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Degeneration of paramedian nuclei in the thalamus induces Holmes tremor in a case of artery of Percheron infarction

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Abstract

Rationale: Holmes' tremor is an uncommon neurologic disorder following brain insults, and its pathogenesis is undefined. The interruption of the dento-rubro-thalamic tract and secondary deterioration of the nigrostriatal pathway are both required to initiate Holmes' tremor. We used nuclear medicine imaging tools to analyze a patient with concurrent infarction in different zones of each side of the thalamus. Finding whether the paramedian nuclear groups of the thalamus were injured was a decisive element for developing Holmes' tremor.

Patient concerns: A 36-year-old woman was admitted to our department due to a bilateral paramedian thalamic infarction. Seven months after the stroke, a unilaterally involuntary trembling with irregularly wavering motions occurring in both her left hand and forearm.

Diagnosis: Based on the distinct features of the unilateral coarse tremor and the locations of the lesions on the magnetic resonance imaging (MRI), the patient was diagnosed with bilateral paramedian thalamic infarction complicated with a unilateral Holmes' tremor.

Interventions: The patient refused our recommendation of pharmacological treatment with levodopa and other dopamine agonists based on personal reasons and was only willing to accept physical and occupational training programs at our outpatient clinic.

Outcomes: We utilized serial anatomic and functional neuroimaging of the brain to survey the neurologic deficit. A brain magnetic resonance imaging showed unequal recovery on each side of the thalamus. The residual lesion appeared larger in the right-side thalamus and had gathered in the paramedian area. A brain perfusion single-photon emission computed tomography (SPECT) revealed that the post-stroke hypometabolic changes were not only in the right-side thalamus but also in the right basal ganglion, which was anatomically intact. Furthermore, the brain Technetium-99m-labeled tropanes as a dopamine transporter imaging agents scan (^{99m} Tc-TRODAT-1) displayed a secondary reduction of dopamine transporters in the right nigrostriatal pathway which had resulted from the damage on the paramedian nuclear groups of the right-side thalamus.

Lessons: Based on the functional images, we illustrated that a retrograde degeneration originating from the thalamic paramedian nuclear groups, and extending forward along the direct innervating fibers of the mesothalamic pathway, played an essential role towards initiating Holmes' tremor.

Abbreviations: AOP = artery of Percheron, ECD = ethylene cysteine diethyl ester, FLAIR = fluid attenuation inverse recovery, MRA = magnetic resonance angiography, MRI = magnetic resonance imaging, NIHSS = National Institute of Health Stroke Scale, PFO = patent foramen ovale, SPECT = single-photon emission computed tomography, T2WI = T2-weighted image, *Tc*-99m *TRODAT*-1 = *Technetium*-99m-labeled tropanes as dopamine transporter imaging agents.

Keywords: artery of percheron, bilateral thalamic infarction, case report, Holmes tremor, mesothalamic pathway

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1. Introduction

Holmes tremor, a spectrum of pathologic tremors with lesions located in the central nervous system, is an uncommon symptom after various brain insults.[1] Holmes tremor is characterized by rhythmic and irregular oscillation of the upper extremities, with frequency occurring between 3 Hz and 4.5 Hz at rest and widening obviously in amplitude during movements or goal-direction tasks. Holmes tremor has been introduced as other names in various formal documents, including midbrain tremor, mesencephalic tremor, rubral tremor, thalamic tremor, and cerebellar outflow tremor because those lesions leading to Holmes tremor have been frequented in such areas. However, these names may also imply the incorrect idea of the pathogenesis of Holmes tremor.

The accurate pathogenesis of Holmes tremor is undefined. The unique presentation of Holmes tremor implies that its mechanism involves the interruption of neural pathways or nuclei in motor control, such as basal ganglion or substantia nigra, though studies reveal that the dento-rubro-thalamic tract is the site where the Holmes tremor originates.[1] However, lesions only in the dento-rubro-thalamic tract are insufficient for the emergence of Holmes tremor to occur. Experimental studies have demonstrated that a sole red nucleus lesion did not induce Holmes tremor.[2,3] It has been shown that another element is the nigrostriatal pathway. Seidel et al[4] verified that the dysfunction of the nigrostriatal pathway and dento-rubro-thalamic tract were both equally important in order to induce Holmes tremor. Nonetheless, how a lesion in the dento-rubro-thalamic tract interacts with the nigrostriatal pathway remains unclear. It is regarded as the key factor in the development of Holmes tremor.

