

A Rare Case of Painful Trigeminal Neuropathy Secondary to Lateral Medullary Infarct: Neuroimaging and Electrophysiological Studies

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Abstract-

Purpose: To report a rare case of painful trigeminal neuropathy after lateral medullary infarct and probe its underlying pathogenesis on the basis of neuroimaging and electrophysiological study.

Case Report: A 45-year-old man presented acute onset of unsteady gait followed by paroxysmal and electric shock-like headache in the distribution of ophthalmic branch of left trigeminal nerve in 2 days. Neurological examinations showed hypoesthesia in the distribution of mandibular branch of left trigeminal nerve and left appendicular ataxia. Muscle powers and deep tendon reflexes were normal. Brain magnetic resonance imaging revealed infarct within the left cerebellum and middle portion of dorsolateral medulla. Vascular compression at the root entry zone of trigeminal nerve was excluded. Painful trigeminal neuropathy secondary to lateral medullary infarct was diagnosed. Ancillary blink reflex study 3 days after the stroke event showed abnormal late responses (R2), either ipsilateral or contralateral, after stimulation of left supraorbital nerve, suggesting left medullary lesion. Follow-up study 3 weeks later demonstrated normalization in absolute latencies of bilateral late responses, in line with remission of pain paroxysms on low-dose gabapentin treatment.

Conclusion: Painful trigeminal neuropathy attributed to lateral medullary infarct is a unique disease entity. Ophthalmic branch involvement, coexisting sensory deficits, absence of triggers, and rapid involvement and remission are its characteristics. Our neuroimaging study delineated ischemic stroke pathology within descending tract and spinal nucleus of trigeminal nerve. Serial electrophysiological studies provide evidences supporting ephaptic transmission as the main pathogenesis concordant with dynamics of neuropathic pain and therapeutic implications.

Key Words: Lateral medullary infarct, trigeminal neuralgia, painful trigeminal neuropathy, brain MRI, blink reflex

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INTRODUCTION

Trigeminal neuralgia (TN) is a disorder characterized by recurrent, brief, shock-like pain limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli⁽¹⁾. Although its incidence is relatively rare⁽²⁾, the paroxysmal and excruciating characteristics often draw clinicians' attention during daily practice. In the realm of the International Classification of Headache Disorders, classical TN is applied to those cases without apparent cause other than neurovascular compression. By contrast, painful trigeminal neuropathy covers the rest of the spectrum as symptomatic TN nominated previously^(1,3). While sharing similar hallmarks with classical TN, painful trigeminal neuropathy may present additional clinical features and allude its underlying structural changes other than

vascular compression, such as tumor, multiple sclerosis⁽⁴⁾, and stroke⁽²⁾. In view of a priori knowledge suggesting (i) painful trigeminal neuropathy accounts for 15% of cases of overall TN; stroke has been proven as the minority of causative pathology⁽⁴⁾; (ii) most case reports of painful trigeminal neuropathy after stroke associate pons as part of the causative neural substrates⁽⁵⁻⁷⁾, we herein presented a case of painful trigeminal neuropathy secondary to lateral medullary infarct.

CASE REPORT

A 45-year-old man without known systemic disease presented acute onset, persistent dizziness, unsteady gait, and clumsiness of left limbs. On neurologist visiting, he was alert and oriented. Cranial nerves evaluation showed hypoesthesia in the distribution of mandibular branch of

