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Upbeat nystagmus is a useful sign in the regional diagnosis of trigeminal nerve disorder with multiple sclerosis

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Abstract

Trigeminal nerve disorder is an important neurological sign that is often seen with multiple sclerosis (MS). We investigated eye movements in three MS patients with trigeminal disorder due to pontine lesions near the trigeminal root entry zone (REZ). Upbeat nystagmus was observed in all MS patients with trigeminal REZ lesions. We conjecture that trigeminal nerve disorder and upbeat nystagmus appeared due to simultaneous damage to both the trigeminal nerve and the vestibulo-ocular reflex pathway.

If upbeat nystagmus appears in MS patients exhibiting a trigeminal nerve disorder, such as trigeminal neuralgia, and paralysis, pontine lesions near the trigeminal REZ should be considered. Upbeat nystagmus can be understood as a useful sign for the clinical regional diagnosis of trigeminal nerve disorder.

1. Introduction

Trigeminal nerve disorders such as trigeminal paralysis and trigeminal neuralgia at the brainstem level are often seen in patients with multiple sclerosis (MS). The regional diagnosis of damage to the trigeminal nerve is important in the regional diagnosis of MS lesions. Trigeminal nerve root entry zone (REZ) lesions reportedly account for approximately 10% of lesions in MS patients (Sugiyama et al. 2015).

In MS patients with only a clinical trigeminal nerve disorder, there are some cases in which a lesion cannot be detected by either neurophysiological examination or magnetic resonance imaging (MRI) (Bergamaschi et al. 1994; Koutsis et al. 2016). On the other hand, although we were not able to detect a lesion by clinical examination or MRI, we may estimate the causative lesions of trigeminal nerve disorder by neurophysiological methods alone (Bergamaschi et al. 1994; Koutsis et al. 2016). Furthermore, 41.4% of MS patients without clinical trigeminal nerve disorder had trigeminal nerve function disorder, which was detected via a neurophysiological method (Eisen et al. 1981). From these previous reports, it is difficult to estimate the causative lesions of trigeminal nerve disorder using MRI methods alone in MS patients. If accompanying neurologic signs are

indicated in the case of a trigeminal nerve disorder due to the pontine lesions of MS, regardless of whether lesions are visible via MRI, we can estimate the presence of pontine lesions.

2. Case 1

A 47-year-old woman developed sudden hypesthesia and dysesthesia of her left lip after having experienced transient dizziness the previous month. The paresthesia worsened over the next 2 weeks, extending to the entire left side of the face and inside the mouth. Left trigeminal paralysis appeared 4 days later, and the patient presented for examination with this as her chief complaint. In addition to hypesthesia, dysesthesia, and neuralgia in the left V1–V3 territory, primary position upbeat nystagmus was observed when the eyes were open in darkness (Video 1). Nystagmus was not induced during fixation. No other neurological abnormalities were identified. The only abnormal result from cerebrospinal fluid testing was a mild elevation of protein concentration. Oligoclonal bands were not detected. Serum anti-aquaporin-4 (anti-AQP-4) antibody tests yielded negative results. Contrast-enhanced MRI revealed a hyperintense lesion near

the left trigeminal nerve REZ on T2-weighted imaging (Fig. 1A). Upbeat nystagmus was confirmed via electronystagmography (Fig. 1D). Following the Revised McDonald Diagnostic Criteria (Polman et al. 2005), clinically isolated syndrome (CIS) MS was diagnosed.