In this study, we report a patient suffering from unilateral Holmes tremor following a rare bilateral paramedian thalamic infarction, which was caused by the occlusion of the artery of Percheron (AOP). A post-stroke brain perfusion single-photon emission computed tomography (SPECT), as well as a *Technetium*-99m-labeled tropanes as dopamine transporter imaging agents scan (^{99m}Tc-TRODAT-1) demonstrated that the various injured nuclear groups of each side of the thalamus caused varying degrees of dysfunction in the ipsilateral nigrostriatal pathway. This observation indicates that a neurological link between the dento-rubro-thalamic tract and the nigrostriatal pathway modulated these 2 pathways and initiated the Holmes tremor.

2. Case presentation

A 36-year-old woman, without any remarkable medical history, was presented to our emergency room after being found unconscious and weak in her left extremities. At that time the patient arrived at the emergency room, the Glasgow Coma Scale was evaluated as E2M6V2. The patient's vital signs were within normal range (blood pressure was measured as 142/87 mmHg, temperature 36.0 °C, heart rate 65 beats per minute, and respiratory rate 18 breaths per minute). Physical examination revealed that her pupils were anisocoric and any pupillary light reflex in her right eye was absent. The right eye was deviated laterally and was unable to move medially, neither in a convergence nor saccade shifting motion. Muscle strength in her left upper and lower extremities was determined to be grade 3 on a manual muscle testing scale. Her score from the National Institute of Health Stroke Scale (NIHSS) was calculated as being 28 points at that time. A brain computer tomography (CT) scan without contrast was performed 3 hours after the symptoms occurred and revealed a low-density area over the right temporo-occipital lobe, which was compatible with an acute cerebral infarction.

During the admission procedure in our hospital, the patient was hydrated, and the administering of an anti-platelet agent with clopidogrel was carried out. Besides, a magnetic resonance imaging (MRI), as well as a magnetic resonance angiography (MRA) was arranged as part of the stroke survey 5 days after the symptoms occurred. T2-weighted images (T2WI) and fluid attenuation inverse recovery (FLAIR) images disclosed a diffusion restriction and enhancement in the paramedian area of the bilateral thalami and right temporo-occipital junction, which was compatible with an acute infarction (Fig. 1A and B). An MRA displayed a narrow P1 segment of the right posterior cerebral artery with a very small caliber (Fig. 1C). Two weeks after admission, a microbubble test, which was carried out simultaneously with an intravenous contrast bubbles injection, while placing an ultrasound probe on the carotid arteries, exhibited the presence of a patent foramen ovale (PFO) between atria. Thus, a percutaneous cardiac catheterization and trans-

