Deep Brain Stimulation for Holmes Tremors and Literature Review

Introduction

Holmes tremor (HT) or rubral tremor is a syndrome of rest, postural, and intention tremor that usually emerges from rhythmic proximal more than distal muscle contractions. It is an irregular, slow-frequency (<5 Hz) tremor with a large amplitude.[1] HT is a rare and complex tremor syndrome that is difficult to treat. Medical management for HT is often unsatisfactory and it requires surgical therapy like stereotactic thalamotomy or Deep brain stimulation (DBS) to control the tremors. In a retrospective study by Raina *et al*.,[2] levodopa treatment was effective in 13 out of 24 patients (54.16%).

Hereby we describe a 27-year-old woman with HT secondary to low-grade glioma in the midbrain who underwent a successful unilateral ventralis intermedius nucleus (VIM) Deep Brain Stimulation to control her tremors. We will review the various causes, pathophysiology, and treatment options available for HT in this article.

Case History

A 27-year-old woman presented with gradually progressive left eye ptosis with restricted ocular movements and it was associated with right upper and lower limb weakness from 12 years of age. Her MRI Brain showed moderately sized irregular thick wall cystic lesions in midbrain & pons. She underwent CT-guided stereotactic biopsy and which revealed low-grade glioma. She was started on steroids and radiotherapy. 3 months later, she noticed dysarthria and worsening ptosis, right-sided limb weakness. Subsequently, developed a coarse tremors of the right proximal upper limb more than the lower limb which worsened with posture suggestive of Holmes tremors. The patient had difficulty in doing her daily activities like combing, eating, and writing, sometimes patient injured herself while brushing. The patient started to use their left hand to write, brush, and takes the help from her mother to dress up. Propranolol 40 mg BD, Trihexyphenidyl 2 mg TDS, Topiramate 50 mg BD, Sodium valproate 1 gm BD, Gabapentin 600 mg/day, and Levodopa 125 mg QID were tried with various combinations for more than 10 years for her tremors. She noticed a mild improvement in her tremors and it was affecting her quality of life. Hence, this patient was taken up for unilateral VIM DBS with linear leads. She noticed a significant improvement in tremors, as she is able to write with her right hand, draw a circle, and hold a glass of water with minimal spillage. Improvement in tremors is provided in the Video 1. patient's writing on 3 and 6 months follow up seen in Figure 1 The patient was followed up for 3 years and improvement is lasting to date. The Fahn- Tolosa – Marin tremor rating scale was used for the assessment of tremors. Before DBS tremor rating score was 19,12,24 respectively for subtotal A, B, C, and the total score was 55. After DBS her tremor rating score was 13,4,11 respectively for subtotal A, B, C, and the total score was 28. It reduced from 55 to 28.

Discussion

Holmes's tremor (HT) was first described by Gordon Holmes in 1904 as 3-4 Hz flexion–extension oscillation, present at rest and exacerbated with posture and intensified with action.[1] This tremor is also described as mesencephalic or thalamic tremor based on the areas involved. Definition of Holmes tremor is derived from the consensus statement of the movement disorder society on tremor (1998), described as rest, postural and intentional tremor with irregular amplitude with slow frequency, less than 4.5 Hz.[3] The Fahn- Tolosa – Marin tremor rating scale is used to measure tremor severity.

Holmes Tremor is usually caused by lesions involving the brainstem, thalamus, and cerebellum. HT can occur due to various causes like stroke (hemorrhagic or ischemic- atherosclerotic, embolic, vertebral dissection, infective -vasculitis), Head Trauma, Tumors, Neurodegenerative (multiple sclerosis), Infections, Progressive multifocal leukoencephalopathy, vascular lesions (cavernoma, arteriovenous malformations), and Radionecrosis. Gabriela B. Raina described clinical, and radiological features along with their etiologies in 29 patients with Holmes tremor, the most common cause identified was vascular etiology (48.3%) followed by traumatic brain injury (17.24%) and other causes represented 34.5%. The median latency for tremor to develop was approximately 2 months (range- 7 days to 228 months). The average age at diagnosis was 30.6 years with a female to male ratio of 2:1.[2,3] In our case patient developed tremors after 3 months of radiotherapy for glioma.