3. Case 2

A 43-year-old woman suffered left trigeminal paralysis; 4 months later, she also developed transverse myelopathy at the thoracic spinal cord level and below. MRI revealed lesions in the left middle cerebellar peduncle and cervical spinal cord, and MS was diagnosed. Symptoms showed almost complete resolution after steroid pulse therapy. After 6 years, the patient developed right trigeminal paralysis, trigeminal neuralgia, and oscillopsia. She was admitted to the hospital 2 weeks later with vertigo, vomiting, and double vision. Hypesthesia, dysesthesia, and neuralgia in the right V1–V3 territory were identified on admission. Upbeat nystagmus was observed during fixation and absence of fixation. Her cerebrospinal fluid test results were all normal. Oligoclonal bands were not detected. Serum anti-AQP-4 antibody tests yielded negative results. MRI of the brain

revealed a hyperintense linear lesion near the right trigeminal nerve REZ on T2-weighted imaging (Fig. 1B).

4. Case 3

A 23-year-old woman noticed dysesthesia of the right arm, which spread to the right side of the trunk and right leg within 2 weeks. Three weeks after onset, she also developed paralysis of the right arm and leg, followed immediately by hypesthesia and pain on the right side of the mouth; she became unable to walk unaided. When the patient was admitted to the hospital 4 weeks after onset, in addition to hypesthesia in the right V1 and V3 territories and dysesthesia and neuralgia in the right V2 territory, primary position upbeat nystagmus was observed only during absence of fixation. Incomplete paralysis of the right arm and leg, hypesthesia, and an exaggerated deep tendon reflex were also present. Cerebrospinal fluid test results were all normal. Oligoclonal bands were not detected. Serum anti-AQP-4 antibody tests were negative. MRI revealed a hyperintense lesion near the left trigeminal nerve REZ on T2-weighted imaging (Fig. 1C). CIS MS was diagnosed.

5. Discussion

Upbeat nystagmus occurs in association with various disorders, such as infarction (Hirose et al. 1998), multiple sclerosis (Fisher et al. 1983), Wernicke's encephalopathy (Abouaf et al. 2011), cerebellar vermis tumor (Higashi-Shingai et al. 2011), and poisoning (Nakamagoe et al. 2013). Though many patients developed primary position upbeat nystagmus due to medullary lesions (Hirose et al. 1998), an unaccompanied symptom of upbeat nystagmus is an insufficient regional diagnostic sign. Upbeat nystagmus increases the utility of the regional diagnostic sign when it is co-localized with another pontine sign, such as trigeminal nerve dysfunction.

The pons is one area in which a lesion responsible for upbeat nystagmus may be located, and midline lesions in the upper pons and lesions close to the midline have previously been reported (Ranalli et al. 1988; Pierrot-Deseilligny et al. 2005). Damage to the ventral tegmental tract (VTT) in these lesions contributes to the development of nystagmus (Pierrot-Deseilligny and Milea 2005). The literature describes the VTT as being located ventrolateral to the cerebellar peduncle at the level of the lower pons, arching in the

central region above the level of the mid-pons, and crossing over in the upper pons to reach the basilar part of the pons (Ranalli et al. 1988; Pierrot-Deseilligny et al. 2005). The detailed course of the VTT in the brainstem has yet to be ascertained. In light of the locations of our three patients' lesions, the VTT may run near the trigeminal nerve root in the mid-pons. In Case 1, upbeat nystagmus was the only symptom other than trigeminal neuralgia and trigeminal paralysis. This could be explained if the localized pontine lesion in this case were closest to the course of the VTT. Figure 1E illustrates the mechanism of onset for upbeat nystagmus due to lesions near the trigeminal nerve REZ in the pons. This is the first report for the clinical combination of upbeat nystagmus and trigeminal nerve disorders.

The VTT has been conjectured to run near the trigeminal nerve root at the level of the trigeminal nerve REZ in the mid-pons. When examining patients with trigeminal nerve disorder, the confirmation of upbeat nystagmus may indicate the spread of damage to the mid-pons, representing a clinically important finding. However, upbeat nystagmus may have few subjective symptoms and be difficult to detect in gaze. In some cases, upbeat nystagmus can only be detected when the eyes are open in a dark room or with Frenzel

goggles. It is known that upbeat nystagmus, central vestibular nystagmus caused by disorders of the central vestibular circuits, is affected by visual input and may be suppressed by gaze fixation (Leigh and Zee 2005). In two of our cases, upbeat nystagmus was clearly observed when the eye was open in the dark; however, it was difficult to recognize it during gaze fixation. Therefore, we must carefully observe the nystagmus during absence of fixation, as it is easy to overlook upbeat nystagmus due to pontine lesions under clinical observation of gaze fixation alone.