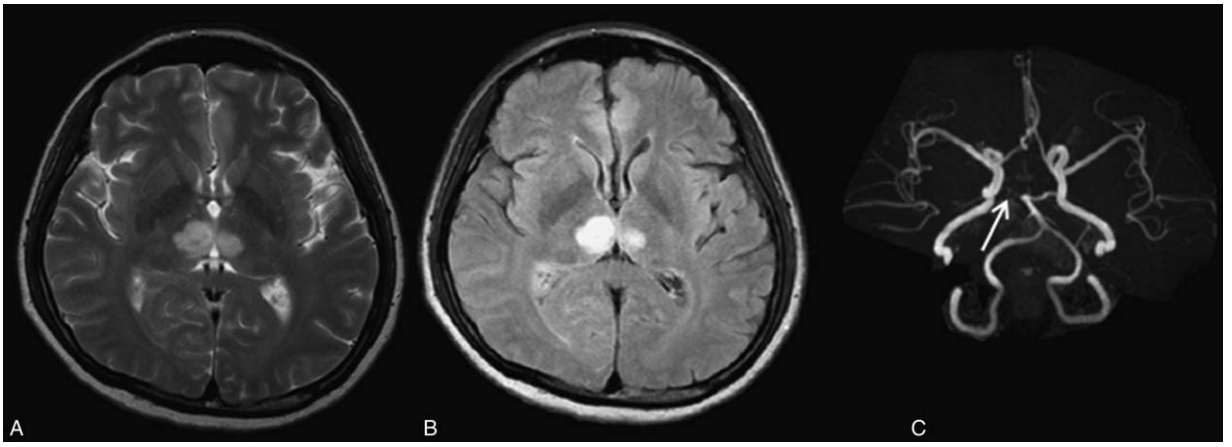

Figure 1. Axial brain MRI performed 8 days after the onset of symptoms shows acute ischemic change with an abnormally high signal at bilateral paramedian thalamus in (A) T2-weighted image and (B) fluid attenuation inverse recovery (FLAIR) image. (C) Magnetic resonance angiography shows the narrow P1 segment (white arrow) of the right posterior cerebral artery, while the left posterior cerebral artery is intact. MRI = magnetic resonance imaging.

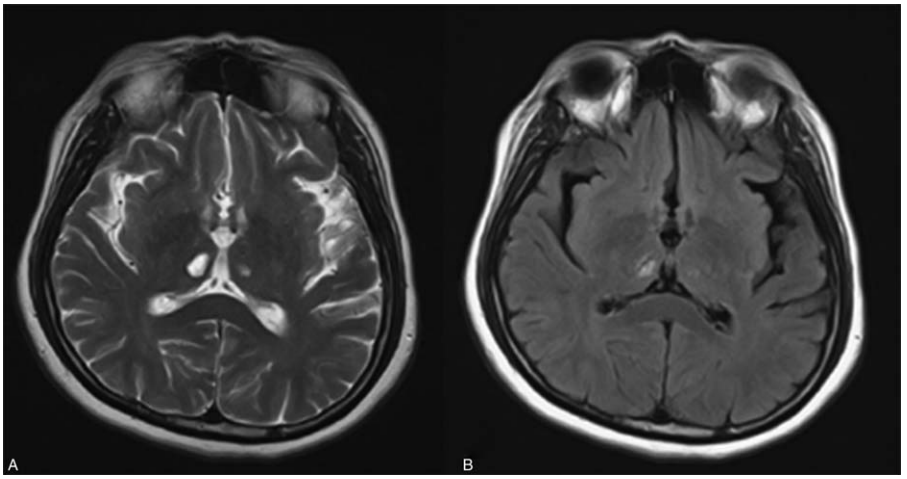

Figure 2. Axial brain MRI performed 7 months after the stroke shows unequal recovery at each side of the thalamus in (A) T2-weighted image and (B) fluid attenuation inverse recovery (FLAIR) image. The residual damage in the right thalamus was larger than those in the other side and had gathered in the paramedian area. MRI = magnetic resonance imaging.

catheter closure of the PFO (6.4 mm in diameter of stretched size), with an amplatzer occlude, was performed without complication.

Seven months after the stroke, we discovered involuntary trembling with an irregularly wavering motion occurring in both her left hand and forearm. The coarse tremor was rhythmic at a frequency of 4 Hz when her left hand was resting and was unable to be suspended at will. Furthermore, we also found that the amplitude was markedly enhanced when the patient raised her left arm up or reached forward. Due to these conditions, we again examined the patient comprehensively for this recently emerging tremor. The informed consent of the patient was obtained after we explained the purpose, benefits, and risks of these examinations to the patient. The lab data profile showed there were no abnormalities in the immune system, intoxication levels, electrolyte levels, or function of vital organs. We then utilized serial anatomic and functional neuroimaging of the brain to survey the neurologic deficit. We repeatedly arranged MRIs for further exploration. The T2WI and FLAIR images exhibited an old and shrinking ischemic area over the paramedian zones of the bilateral thalami (Fig. 2A and B). A brain SPECT imaging, with radiopharmaceutical agent of ^{99m}Tc-ethylene cysteine diethyl ester (ECD), revealed a much diminished cerebral perfusion in the right-side thalamus (Fig. 3), which was compatible with the ischemic area from the anatomic neuroimaging. However, another hypometabolic region was located in the right basal ganglion, which was anatomically intact. Furthermore, a brain *Tc*-99m *TRODAT*-1 scan image was performed to receive more information on the basal ganglion and to also better understand the role of the dopaminergic system in the symptom of tremor. A qualitative visual scale for assessing the striatal uptake,[5] which had been designed in 2004 and is now universally used, was applied in our case. The visual scale of the striatal uptake shows a decrease in the right caudate and putamen (Fig. 4). This asymmetric reduction of bilateral striatal metabolism was interpreted as a scale 1 by the attending nuclear medicine physician.