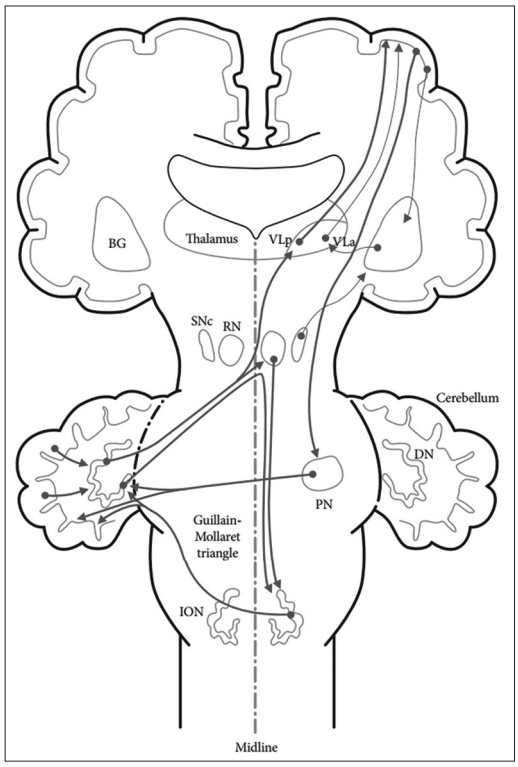

Figure 1: Schematic diagram of cerebellar circuits. One is cortico-cerebellar- cortical circuit and other is dentato-rubro-olivary circuit (Guillain –Mollaret triangle). BG: Basal ganglia, ION: inferior olivary nucleus, PN: Pontine nuclei, RN: red nucleus, SNc: Substantia nigra pars compacta, VLa: ventral lateral anterior nucleus of the thalamus, VLp: ventral lateral posterior nucleus of thalamus[4]

The Clinical features associated with Holmes tremor are hemiparesis, ataxia, hypoesthesia, dystonia, cranial nerve involvement – dysarthria, dysmetria, and bradykinesia. In our case patient had ophthalmoparesis, weakness, and rubral tremors.

The Exact pathophysiology of HT remains unknown. It is hypothesized to be a two-hit lesion disrupting the nigrostiatal pathway and cerebello-thalamo-cortical or dentato-rubroolivary circuits [Figure 1]. The main afferent of the cerebellum are the cortico-ponto-cerebellar tract, which starts from the frontal lobe, synapses on pontine nuclei, and reaches the cerebellum via the middle cerebellar peduncle. The main efferents of the cerebellum are the dentate-rubro-thalamo-cortical tract. It starts from the dentate nucleus, passes through the superior cerebellar peduncle, and crosses to the contralateral red nucleus, synapses with the ventrolateral thalamus, and reaches finally to the motor cortex.

In the Dentate – rubro-olivary circuit, efferent fibers from the dentate nucleus passes through the superior cerebellar peduncle and synapse with the contralateral red nucleus. Fibers from the red nucleus pass through the central tegmental tract and synapse with the ipsilateral Inferior olivary nucleus (ION). The efferent fibers from ION pass through the inferior cerebellar peduncle and synapses with the contralateral cerebellum to complete a triangular circuit – Guillain Mollaret triangle. Both these circuits are subcortical and utilize the thalamus as their relay station. Damage to the cerebello-thalamic circuit is attributes to kinetic/postural tremor and damage to the nigrostriatal pathway might result in tremor at rest.[4] The onset of tremors after the initial insult is delayed. One possible explanation was unbalanced motor recovery and subsequent development of pathological pathways reflecting neuroplasticity.

Hypertrophic Olivary degeneration (HOD) is a trans-synaptic degeneration caused by a lesion in the anatomic triangle of Guillain –Mollaret [Figures 1 and 2].

