



# Trigeminal neuralgia in a patient with multiple sclerosis: Coincidental? An attack? Teriflunomide induced?

*Multipl sklerozlu bir hastada trigeminal nevralkji: Rastlantısal? Bir atak? Teriflunomid kaynaklı?*

**Sevda DİKER**

## Summary

Trigeminal neuralgia attributed to multiple sclerosis (TNMS) occurs in 2–5% of patients with multiple sclerosis (MS). Although treatment strategies are similar with classical trigeminal neuralgia, TNMS tends to become medically resistant and requires polytherapy. Demyelinating lesions in critical regions are the most common etiology. However therapies used to treat MS may trigger trigeminal neuralgia, as other pain disorders like migraine or daily headaches. Herein is reported a case with MS who suffered severe trigeminal neuralgia five months after switching to teriflunomide, an oral immunomodulator drug approved for relapsing remitting MS. Possibilities for the etiology of trigeminal neuralgia in the case are discussed.

Keywords: Multiple sclerosis; teriflunomide; trigeminal neuralgia.

## Özet

Multipl skleroza bağlı trigeminal nevralkji (TNMS), multipl skleroz (MS) hastalarının % 2–5’inde görülür. Tedavi stratejileri klasik trigeminal nevralkji ile benzer olsa da, TNMS medikal tedaviye dirençli hale gelebilir ve çoklu tedavi ihtiyacı doğabilir. Kritik bölgelerdeki demiyelinizan lezyonlar en sık etiyolojidir. Ancak MS tedavisinde kullanılan terapiler, migren ya da günlük baş ağrısı benzeri diğer ağrı bozuklukları gibi trigeminal nevralkjiyi de tetikleyebilmektedir. Burada relaps-remisyonlar ile giden MS için onaylanmış bir oral immunmodulator ilaç olan ‘teriflunomid’e geçtikten beş ay sonra trigeminal nevralkji gelişmiş bir MS vakası bildirilmiştir. Vakada trigeminal nevralkji için olası etiyolojiler tartışılmıştır.

Anahtar sözcükler: Multipl skleroz; teriflunomid; trigeminal nevralkji.

## Introduction

Trigeminal neuralgia (TN) is characterised by recurrent episodes of excruciating pain lasting several seconds or longer in the sensory distribution of the trigeminal nerve. Pain may be initiated by stimulation of trigger points on the face, lips, or gums or by movement of facial muscles or chewing.<sup>[1]</sup> Multiple sclerosis is a frequent cause of symptomatic TN and is detected in 2–4% of TN cases. Conversely, trigeminal neuralgia attributed to MS (TNMS) occurs in 2–5% of patients with MS.<sup>[2,3]</sup> Although treatment strategies are similar with classical TN, TNMS tends to become medically resistant and requires polytherapy. Usually, an active plaque at the trigeminal root entry zone or in the pons affecting the trigeminal pathways is responsible from the symptoms.

Interestingly, the therapies for MS have been shown to play role in TN, like interferon beta 1a, which was previously related to recurrence of TN in an MS patient.<sup>[4]</sup> Herein is reported a patient with MS who was attack free for seven years and had developed refractory TN 5 months after switching from beta-interferon to teriflunomide therapy, which is an oral immunomodulator drug approved for RRMS.

## Case Report

A fifty-seven year old male patient admitted to emergency service due to very severe trigeminal neuralgia attacks on the left maxillary and mandibular distribution. He was diagnosed with multiple sclerosis eight years ago. He was prescribed interferon beta-1b subcutaneous injection, 8 million IU every

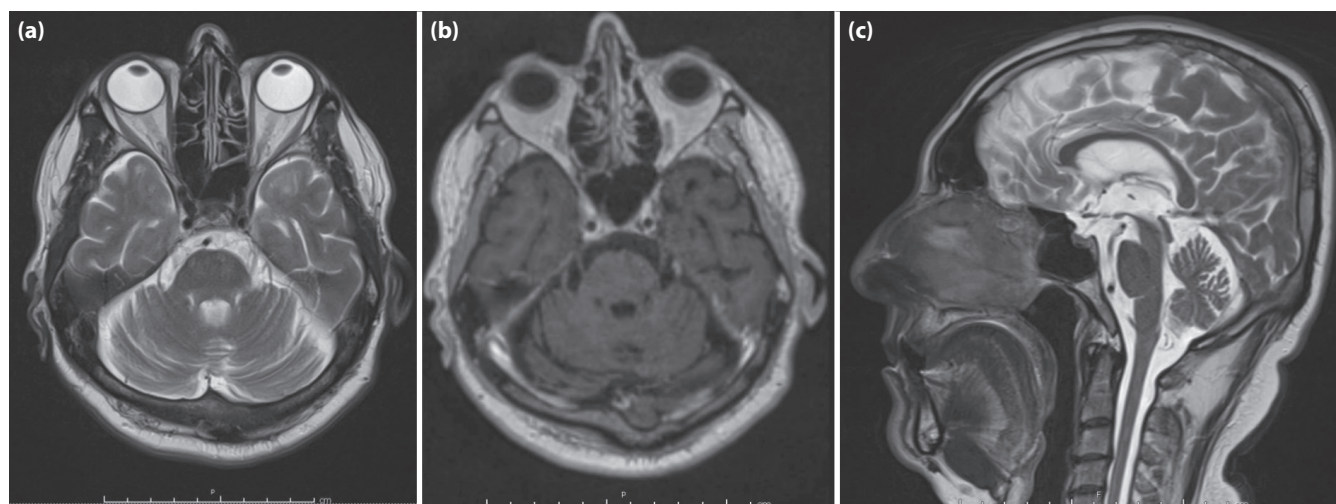
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**Figure 1.** Axial T2 weighted (a) and contrast-enhanced T1 weighted (b), and sagittal T2 weighted (c) brain MRI of the patient showed absence of any demyelinating plaque that could cause TN. (MRI: Magnetic resonance imaging; TN: Trigeminal neuralgia).