We recommended pharmacological treatment with levodopa and other dopamine agonists to control the symptom. However, the patient refused any medication as a treatment for the newly evolving tremor based on personal reasons and was only willing to accept physical and occupational training programs at our outpatient clinic. Although the tremor continued without progression or improvement, there were varying degrees of recovery in other post-stroke sequelae, including muscular strength, coordination, spasticity, oral fluency, and cognitive impairment. We summarized the patient's condition in the timeline (Fig. 5). To date, there has been neither clinical deterioration nor any cerebral vascular event with this patient.

3. Discussion

Bilateral thalamic infarction is a rare cerebral vascular event. This unique ischemic stroke occurs in the occlusion of the artery of Percheron (AOP), a small perforating cerebral blood vessel,

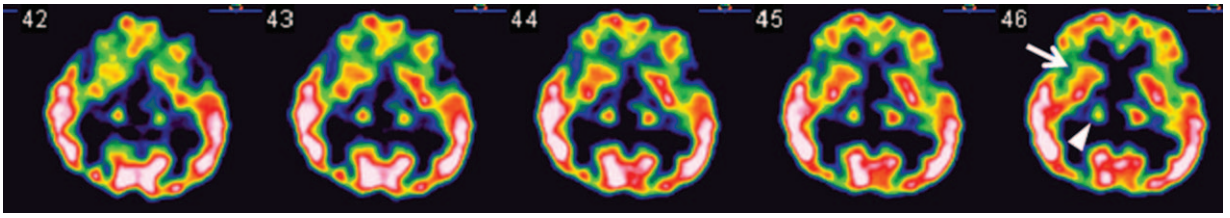

Figure 3. Axial brain perfusion SPECT with ^{99m}Tc-ECD revealed hypometabolic change of the right-side thalamus (white arrowhead) and the right-side, anatomically intact, basal ganglion (white arrow) in the serial images. ECD = ethylene cysteine diethyl ester, SPECT = single-photon emission computed tomography.