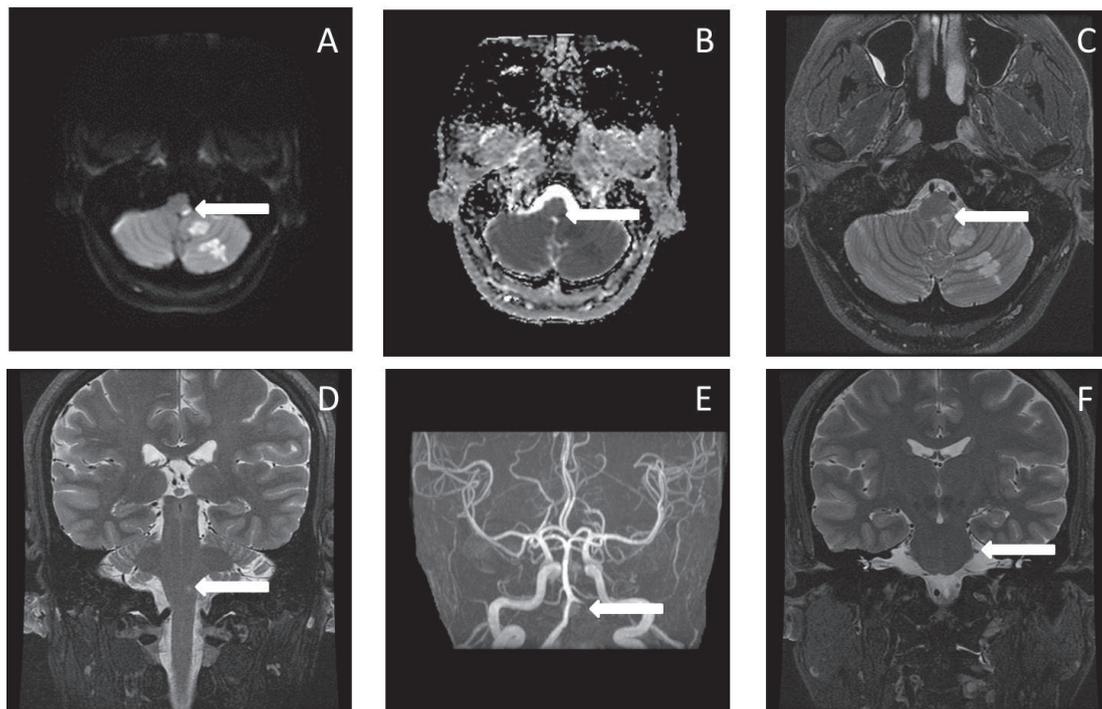


Figure 1. Brain MRI demonstrates areas of restricted diffusion on (A) diffusion-weighted imaging (b value = 1000 sec/mm²) and (B) corresponding apparent diffusion coefficient imaging in the left lateral medulla (arrows) and left cerebellum, compatible with ischemic stroke. On (C) axial and (D) coronal fast-spin echo, fat-suppressed T2-weighted imaging (TR/TE = 6528/85 msec with 2 mm slice thickness), a superficial and ovoid-shaped hyperintense lesion locates within the most dorsal position, middle portion of left medulla (arrows). (E) MRA shows left vertebral artery occlusion (arrow). (F) Vascular compression at the root entry zone of the left trigeminal nerve (arrow) is excluded.

the left trigeminal nerve and otherwise normal. Cerebellar function tests revealed appendicular ataxia of the left limbs and drunken gait. Symmetric and competent muscle power of four limbs with normoreflexia throughout was documented.

Brain magnetic resonance imaging (MRI) one day after onset of disease revealed scattered hyperintensities on diffusion weighted imaging with corresponding hypointensities on apparent diffusion coefficient imaging within the left cerebellar hemisphere and left dorsolateral medulla, compatible with acute infarct (Figure 1A, B). Horizontally, a superficial, ovoid in shape, hyperintense lesion restricted within most dorsal position of medulla was identified on T2-weighted imaging, presumably involving descending tract and spinal nucleus of trigeminal nerve (Figure 1C). Longitudinally, the lesion was located at the middle portion of left medulla (Figure 1D).

Magnetic resonance angiography showed left vertebral artery occlusion (Figure 1E). There was no vascular compression at the root entry zone of the left trigeminal nerve (Figure 1F).

Two days after the stroke onset, he started having brief electric shock-like headache. The intense, stabbing, and cutting pain that radiated toward frontal and periorbital regions of left side lasted for seconds in a paroxysmal and unexpected manner. He was bothered by facial grimaces whenever pain attacked; dysphoria and baseline pain of moderate severity lingered between the episodes of lancinating pain.

Painful trigeminal neuropathy secondary to lateral medullary infarct was diagnosed based onto close temporal associations. Ancillary blink reflex was conducted to elucidate underlying pathogenesis within trigeminal neuronal circuits. After stimulation of the affected left