other day, in 2011 after his last attack and, due to his wish to continue an oral therapy, was switched to teriflunomide, 14 milligrams(mg) orally once a day, 5 months ago. On admission, the patient reported that the TN had been present for one month and grew worse despite polytherapy. He had been taking carbamazepin 600 mg, gabapentin 300 mg, clonazepam 2 mg and baclofen 5 mg, per oral daily. Contrast enhanced Brain MRI (1.5 Tesla) revealed chronic demyelinating lesions in the brainstem, supratentorially in the pericallosal, periventricular and subcortical regions some of which were in cyst formation as black holes. Trigeminal nerve entry zone was not involved on either side. None of the lesions showed contrast enhancement nor the trigeminal nerve on the left side. No vascular compression or space occupying non vascular lesion was detected (Figure 1). After hospitalisation, gabapentin daily dosage was increased gradually up to 1800 mg, carbamazepin dosage to 800 mg and amitriptyline 10 mg was added. No improvement was achieved and the patient was suffering intolerable pain. Although there was not any active lesion that could lead to TN, intravenous methylprednisolone 1000 mg per day was started as a rescue treatment. On the same day, the patient reported significant improvement and after the second infusion nearly total recovery was achieved. Upon his request, the patient switched back to interferon beta 1b injections and stopped teriflunomide. At the sixth month follow up, he complained of rare mild attacks, and under combination therapy of carbamazepin, gabapentin and duloxetine, did not suffer any severe pain. His control MRI was also unchanged.

## Discussion

Trigeminal neuralgia attributed to MS comes into question when recurrent paroxysms of unilateral facial pain on trigeminal distribution have occurred in an MS patient with evidence of impairment of trigeminal pathways shown either by MRI as a demyelinating plaque at the trigeminal root entry zone or in the pons affecting the intrapontine primary afferents, or by routine electrophysiological studies such as blink reflex or trigeminal evoked potentials. Besides intrapontine area, contralateral insula and hippocampus are the two other regions shown recently to be associated with TNMS.<sup>[5]</sup> Cranial MRI helps to distinguish any causative demyelinating lesion or neurovascular compression.

Although symptomatic treatment options are same with the classical TN, patients with TNMS benefit less from pharmacological and surgical interventions than those with classical TN and become medically refractory and require multiple repeat surgical procedures.<sup>[6]</sup> While carbamazepin is the firstline and usually effective in classical TN, TNMS patients usually need polytherapy.

The relationship between MS therapies and pain disorders has been evaluated in many studies.<sup>[7,8]</sup> La mantia et al.<sup>[9]</sup> showed that the life-time prevalence of primary headaches was higher in MS patients treated with IFNs (72%) compared to patients treated with other immunotherapies and concluded that aggravation of pre-existing primary headaches or the occurrence of de novo headaches with the

clinical characteristics of migraine or tension-type headaches must be taken into account among the side-effects of IFNs in MS patients. In terms of TN, a case demonstrating recurrence of painful trigeminal neuropathy as well as weekly migraine attacks after starting interferon beta-1a treatment was reported previously.<sup>[4]</sup> In that case, a non-contrast enhancing MS plaque was located in the area of the right trigeminal nucleus caudalis within the medulla oblongata. Similar to the presented case, intravenous corticosteroids with oral tapering for 14 days led to significant improvement of the symptoms. While it is unclear how interferon treatment may aggravate trigeminal neuralgia, it has previously been suggested that an increase of cytokines such as interleukin 6 and TNF-alpha following interferon beta administration, may explain the worsening of pain disorders in MS.<sup>[4,10]</sup>

Among newer MS treatments, fingolimod was reported to cause new onset daily persistent headaches that were controlled mainly by anti-inflammatory drugs and did not require withdrawal of fingolimod.<sup>[11]</sup>

Teriflunomide is an oral, immunomodulator drug for relapsing remitting MS and is the active metabolite of leflunomide that inhibits pyrimidine biosynthesis and disrupts the interaction of T cells with antigen presenting cells. The most common adverse effects of teriflunomide are diarrhea, nausea, hair thinning, elevated alanine aminotransferase levels, neutropenia and lymphopenia.<sup>[12]</sup> Teratogenicity risk is the another important issue which should be taken into account for patients of childbearing age. Headaches were reported among the side effects, however were not more frequent than seen in the placebo groups.<sup>[12]</sup> There has not yet been a report about TN as a side effect of teriflunomide.