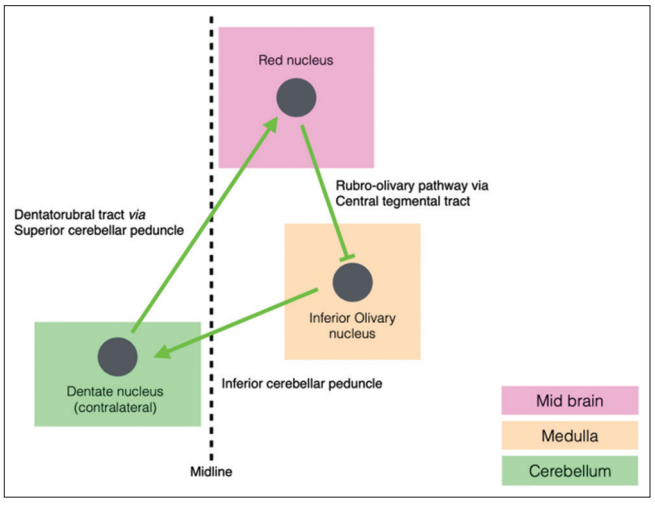

Figure 2: Guillain Mollaret triangle with its connections[5]

Table 1: Studies reporting VIM DBS for HT

Study	Number of Patients and Etiology	Target	Outcome	Follow up
Pahwa *et al*	Mid brain cavernous hemangioma (symptoms for 3 years)	Right VIM	Significant improvement in postural and resting tremor; kinetic component persisted	10 months
Samadani *et al* 2003	Left midbrain cavernous malformation (Symptoms for 4 years)	Right VIM	57% increase in dexterity and four-point decrease in functional disability in TRS	N/A
Nikkhah *et al*. 2004	1. Right infarct midbrain (tremor symptoms 6 months); 2. Left thalamic AVM	2 patients with contralateral VIM	Almost complete tremor resolution (80% improvement). Dystonia and rigidity benefit reported	7 months and 6 months respectively
Piette *et al*. 2004	Pontine tegmental hemorrhage	Right VIM	Major functional improvement	16 months
Diederich *et al*.	1.Left venous pontine angioma (symptoms for 7 years) 2.Right midbrain hemiatrophy (symptoms for 32 years)	2 patients with contralateral VIM	Substantially ameliorated postural > rest > intention component	7 years and 5 years respectively
Peker *et al*. 2008	Left thalamic abscess (symptoms 18 months)	Right VIM	90% overall improvement	2.5 years
Acar *et al*. 2010	Subarachnoid haemorrhage (symptoms less than 1 month)	Bilateral VIM	No tremor and reduction in disability due to trempr	3 months
Castrop *et al*. 2013	1. Hypertensive mesencephalic hemorrhage (symptoms for 1 month). 2. Pontomesencephalic AVM hemorrhage (symptoms for 2 years)	2 patients with contralateral VIM	Good tremor suppression, whereas the other symptoms remained unchanged	7 years and 6 years respectively

HOD is a very rare type of degeneration that causes hypertrophy rather than atrophy of ION. The dentate nucleus inhibits the inferior olivary nucleus. Any pathologic lesion interrupts the inhibitory modulation, and ION enlarges and develops soma-somatic gap junctions within a few weeks. Palatal tremor is suggested to be secondary to abnormalities in the central tegmental tract, that is; the rubro-olivary pathway. The classical presentation of HOD is palatal myoclonus. HOD rarely presents with Holmes tremor (HT).[6] The absence of HOD in our case may be due to the fact that there was less involvement of the dentato-rubral or rubro-olivary pathway.

Medical management is cumbersome and often unsatisfactory. Many medications have been used with varying degrees of success. It was used to modulate the dopaminergic or cerebello-thalamic pathways. Common medications used for HT are levodopa, levetiracetam, trihexyphenidyl, levodopa, propranolol, bromocriptine, benzodiazepines, and primidone with variable success. Mohammed Alqwaifly performed a systematic review of the literature using Pubmed for the medical management of Holmes tremors. He found 27 cases out of which Levodopa was used in the treatment of 21 patients (77%) either as monotherapy or in combination with other drugs.[7] The outcome suggested that patients with Holmes tremor responded better with levodopa compared to other drugs. Botulinum toxin was also tried in a few patients with variable success.[8]