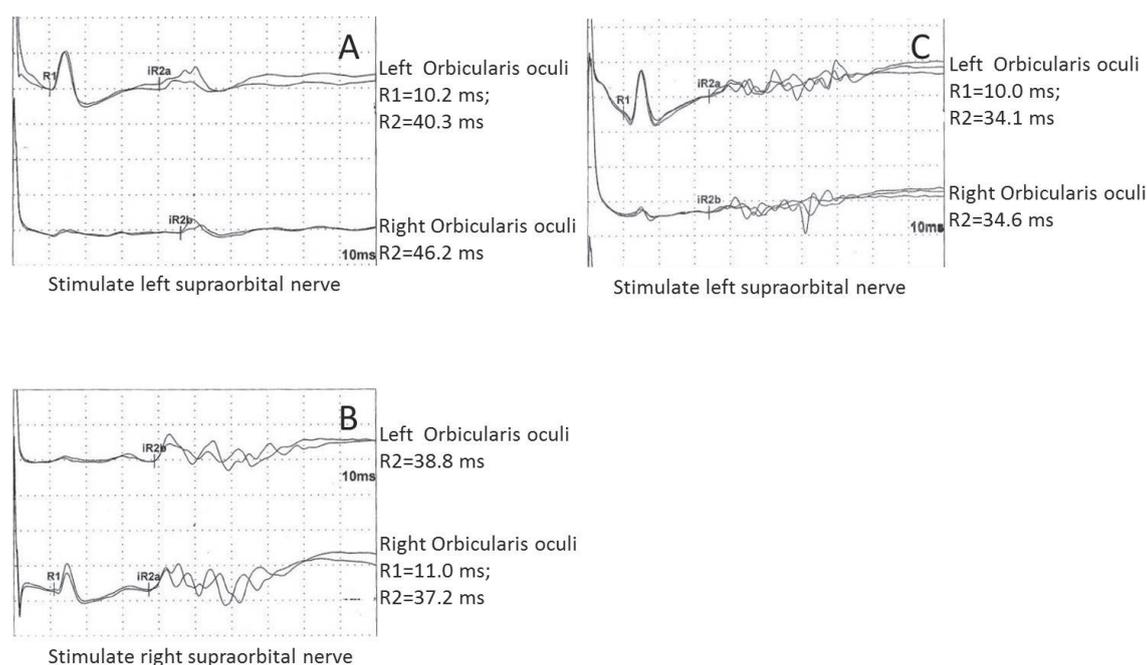


Figure 2. Blink reflex studies during the attack of painful trigeminal neuropathy (3 days after left lateral medullary infarct). (A) Stimulation of the left supraorbital nerve produces borderline ipsilateral R2 response and a delayed contralateral R2 response, in the presence of normal ipsilateral R1 response. (B) Stimulation of the right supraorbital nerve produces normal responses. (C) Follow-up blink reflex studies (3 weeks after left lateral medullary infarct): normalization of absolute latencies of both ipsilateral and contralateral R2 responses by left supraorbital nerve stimulation.

side, a borderline ipsilateral R2 component (40.3 ms; ref.: <41ms) and a prolonged contralateral R2 component (46.2 ms; ref.: <44 ms), in the presence of normal ipsilateral R1 component (10.2ms, ref: <13 ms), was recorded on the orbicularis oculi (Figure 2A). The latency difference between ipsilateral and contralateral R2 components following left side stimulation was abnormal (5.9 ms; ref.: <5 ms). While both ipsilateral and contralateral R2 components (37.2 ms and 38.8 ms, respectively) after right side stimulation were present with normal latency (Figure 2B), the side-to-side differences of contralateral R2 component was abnormal (7.4 ms; ref.: <7 ms). The result was suggestive of left medullary lesion.

Treatment with gabapentin with humble titration (300 mg-600 mg/day) was commenced. He had a good recovery 2 weeks after treatment, in association with improvement of visual analogue scale (6 decreased to 2) as well as a ninety percentage improvement in pain intensity from brief pain inventory. Follow-up study of blink reflex 3 weeks later revealed normalization of absolute latency of ipsilateral R2 component (34.1ms) and contralateral R2 component (34.6ms) by left supraorbital nerve stimulation, suggesting resolution of previously-damaged circuits (Figure 2C).

DISCUSSION

The aim of our report is to integrate neuroimaging and electrophysiological studies with clinical presentations in a case with painful trigeminal neuropathy after recent lateral medullary infarct, in which the area has been rarely reported before. Albeit some portion of patients with lateral medullary infarct experience sensory symptoms over face⁽⁸⁾, limited case reports detail the linkage with TN^(2,9). From clinical viewpoints, there are some features enabling differentiation between painful trigeminal neuropathy of our case and classical TN. First, painful trigeminal neuropathy in a distribution of ophthalmic branch but without noticeable triggers contrasts to classical TN, in which involvement of maxillary and/or mandibular branches as well as variable triggers are typically detected^(1,6). Moreover, this case shares both sensory deficits and pain paroxysm alongside trigeminal nerve territory, as one of the distinguishing features from classical TN⁽¹⁰⁾. Lastly, while baseline headache and

dysphoria may develop with time in classical TN⁽¹¹⁾, this case present more rapid evolvement and remission. It is also worthy to put notions that our patient has painful paroxysm 2 days after stroke event, contrasting cases during subacute to chronic stage of stroke in previous literatures^(2,12). It is therefore plausible to infer the pathogenesis of painful trigeminal neuropathy after stroke may not be identical, in the context of divergent latencies as well as variable neurological signs.