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Conflict of interest: All authors declare that they have no conflicts of interests.

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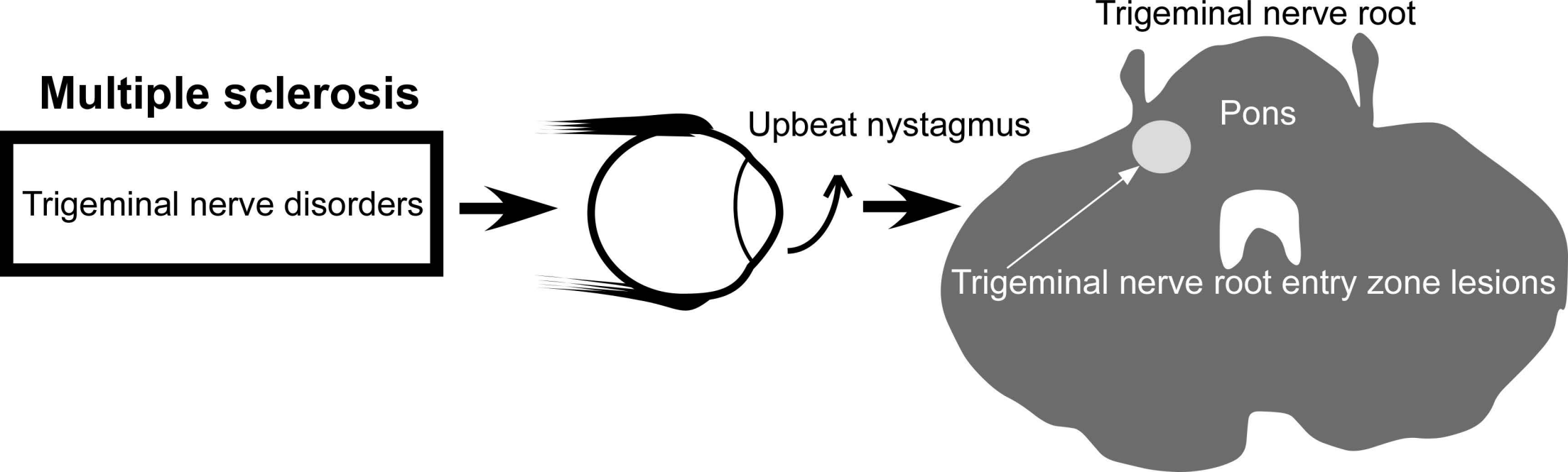
Figure Legend