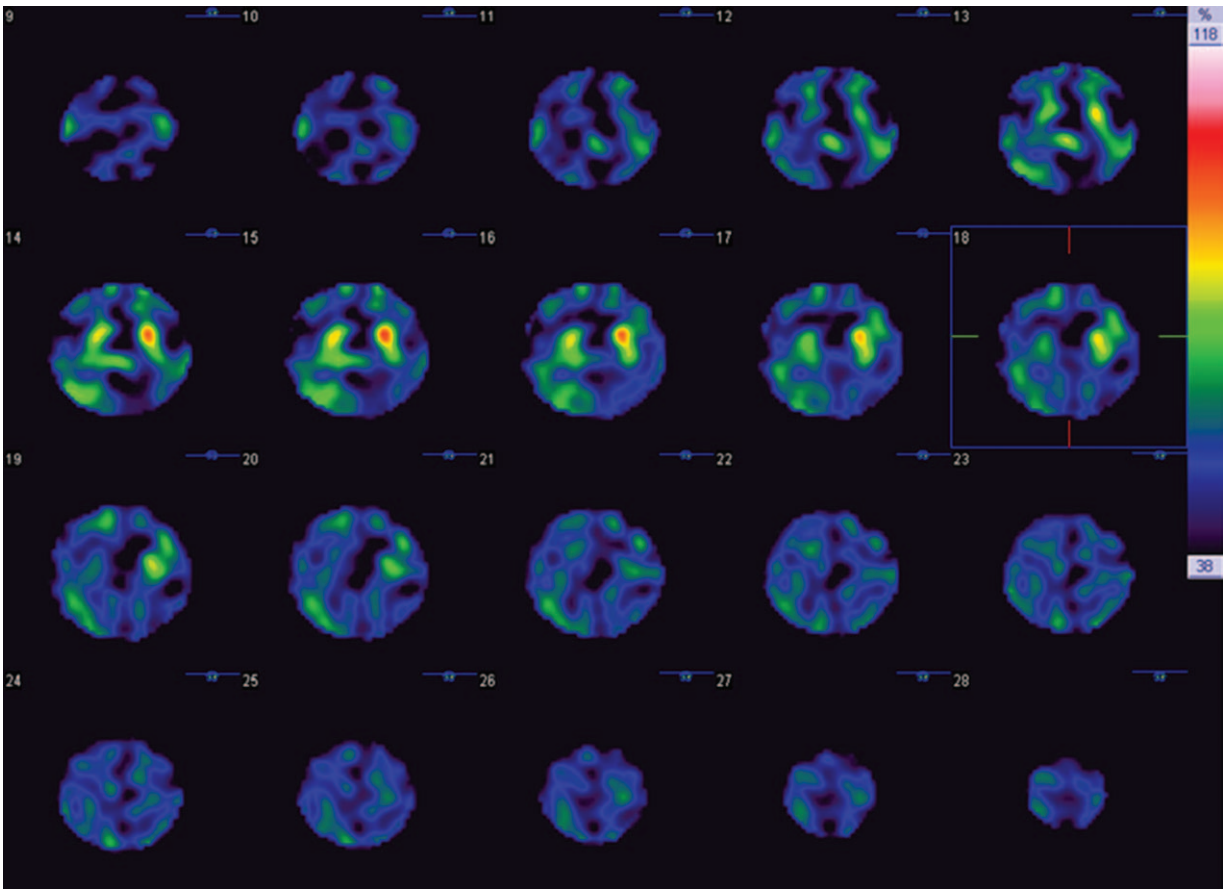

Figure 4. Axial ^{99m}*Tc TRODAT*-1 brain scan shows obvious secondary reduction in the expression of dopamine transporter of the right basal ganglion, ipsilateral to the primary lesion in the thalamus. Qualitative visual scale for assessing the difference between the bilateral striatal uptake was interpreted as scale 1. ^{99m}*Tc TRODAT*-1 = *Technetium*-99m-labeled tropanes as dopamine transporter imaging agents.