Although great attempts of previous neuroimaging studies have been made, the anatomical loci associated with painful trigeminal neuropathy are not uniform. Some literatures of pontine infarct highlight the role of trigeminal dorsal root entry zone⁽⁶⁾; other few case reports of medulla infarct hypothesize lower levels of the dorsolateral medulla⁽⁹⁾ as a pivotal area leading to irritation of central trigeminal pathway. This indicates abnormal trigeminal neuronal circuits, rather than a single anatomical locus, as the major downstream pathogenesis of stroke-related painful trigeminal neuropathy. With regards to the exact mechanisms of increased neuronal trigeminal nucleus activities, some state pathologic multineuronal reflex of the trigeminal circuits as the fundamental pathogenesis, others suggest ephaptic transmission within the central trigeminal pathways as the crucial mechanism⁽⁵⁾. Our comprehensive MRI evaluation not only delineates precise anatomical correlates but also excludes subtle vascular contact abutting dorsal root entry zone of trigeminal nerve. The vascular compromise is convincingly regarded as the aetiopathological process leading neuronal hyperexcitation, as the consequences of hypoxia. As dorsolateral medulla dictates both descending tract and spinal nucleus of trigeminal nerve, infarct of this area gives rise to ipsilateral trigeminal symptoms and signs. Previous cohort study has addressed the heterogeneity of sensory symptoms among lateral medullary infarct⁽⁸⁾. That a certain portions of patients experience headache but no trigeminal symptoms indicates neuronal hyperexcitation may sometimes develop at the very beginning of cerebrovascular disease⁽⁸⁾. We therefore hypothesize neuronal hyperexcitation secondary to descending tract and spinal nucleus of trigeminal nerve as the major pathogenesis for painful trigeminal neuropathy in our case, who shares both sensory deficits and pain paroxysm alongside trigeminal nerve territory.

In concordance with neuroimaging observations, our electrophysiological studies provide constellation evidences supporting dynamic changes of central trigeminal circuits. Given the very paroxysmal nature, as the key feature of TN, is hardly reconciled in purely anatomical terms, our serial electrophysiological studies provide evidences supporting ephaptic transmission as the main pathogenesis correlating clinical observations. We infer that neuronal injury along the trigeminal circuits of our case is partially injured on the basis of temporary abnormal late response. It has been suggested that increased excitability, regardless of underlying etiologies, in some of the trigeminal afferents would subsequently lead to TN⁽¹³⁾. Under certain circumstances, dorsal root ganglia cells would be observed to generate membrane potential oscillations, simulating ectopic impulses in TN⁽¹⁴⁾. While conventional synaptic transmission depends on vesicular neurotransmitter release, ephaptic transmission transmits current through extracellular potential gradients and voltage sensitive channels on the opposing membrane⁽¹⁵⁾. On reaching certain threshold, the increased spike activities may cross-excite neighboring C-cells through an extracellular electrical field⁽¹⁶⁾, contributing lancinating pain as nociceptors being activated⁽¹⁷⁾. The satisfactory control of antiepileptic drugs toward classical TN⁽⁴⁾ and painful trigeminal neuropathy might be attributed to blockade, or at least modulation, of ephaptic transmission.

It is also interesting that our patient experienced remarkable improvement on low-dose gabapentin treatment. Aside from its primary property related with gamma-aminobutyric acid, it is believed to involve interaction with voltage-gated calcium channels, especially at low concentrations⁽¹⁸⁾. Stabilization of calcium influx may lower excitability and modulate membrane potentials of neurons, in turn mitigate pain paroxysm observed clinically. On the basis of satisfactory response of low-dose gabapentin in treating stroke-related painful trigeminal neuropathy, we postulate that gabapentin facilitates neuron quenching mechanism by blocking the ephaptic transmission through voltage sensitive calcium channels within injured circuits.

Although lateral medullary infarct was visualized in our MRI, some debate about the causality between lateral medullary infarct and painful trigeminal neuropathy might

still exist. A newly-evolved infarct other than the regions primarily identified might develop, as pain paroxysms happened one day after MRI evaluation. However, the possibility of stroke-in-evolution is limited on the basis of stationary neurological signs, close temporal relationship, and different penetrating arteries supplying lateral medulla and lateral pons.

In sum, we present a patient of painful trigeminal neuropathy secondary to lateral medullary infarct, contrasting pontine-infarct related trigeminal neuralgiform pain mostly mentioned. The ophthalmic branch of trigeminal nerve involvement without noticeable triggers as well as rapid evolvement and remission serve as its unique clinical presentations. By neuroimaging observations, ischemic stroke pathology within descending tract and spinal nucleus of trigeminal nerve is stringently delineated. Serial electrophysiological studies provide evidences supporting ephaptic transmission as the main pathogenesis concordant with dynamics of neuropathic pain and therapeutic implications.

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