Katedra i Klinika Neurologii Uniwersytetu Medycznego w Lublinie
Chair and Department of Neurology of Medical University of Lublin, Poland

EWA PAPUĆ, REMIGIUSZ FICEK, MAGDALENA GODEK,
MARTA TYNECKA-TUROWSKA, KONRAD REJDAK

Holmes tremor – case presentation and literature overview

Drżenie Holmesa – opis przypadku i przegląd literatury

Key words: thalamic stroke, thalamic tremor, deep brain stimulation, periaqueductal grey matter, periventricular grey matter, neuropathic pain

Słowa kluczowe: udar wzgórza, drżenie wzgórzowe, głęboka stymulacja mózgu, istota szara okołowodociągowa, istota biała okołokomorowa, ból neuropatyczny

INTRODUCTION

Holmes tremor is a rare type of movement disorder, characterized by low-frequency rest and postural tremor, usually related to brainstem pathology. It was first described in 1904 by Gordon Holmes [8, 14]. Holmes tremor is rare, and usually exacerbated by specific postures, with frequency mostly below 4.5 Hz. It arises as a delayed manifestation of lesions in the upper part of brainstem, often as a consequence of stroke or trauma. It typically occurs with a delay, from 4 weeks to 2 years between the moment of lesion formation and the first occurrence of tremor.

It is claimed that both the dopaminergic nigrostriatal and the cerebello-thalamic systems must be involved for the occurrence of this type of tremor [9]. Pharmacological treatment is usually not very effective, and surgical procedures, such as stereotactic thalamotomy or thalamic stimulation, are often required for refractory cases [45, 24, 36].

CASE DESCRIPTION

We present a patient who experienced ischemic stroke within the posterolateral part of left thalamus with subsequent chronic central pain and rest thalamic tremor which occurred 4 months after the stroke. On neurological examination the patient presented sensi-motor right hemi-syndrome and thalamic tremor. Brain MRI revealed a cerebral infarction in the left postero-lateral thalamic area, medial left temporal lobe and inferomedial temporal area extending to left occipital lobe. No abnormalities were found in the basal ganglia or brainstem. The dentate nucleus, superior cerebellar peduncle, red nucleus, and ventrolateral nucleus were all intact. Surface EMG (recorded from the muscles of the upper right limb) revealed rhythmic grou-

ping discharges of 3,5 Hz that appeared synchronously between the wrist extensor and flexor muscles.

For the thalamic tremor, the patient was treated with propranolol at doses 60 mg/day (20 mg per day at 3 doses), slowly increasing to 240 mg within 6 weeks. Nevertheless the symptoms of tremor were still persistent. Thus, the patient was later given clonazepam at doses 1 mg 3 times per day, also with moderate improvement. Unfortunately, because of excessive sedative effect, clonazepam had to be withdrawn. After administration of levetiracetam, at doses 1500 mg 2 times per day, the tremor showed some improvement, nevertheless the patient experienced mood changes, with agitation, and stopped taking levetiracetam. We decided to administer the patient levodopa at dose 200 mg once per day, and slowly increased the doses to 600 mg/per day. With increasing the dose of levodopa, we observed as the tremor lessens gradually, but to the level which was satisfactory for the patient.

In the treatment of severe central pain, the patient was treated with tricyclic and heterocyclic antidepressants, opioid analgesics including morphine, benzodiazepines, non-narcotic analgesics, carbamazepine and gabapentine, without major effect. Finally, the patient underwent also a series of transcranial magnetic stimulation, without satisfactory results. Before the surgery the patient received buprenorphine 1,6 mg/day and gabapentine 2400 mg/day. After 2 years of ineffective pain treatment he was referred for DBS surgery. The patient was offered implantation of electrodes to periventricular grey matter (PVG)/ periaqueductal grey matter (PAG) as well as implantation of an electrode to ventroposterolateral thalamic nucleus (VPL). Microelectrode recording, microstimulation, and macrostimulation were all used in the process of target localization, apart from defining the exact target for stimulation by the stereotactic MRI. Correct target localization in the VPL was confirmed when a 50Hz stimulation elicited paresthesia in the contralateral limb. Once the physiologic targets have been defined with stimulation, permanent electrodes were introduced (electrode type 3389), and the leads were externalized through a separate stab wound in the scalp for trial stimulation. Each electrode was externalized for 2 days to test the stimulation effects, and to internalize one or both of these electrodes based upon the results of trial stimulation. Different possible stimulation combinations were explored during the trial stimulation with frequencies ranging from 5 to 100 Hz, intensity ranged from 1.5 to 2.5 V, the pulse width was kept constant at 210 ms.