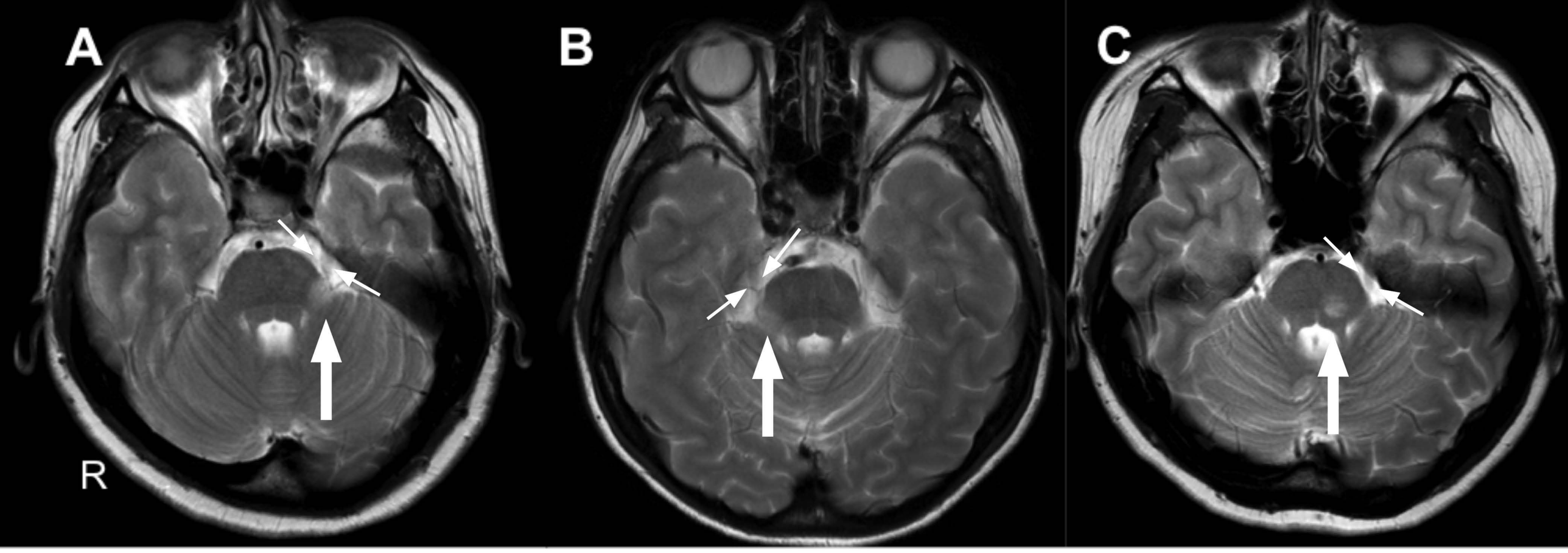
Fig. 1. (A–C) T2-weighted MRI of the brain in Cases 1 (A), 2 (B), and 3 (C) (1.5T; repetition time, 3000 ms; echo time, 80 ms). White upward arrows (↑) indicate lesions, and white facing arrows (→←) indicate the trigeminal nerve root. **(D)** Electronystagmogram for Case 1 (direct current recording). The top trace shows vertical nystagmus eye movements, and the bottom trace shows velocity waveforms. Saw-shaped waveforms point upward during the rapid phase and downward during the slow phase. **(E)** Schematic of the mechanism of action underlying the appearance of upbeat nystagmus as a result of damage near the trigeminal nerve root entry zone (REZ) in the pons. Vestibular information from the anterior semicircular canal is sent to the vestibular nucleus and then transported to the oculomotor neurons via the ventral tegmental tract (VTT). This represents part of the vestibulo-ocular reflex pathway. The VTT is located ventrolateral to the cerebellar peduncle at the level of the lower pons, arching in the central region above the level of the mid-pons, and crossing over in the upper pons to reach the basilar pons. Excitatory input from the superior vestibular nucleus (SVN) projects to the oculomotor nucleus via the VTT, ultimately causing contraction of the

superior rectus muscle. Damage to the VTT weakens input from the SVN and, thus, to the superior rectus muscle, resulting in a relative increase in muscle tone of the inferior rectus muscle. This, in turn, leads to downward movement of the eye, constituting the slow phase of nystagmus. A compensatory upward rapid phase is then generated. This sequence of eye movements is known as upbeat nystagmus.

Video 1 caption

The patient wore goggles fitted with an infrared camera (Case 1). Primary position upbeat nystagmus was observed when the eyes were open in darkness.