The presented case raises two questions: Firstly, if there occurs TN in the course of MS, is a normal MRI sufficient to totally exclude any active lesion in the trigeminal pathway? Slice thickness and resolution capacity of the MRI sequences are important points here. In the presented case, although symptomatic polytherapy for TN had been started, the patient did not benefit until intravenous high dose methylprednisolone, which was followed by oral tapering.

Taking into account the response to corticosteroids, there could be an inflammatory mechanism leading to development of TN. Even though it could of course be a less specific effect of steroids on neuronal cell membranes, trying pulse steroid treatment in refractory cases of TN in MS patients, even when routine MRIs exclude any causative demyelinating lesion, is reasonable.

Secondly, could teriflunomide be a trigger of TN? The patient had a seven year attack free period before starting teriflunomide and developed severe TN five months after. Repeated cranial MRIs excluded any causative lesion in the aforementioned regions. Regression of the symptoms after cessation of the drug may be an indirect evidence for the pain triggering effect of the agent. As teriflunomide can be detected in the serum even two years after its cessation, a clear regression of the complaints would not be seen. However even if merely withdrawing the drug had resulted in the neuralgia disappearing it would be unconvincing; because TN is a condition that is prone to periods of remission. Suggesting that teriflunomide was responsible for the exacerbation in his neuralgia would thus be speculative at this point.

Finally, TN in the course of MS is not very rare and is more resistant to treatments than classical TN. It is known that drugs used to treat MS may aggravate or trigger pain disorders. Follow-up of MS patients for pain disorders and further information from new cases may expand our knowledge about the effect of MS therapies on pain disorders.

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## References

1. Adams RD, Victor M, Ropper AH. Principles of Neurology, 6th ed, McGraw-Hill School Education Group, 1997, p187.
2. Hooge JP, Redekop WK. Trigeminal neuralgia in multiple sclerosis. *Neurology* 1995 ; 45 : 1294–1296.
3. Solaro C, Bricchetto G, Amato MP, Cocco E, Colombo B, D'Aleo G, et al. The prevalence of pain in multiple sclerosis: a multicenter cross-sectional study. *Neurology* 2004 ; 63 : 919–921.
4. Bischof A, Sprenger T. Interferon beta-associated recurrence of painful trigeminal neuropathy attributed to a multiple sclerosis plaque. *J Headache Pain* 2014; 15 : 21.

5. Fröhlich K, Winder K, Linker RA, Engelhorn T, Dörfler A, Lee DH, et al. Supratentorial lesions contribute to trigeminal neuralgia in multiple sclerosis. *Cephalalgia* 2017; 38(7):1326-1334.
6. Krishnan S, Bigder M, Kaufmann AM. Long-term follow-up of multimodality treatment for multiple sclerosis-related trigeminal neuralgia. *Acta Neurochir (Wien)* 2018;160(1):135-144.
7. Filippini G, Munari L, Incorvaia B, Ebers GC, Polman C, D'Amico R, et al. Interferons in relapsing remitting multiple sclerosis: a systematic review. *Lancet* 2003; 361: 545 -552.
8. Pöllmann W, Erasmus LP, Feneberg W, Then Bergh F, Straube A. Interferon beta but not glatiramer acetate therapy aggravates headaches in MS. *Neurology* 2002; 59: 636-639.
9. La Mantia L, D'Amico D, Rigamonti A, Mascoli N, Bussone G, Milanese C. Interferon treatment may trigger primary headaches in multiple sclerosis patients. *Mult Scler* 2006;12(4):476-480.
10. Nakatsuji Y, Nakano M, Moriya M, Kishigami H, Tatsumi C, Tada S, et al. Beneficial effect of interferon-beta treatment in patients with multiple sclerosis is associated with transient increase in serum IL-6 level in response to interferon-beta injection. *Cytokine* 2006;15(1-2):69-74.
11. Fragoso YD, Adoni T, Gomes S, Goncalves MV, Matta AP, Mendes MF, et al. Persistent headache in patients with multiple sclerosis starting treatment with fingolimod. *Headache* 2015;55(4):578-9.
12. He D, Zhang C, Zhao X, Zhang Y, Dai Q, Li Y, et al. Teriflunomide for multiple sclerosis. *Cochrane Database Syst Rev* 2016; 22;3:CD009882.