Eventually, after trial stimulation and assessment of pain intensity on visual analogue scale (VAS), PVG/ PAG was chosen as target for permanent stimulation and the patient was implanted with a subcutaneous pulse generator (Soletra, Medtronic Inc). Results of VPL stimulation for pain reduction were comparable with PVG/PAG, but both electrodes were internalized.

After a few months the patient reported increase of pain intensity, difficult to alleviate only with PVG/PAG stimulation. Thus, we decided for additional VPL stimulation. Baseline pain intensity was assessed using the McGill-Melzack visual analogue scale for 7.9 points for PVG/PAG stimulation and 4.9 points with PVG/PAG and VPL stimulation (the score was averaged over ten trials). The para-

meters of permanent stimulation were chosen as follows: amplitude 1.6 V, pulse width 210 μs, frequency 50 Hz, on the contact number 2 (assuming contact 0-the deepest, contact 3-the most superficial).

Interestingly, soon after starting simultaneous PAG/PVG and VPL stimulation, we observed not only alleviation of chronic pain in the right upper limb, but also significant alleviation of the patient's thalamic tremor, which persisted over subsequent months.

DISCUSSION

Tremor rarely occurs as a consequence of thalamic lesion. Posterolateral thalamic region is usually responsible for delayed tremor [34]. The reason why lesions in the posterolateral thalamus induce tremor is unknown. It is still uncertain at present which mechanism contribute to the genesis of thalamic tremor: interruption of ascending inputs to the posterolateral thalamus from the brainstem or cerebellum, or destruction of the posterolateral thalamic neurons themselves [26]. Interestingly, at the same time the thalamic ventral intermedius nucleus (Vim) is a target site for stereotaxic surgery to alleviate tremor.

Holmes tremor has some characteristic features: 1) it is predominantly unilateral; 2) it is not only present at rest, but may be also postural and action tremor, usually disappears during sleep; 3) it has low-frequency below 4.5 Hz (typically about 1.1 Hz); and 4) it occurrs 6 months after a brainstem vascular damage [9].

It is hypothesized that two different neural pathways may be responsible pathophysiologically for the Holmes tremor. One involves the substantia nigra or nigrostriatal dopaminergic fibers, it is hypothesized that dopaminergic denervation of the striatum id responsible for the Holmes tremor [7]. On the other hand, Remy et al. [29] found a marked decrease in 18F-dopa re-uptake in the caudate and putamen in a patient with Holmes tremor due to a midbrain lesion, likely reflecting the ipsilateral severe striatal dopaminergic denervation. Such dopaminergic denervation may play a role in resting tremor, like that in Parkinson disease [7]. The structure involved in the genesis of Holmes tremor may be the dentate projection pathway, one of non-dopaminergic structures. The ascending arm of this pathway includes the dentate-rubral and dentate-thalamic tracts; the descending arm includes the dentate-olivary and dentate-rubro-olivary tracts, which form the rubro-olivo-cerebellar-rubral circuits. Interruption of these circuits may be responsible for postural and intentional tremors [8]. Midbrain lesions, such as hemorrhage, ischemia, and neoplasm may interrupt elements of both dopaminergic and non-dopaminergic pathways, producing the characteristic combination of resting, postural, and kinetic tremors seen in HT. This complex mechanism may account for the variability of response to pharmacotherapy. Isolated cases of partial or complete relief have been reported with several drugs, including propranolol, clonazepam, and levetiracetam [36]. Although, many treatment strategies have been tried, there is no gold-standard treatment for this type of tremor. It is worth noting, that dopaminergic denervation should not be underestimated in all cases of Holmes tremor, and dopaminergic agents should be tried in

every patient before considering invasive therapies, such as deep brain stimulation or thalamotomy.

