematology](#) test results showed that [protein C](#), [protein S](#), [antithrombin III](#), and [factor V leiden activated protein C resistance](#) were within the normal range. Because the patient's symptoms were initiated 6 hours ago, the patient was managed with [atorvastatin](#), [aspirin](#), and [clopidogrel](#). After 7 days of hospitalization, the patient was discharged and referred to the rehabilitation department. Throughout her hospitalization and cardiac monitoring, no signs indicative of paroxysmal [arrhythmia](#) were observed. Because we did not find any reason for her stroke except for the addition of [TFN](#), we changed her therapy to [ocrelizumab](#) due to its efficacy in managing MS with other possible autoimmune diseases in our patient and the probable [drug reaction](#). After 2 months of follow-up and rehabilitation, her extremity's forces improved (upper = 4 out of 5, and lower = 3 out of 5).



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Fig. 1. Brain magnetic resonance imaging image showing a hyperintense area with restricted diffusion in left basal ganglia on [diffusion weighted imaging](#) (A) and low intensity on the apparent diffusion coefficient map (B).

Discussion

Several articles have shown a higher incidence of AIS in patients with MS compared with non-MS counterparts. Among the most accepted hypotheses presented to justify the higher prevalence of ischemic events in patients with MS is [chronic inflammation](#) caused by the autoimmune disease, which, by inducing dysfunction in [endothelial cells](#), accelerates the process of [atherosclerosis](#) and thus increases the risk of developing thrombosis in AIS.⁶ A prolonged course of [demyelination](#), [remyelination](#), axon loss, and finally, [neurodegeneration](#) increases the chance of developing [atherosclerosis](#) and accelerates its process.⁷

Among the diagnostic challenges of AIS in patients with MS is determining whether the resulting neurologic deficit is an RRMS flare or a focal neurologic deficit due to AIS. One helpful distinguishing factor is that MS lesions do not typically appear in the [basal ganglia](#),⁸ as reported in our patient.

TFN is an oral drug approved by many countries, including the United States, for RRMS treatment. TFN is the [active metabolite](#) of [leflunomide](#),⁹ which reversibly inhibits the [mitochondrial enzyme](#) dihydro-orotate dehydrogenase.¹⁰ This enzyme is required for de novo [pyrimidine biosynthesis](#) in activated lymphocytes. Therefore, by inhibiting this enzyme, the proliferation of B and [T lymphocytes](#) is reduced. By decreasing the number of activated cells passing through the blood-brain barrier, the chance of potential damage to the tissue of the [central nervous system](#) is reduced. The most commonly reported side effects of TFN therapy include hair thinning (alopecia), diarrhea, nausea, and increased [alanine aminotransferase](#) concentrations.¹¹ It is said that TFN may increase the chance of thrombosis. Krajnc et al¹² reported 3 cases of [pulmonary embolism](#) in patients with MS 2 years after the initiation of TFN treatment.

The exact mechanism of the thrombogenic effect of TFN therapy in patients with MS is still not well understood. In a number of articles, it has been shown that TFN inhibits the [cyclooxygenase 2](#) enzyme. As we now well know, inhibiting this enzyme leads to an increased chance of vascular events.¹³ In an in vitro study by Nielsen et al,¹⁴ they found that TFN therapy increases [platelet aggregation](#).

Here, we report a patient with RRMS presenting with AIS. Due to the complication of frequent [mouth ulcers](#), a side effect of interferon therapy, the treatment was changed to TFN. After 35 days, the patient was referred to the center with focal [neurological symptoms](#), and imaging findings were indicative of AIS. Suspecting AIS in the context of [vasculitis](#), along with frequent [mouth ulcers](#) and rheumatologic issues, tests for rheumatologic disorders and those related to an increased hypercoagulable state were requested, all of which yielded negative results. Considering that the only factor that changed in the medical course of this patient was the switch of the patient's [drug therapy](#) to TFN and that all etiologies involved in AIS were ruled out with the help of tests, it is possible that the primary contributor to the patient's AIS was the TFN. Given the limited number of articles reporting on the side effect of [clot formation](#) with the TFN drug, it is not possible to definitively attribute the etiology of this patient's AIS to a side effect of this drug. On the other hand, by excluding other etiologies of AIS and considering the occurrence of AIS only 35 days after the onset of TFN therapy, it seems prudent to associate this cerebrovascular event with TFN.

Conclusions

Since the introduction of the TFN drug as an immune system modulating drug for RRMS, very promising results have been presented for this drug. Over the past few years, due to the emerging reports on the [thromboembolic](#) side effects of this drug, researchers have turned their attention to this issue. It is recommended that practitioners do not consider a new [neurological manifestation](#) in a patient with RRMS who is receiving TFN treatment as a new attack but must rule out AIS by requesting the necessary tests and imaging. Additionally, we suggest that it might be better not to choose TFN as a therapeutic option in patients with MS with concurrent possible autoimmune or hypercoagulable disorders due to the possible higher risk of [thromboembolic](#) events.

Patient consent

Written and oral inform consent was obtained from the patient.

Declaration of competing interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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A. H. M. E. Ketabforoush, A. Tajik, M. A. Habibi, and N. A. Khoshsirat were involved in study concept and design, acquisition of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, administrative, technical, and material support. N. A. Khoshsirat and A. H. M. E. Ketabforoush supervised the study.

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