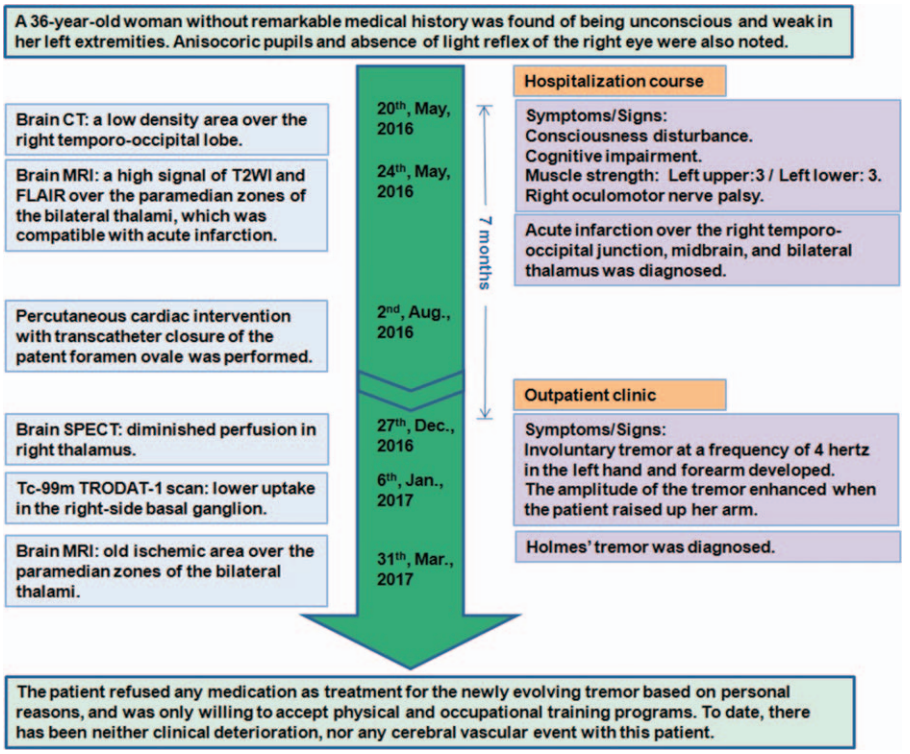

Figure 5. The timeline containing the main symptoms, images, and interventions provides the time course of the patient we reported in this article.

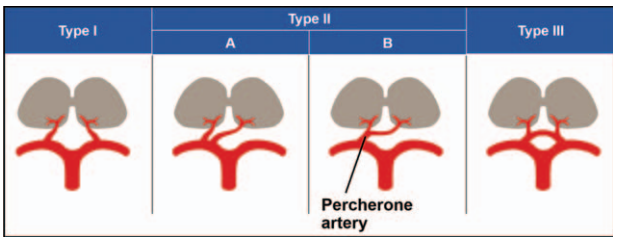

Figure 6. The classification of the artery of Percheron. The type IIb of the artery of Percheron features a single main trunk stemming from the posterior cerebral artery to supply the paramedian nuclear groups of each side of the thalamus.

stemming from the posterior cerebral artery (PCA), and mainly supplying both sides of the paramedian thalami and the midbrain. The AOP was first reported in 1973 by Percheron,[6] who classified the artery into 3 types of variants based on their distinctive structures (Fig. 6). The type IIb variant of the AOP features a single common vascular trunk deriving from the P1 segment of one side of the PCA, and with its branches supplying both sides of the paramedian thalami and the midbrain. Due to the distinctiveness of this vascular structure and the territories supplied by the AOP, the case numbers of bilateral thalamic and midbrain infarction as a result of occlusion in the type IIb variant of the AOP are scarce.[7,8] There is a nuance in the area perfused by the type IIb variant of the AOP amongst known cases, so this disorder yields various symptoms and signs. Typical characteristic clinical manifestations of type IIb variant of the AOP infarction have been reported, such as consciousness disturbance, seizure, ophthalmoplegia, pseudobulbar palsy, hemiparesis, hypersomnia, amnesia, and cognitive impairment.[7–20] Some nuclei responsible for motor control, including basal ganglion, substantia nigra, red nucleus, and thalamus are located in or interconnected closely with the area fed by the AOP. Though much less in numbers, movement disorders (tremors, athetosis, myoclonus, Parkinsonism) following the type IIb variant of the AOP infarction have also been described in a few cases.[21,22] Of all the movement disorders as sequelae of the type IIb variant of the AOP infarction, Holmes tremor has never been mentioned, even though these 2 entities were clinically relevant. To the best of our knowledge, our case is the first to report the type IIb variant of the AOP occlusion-related bilateral paramedian thalamic infarction resulting in Holmes tremor.

The mechanism causing Holmes tremor is complicated and usually comprises ≥2 impaired neural structures. Contemporary pathoanatomical and functional neuroimaging studies have suggested that simultaneous interruption of both the dento-rubro-thalamic tract and nigrostriatal pathway is essential for Holmes tremor.[4,23–25] The case we are presenting here also supports this hypothesis. From the whole brain perfusion SPECT mapping, the patient's right-side thalamus appeared to produce a low signal due to ischemic insult. Interestingly, the ipsilateral basal ganglion was also hypometabolic and presented a lower uptake of ^{99m}Tc-ECD and ^{99m}Tc-TRODAT-1, both in whole brain perfusion SPECT and dopamine transporter scan imaging, even though it had been anatomically intact throughout the whole process. Because the latency from the onset of brain insult to the development of Holmes tremor was varying and ranged from 1 month to 19 years in previously reported cases,[1] we suppose that neural degeneration, rather than direct neural injury in the nigrostriatal pathway, plays a significant role in forming Holmes tremor.