Despite successful management of the primary pathology the occurrence of this movement disorders is unpredictable in the long term [18]. Depending on their severity the quality of patients life becomes seriously impaired [41]. That is why the reduction of all tremor's components is the main goal to improve patients' daily activity. According to the significant majority of reports the most efficient treatment is based on invasive procedures [28]. However, it is worth undertaking pharmacological therapies due to confirmed cases of their satisfactory results. Considering published reports the best initial choice is introducing dopaminergic agents.

Nevertheless, there is a difference in responsiveness between the levodopa and dopamine agonists. It is confirmed by described case of satisfactory response to a piribedil despite previous ineffective course of levodopa/carbidopa treatment [3]. Analogical case with Lack of response to levodopa has been reported while describing administration of another dopamine receptor agonist – cabergoline [1, 13]. Pramipexol is also found to be useful in alleviation different types of tremor either in monotherapy (resting tremor) and adjuvant therapy with levodopa (also postural tremor) [33, 35, 43, 11]. Another agent which belongs to discussed group with confirmed effectiveness is ropinirol [38]. The serious disadvantages of agonists' use are side effects, especially nausea and vomiting.

Additionally, it is worth noting that responsiveness to levodopa depends on the size of the lesion comparing to agonists' use. Despite unsuccessful therapies many physicians claim that levodopa stepwise dosed should be the drug of first choice in the therapy of Holmes tremor [5, 41].

The extremely complex pathophysiology of this disorder has not been explained so far. It is agreed that the onset of symptoms follows simultaneous disruption of dopaminergic nigro-strital and cerebello-thalamic pathways [25, 39, 6, 4, 20]. Analysing many therapeutic attempts with various groups of drugs revealed reports about satisfactionary results of antiepileptic drugs. Zonisamide, levetiracetam, gabapentin, primidon and clonazepam have been administered in several cases of Holmes tremor [38, 37, 40, 16]. The best results were described for levetiracetam and zonisamide. In addition, zonisamid is believed to have influence on dopaminergic system as well. Management with the remaining drugs mentioned here, has led to less significant improvement. Single cases of performed therapies using drugs beneficial in varoius kinds of tremor have been also reported without major improvement. Those agents were beta-blockers (propranolol), anticholinergics (metixene, benzotropin,trihexypenidil) and tolperison [5, 32, 22].

The majority cases of Holmes tremor did not respond to pharmacological treatment. According to available medical data the most effective treatment target is VIM (ventral intermedius nucleus of thalamus) stimulation [17, 26, 10, 31, 19, 2, 21]. Both stereotactic thalamotomy or deep brain stimulation (DBS) of this area have both given satisfactory results in alleviating tremor. The DBS seems to be better choice due to future possibility of modifying stimulation parameters . However the best results are achieved on simultaneous stimulation of additional thalamic

structures which are ventralis oralis anterior (VOA) and posterior (VOP) nuclei. This approach requires implantation of additional lead which makes the whole procedure more battery consuming. Consequently, the need for more frequent battery discharge makes it less convenient. On the other hand the very thalamotomy may be effective only for resting and postural tremor [30]. In result it may require additional pallidotomy to abolish all components of tremor [12]. There are no special guidelines describing therapeutic approach to Holmes tremor. Decision about chosen therapy should be taken carefully including precise assessment of presented symptoms and extensiveness of pathology. However we must keep in mind that the most relevant objective is to improve patient's quality of life. The significant impairment of daily activities causes social dysfunction and serious decrease of patients wellness. The variety of alternative therapies listed above makes decision about proper choice of initial therapy even harder. Every pharmacological attempt requires time for expected improvement. That is why patients have to cope with disabling symptoms for a longer period of time before satisfactory effect occurs. In this particular case there is also additional component of severe pain which amplifies patient's discomfort.