To date, several reports highlighted the ventral intermediate nucleus of the thalamus (VIM) as the preferred target for Deep brain stimulation [Table 1].[9] Globus Pallidus internus (GPi) DBS should be considered in cases where VIM nucleus anatomy is grossly disrupted by intracranial pathology or when intraoperative tremor control is unsatisfactory despite VIM high-intensity stimulation. GPi DBS showed greater control of the resting tremor component and overall tremor reduction.[10] Multiple target sites of DBS have been tried -Dual lead stimulation in VIM and Posterior Subthalamic area (PSA), VIM/ventralis oralis posterior nucleus (Vop) and ventralis oralis anterior nucleus (Voa)/Vop, individual stimulation of Voa, Zona incerta (zi), lenticular fasciculus. Among them dual thalamic stimulation VIM with Voa/Vop or with PSA showed significant improvement as it was proposed to override hypothesized dysfunction in both Cerebello-thalamic and Pallido-thalamic circuits.[9,10] HT usually requires higher voltage and frequency to control the tremors. Other programming options like double monopolar and interleaving stimulation are often utilized to control the tremors.

Vincente Martinez performed a successful treatment of HT with DBS of pre lemniscal radiations. Prelemniscal radiations (Raprl) could be a good target and it can improve the tremors with low current.[11]

The Stereotactic thalamic stimulation surgery for symptomatic HT was disappointing. In recent times Radiofrequency (RF) thalamotomy gaining importance in terms of no hardware failure, battery replacement, and frequency setting adjustments, unlike DBS. Pauwels *et al*.,[12] analyzed a cohort of 27 patients with intractable tremors after unilateral Radiofrequency thalamotomy (RF).19 patients out of 21 reported significant improvement in tremors ($p < 0.001$). Focused ultrasound thalamotomy (FUS) could be another viable option for large lesion-related, complex non operable HT or patients who are not a candidate for DBS. However, there are no case reports are available with FUS. In contrast, Magnetic Resonance Guided Focused Ultrasound Thalamotomy (MRgFUS) lesion in a specific region is known to cause tremor and dystonia or even HT, potentially developing due to plastic changes or maladaptive rearrangement in the thalamus after the lesion.[12]

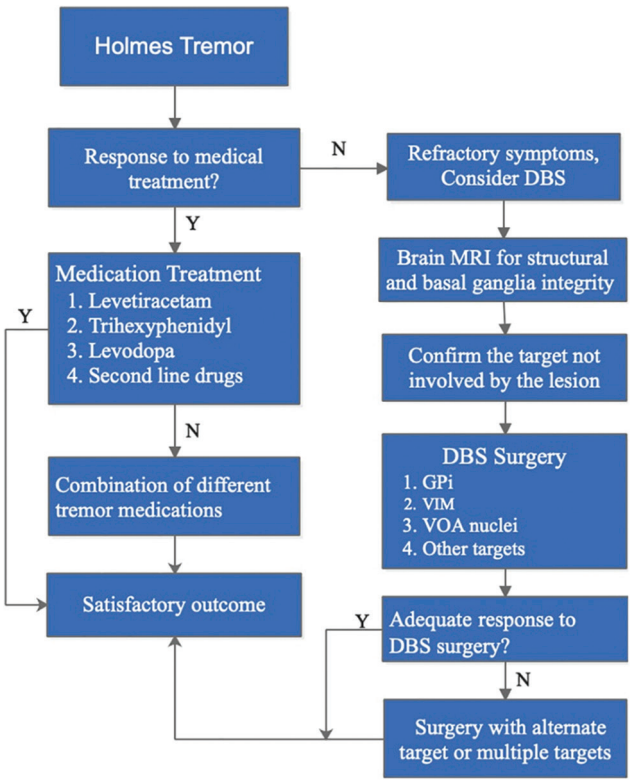

Figure 3: Therapeutic options in treatment of Holmes Tremor[13]