Multiple sclerosis
Trigeminal nerve disorders
Upbeat nystagmus
Trigeminal nerve root
Pons
Trigeminal nerve root entry zone lesions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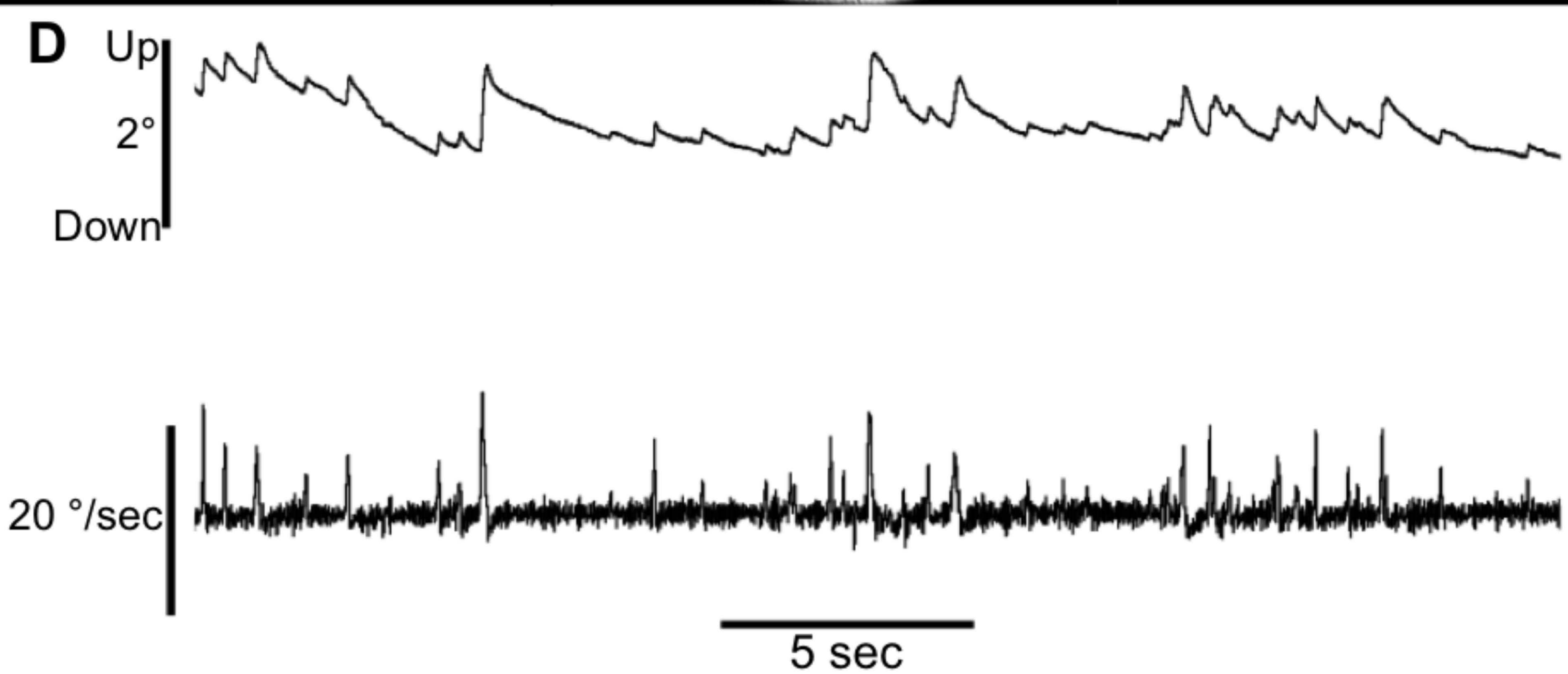
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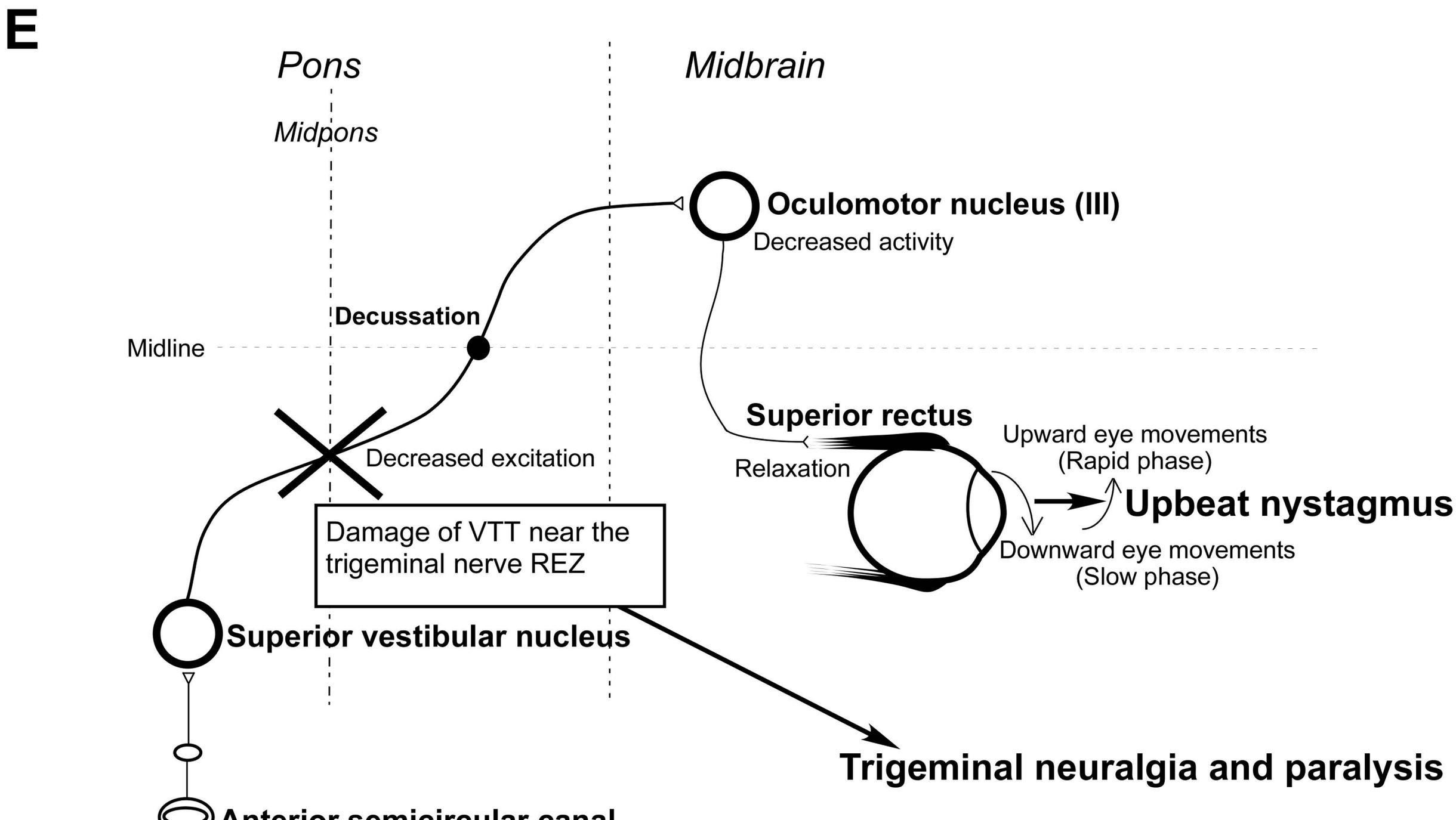
E
Pons
Midbrain
Midpons
Oculomotor nucleus (III)
Decreased activity
Decussation
Midline
Superior rectus
Relaxation
Upward eye movements
(Rapid phase)
Upbeat nystagmus
Downward eye movements
(Slow phase)
Decreased excitation
Damage of VTT near the
trigeminal nerve REZ
Superior vestibular nucleus
Trigeminal neuralgia and paralysis
Anterior semicircular canal