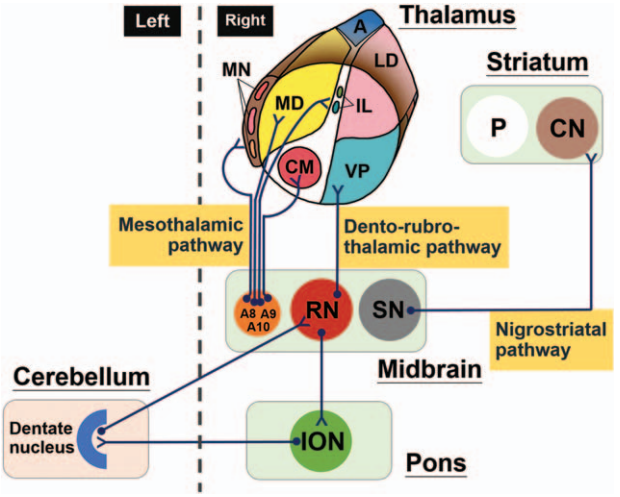

Figure 7. Nuclear groups of the thalamus and the neural network associated with Holmes tremor. A = anterior nucleus, CN = caudate nucleus, CM = central medial nucleus, IL = intralaminar nuclear group, including centrolateral nucleus and paracentral nucleus, ION = inferior olivary nucleus, LD = lateral dorsal nucleus, MD = medial dorsal nucleus, MN = midline nuclear group, including paraventricular nucleus, rhomboid nucleus, and reunions nucleus, P = putamen, RN = red nucleus, SN = substantia nigra, VP = ventral posterior nucleus.

A neurological link between the thalamus and the substantia nigra may explain the neural degeneration. In 2001, Freeman et al[26] discovered that the mesocephalic dopaminergic system has direct neural connection to the ipsilateral thalamus in both rodents and primates. This direct neural connection was called the "mesothalamic pathway." It contained dopaminergic fibers originating from mesocephalic cell groups A8, A9, and A10, which were located in or closely linked with the substantia nigra. The mesothalamic pathway was collateral to the nigrostrital pathway at its beginning in the midbrain level, and then separated to innervate the paramedian nuclear groups of the thalamus. These paramedian nuclear groups of the thalamus which was just supplied by the AOP included the central medial nucleus (CeM), mediodorsal nucleus (MD), intralaminar nuclei (IL), and midline nuclei (MN) (Fig. 7). From the MRI taken of our case during different stages of stroke, both bilateral paramedian thalami were damaged by the occluded type IIb variant of the AOP at first, but an influential difference between the residual lesions on each side of the thalamus existed afterwards. The lesions on the left-side thalamus were almost completely recovered, while the lesions on the other side were not and mainly gathered in the paramedian nucleus groups. We reasonably hypothesized that the less recovery experienced on the right-side thalamus was the contributing factor to trigger a retrograde degeneration from the denervated paramedian nuclear groups. This degeneration, via the dopaminergic fibers of the mesothalamic pathway, secondarily and sequentially attenuated the ipsilateral substantia nigra, nigrostriatal pathway, and basal ganglion, which eventually initiated the unilateral Holmes tremor (Fig. 7).

4. Conclusion

To the best of our knowledge, our presented case is the first report indicating the AOP occlusion-related Holmes tremor with imaging of a brain perfusion SPECT and ^{99m}Tc-TRODAT-1 brain scan to illustrate the importance of the mesothalamic

pathway for initiation of Holmes tremor. Studies using larger case numbers to investigate the relationship between Holmes tremor and the mesocephalic dopaminergic system can be part of any future direction for researchers following-up in this study.

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