Wang *et al*.,[13] tried to formulate a clinical treatment algorithm for Holmes tremor [Figure 3]. Performed systematic analysis in the treatment of Holmes tremors. Compared to the medically treated group, DBS provided greater tremor suppression. Based on clinical and functional improvement, initially, levetiracetam, trihexyphenidyl, or levodopa can be tried as the first line of medical management. The second line of drugs which can be considered are clonazepam, amantadine, biperidine, or botulinum toxin injections. DBS should be offered to patients who are medically refractory. VIM is most commonly used, and Gpi DBS should be considered in cases of thalamic lesions. Very limited experienced with new targets like caudal Zona incerta, particularly when used with thalamic stimulation was noticed.[14]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Neurology team.

Conflicts of interest

There are no conflicts of interest.

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References

1. Holmes G. On certain tremors in organic cerebral lesions. Brain 1904;27:327-75.
2. Raina GB, Cersosimo MG, Folgar SS, Giugni JC, Calandra C, Paviolo JP, *et al*. Holmes tremor: Clinical description, lesion localization and treatment in a series of 29 cases. Neurology 2016;86:931-8.
3. Deuschl G, Bain P, Brin M. Consensus statement of the movement disorder society on tremor. Ad Hoc Scientific Committee. Mov Disord 1998;13(Suppl 3):2-23.
4. Choi S-M. Movement disorders following cerebrovascular lesions in cerebellar circuits. J Mov Disord 2016;9:80-8.
5. Fleet JL, Calver R, Perera GC, Deng Z. Palato-Pharyngo-laryngeal myoclonus with recurrent retrograde feeding tube migration after cerebellar hemorrhagic stroke: A case report and review of hypertrophic olivary degeneration. BMC Neurol 2020;20:222.
6. Wang H, Wang Y, Wang R, Li Y, Wang P, Li J, *et al*. Hypertrophic olivary degeneration; A comprehensive review focusing on etiology. Brain Res 2019;1718:53-63.
7. Alqwaifly M. Treatment responsive Holmes tremor: Case report and literature review. Int J Health Sci (Qassim) 2016;10:558-62.
8. Jomier F, Beaugendre Ahmar Y, Apartis E, Grabli D. Holmes Tremor: Contribution of Botulinum toxin injection strategy guided by electromyographic (EMG) polygraphic recording [abstract]. Mov Disord 2019;34(Suppl 2).
9. Ramirez-Zamora A, Kaszuba BC, Gee L, Prusik J, Danisi F, Shin D, *et al*. Clinical outcome and characterization of local field potentials in holmes tremor treated with Pallidal deep brain stimulation. Tremor Other Hyperkinet Mov (N Y) 2016;6:388.
10. Kilbane C, Ramirez-Zamora A, Ryapolova-Webb E, Qasim S, Glass GA, Starr PA, *et al*. Pallidal stimulation for Holmes tremor: Clinical outcomes and single-unit recordings in 4 cases. J Neurosurg 2015;122:1306-14.
11. Martinez V, Hu SC, Foutz TJ, Ko A. Successful treatment of Holmes tremor with deep brain stimulation of the prelemniscal radiations. Front Surg 2018;5:21.
12. Pauwels RWJ, Oterdoom DLM, Drost G, van Laar T, Van Dijk JMC. Long-term patient- reported outcome of radiofrequency thalamotomy for tremor. Stereotact Funct Neurosurg 2020;98:187-92.
13. Wang KL, Wong JK, Eisinger RS, Carbunaru S, Smith C, Hu W, *et al*. Therapeutic Advances in the Treatment of Holmes Tremor: Systematic Review. Neuromodulation 2022;25:796-803.
14. Eisinger RS, Wong J, Almeida L, Ramirez-Zamora A, Cagle JN, Giugni JC, *et al*. Ventral intermediate nucleus versus zona incerta region deep brain stimulation in essential tremor. Mov Disord Clin Pract 2017;5:75-82.

Submitted: 24-Aug-2022 **Revised:** 12-Mar-2023 **Accepted:** 31-Mar-2023
Published: 15-Jun-2023

Video available on: https://journals.lww.com/annalsofian

DOI: 10.4103/aian.aian_720_22