REFERENCES

1. Akkus DE, Diramali AB. Postischemic delayed Holmes' tremor responding to low-dose cabergoline. Mov Disord 2006, 21:733–734.
2. Acar G1, Acar F, Bir LS, Kızılay Z, Cırak B. Vim stimulation in Holmes' tremor secondary to subarachnoid hemorrhage. Neurol Res 2010;32:992-994.
3. Baysal L, Acarer A,Celebisoy N. Post-ischemic Holmes' tremor of the lower extremities. J Neurol 2009, 256: 2079-2081.
4. Brooks DJ, Playford ED, Ibanez V, et al. Isolated tremor and disruption of the nigrostriatal dopaminergic system: an 18F-dopa PET study. Neurology 1992;42:1554-1560.
5. Boelmans K, Gerloff C, Münchau A. Long-lasting effect of levodopa on holmes' tremor. Mov Disord 2012, 27: 1097–1098.
6. de Recondo A, Rondot P, Loc'h C, et al. Unilateral post-traumatic mesencephalic tremor: a PET study of striatal dopaminergic innervation. Rev Neurol (Paris) 1993;149:46-49 .
7. Defer GL, Remy P, Malapert D et al. Rest tremor and extrapyramidal symptoms after midbrain haemorrhage: clinical and 18F-dopa PET evaluation. J Neurol Neurosurg Psychiatry 1994;57:987-989.
8. 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.
9. Deuschl G, Bergman H. Pathophysiology of nonparkinsonian tremors. Mov Disord 2002;17 Suppl 3:S41-48.

10. Foote KD, Okun MS. Ventralis intermedius plus ventralis oralis anterior and posterior deep brain stimulation for posttraumatic Holmes tremor: two leads may be better than one: technical note. Neurosurg 2005;56 (2 Suppl):445-457.
11. Findley LJ, Gresty MA. Suppression of "rubral" tremor with levodopa. Br Med J1980;281:1043-1045.
12. Goto S, Yamada K. Combination of thalamic Vim stimulation and GPi pallidotomy synergistically abolishes Holmes' tremor. J Neurol Neurosurg Psychiatry 2004;75:1203-1204.
13. Harmon RL, Long DF, Shirtz J. Treatment of post-traumatic midbrain resting-kinetic tremor with combined levodopa/carbidopa and carbamazepine. Brain Inj1991;5:213-218
14. Holmes G. On certain tremors in organic cerebral lesions. Brain 1904;27:327-375.
15. Hubble JP1, Busenbark KL, Wilkinson S, Pahwa R, Paulson GW, Lyons K, Koller WC. Effects of thalamic deep brain stimulation based on tremor type and diagnosis. Mov Disord 1997;12(3):337-341.
16. Jacob PC1, Pratap Chand R. Posttraumatic rubral tremor responsive to clonazepam. Mov Disord. 1998;13(6):977-978.
17. Kim MC, Son BC, Miyagi Y et al. Vim thalamotomy for Holmes' tremor secondary to midbrain tumour. J Neurol Neurosurg Psychiatry 2002 ;73(4):453-455.
18. Koppel BS, Daras M. "Rubral" tremor due to midbrain toxoplasma abscess. Mov Disord 1990;5:254-256.
19. Kudo M1, Goto S, Nishikawa S, Hamasaki T, Soyama N, Ushio Y, Mita S, Hirata Y. Bilateral thalamic stimulation for Holmes' tremor caused by unilateral brainstem lesion. Mov Disord. 2001;16(1):170-174.
20. Lee MS1, Marsden CD. Movement disorders following lesions of the thalamus or subthalamic region. Mov Disord 1994;9(5):493-507.
21. Lim DA, Khandhar SM, Heath S, Ostrem JL, Ringel N, Starr P. Multiple target deep brain stimulation for multiple sclerosis related and poststroke Holmes' tremor. Stereotact Funct Neurosurg 2007; 85:144–149.
22. Liou LM, Shih PY. Successful treatment of rubral tremor by high-dose trihexyphenidyl: a case report. Kaohsiung J Med Sci 2006; 22:149–153.
23. Miwa H, Hatori K, Kondo T et al. Thalarnic tremor: Case reports and implications of the tremor-generating mechanism. Neurology 1996; 46 (1):75-79.
24. Nikkhah G, Prokop T, Hellwig B et al. Deep brain stimulation of the nucleus ventralis intermedius for Holmes (rubral) tremor and associated dystonia caused by upper brainstem lesions: report of two cases. J Neurosurg 2004;100:1079-1083.

25. Paviour DC1, Jäger HR, Wilkinson L, Jahanshahi M, Lees AJ. Holmes tremor: Application of modern neuroimaging techniques. Mov Disord 2006;21(12):2260-2262.
26. Peker S, Isik U, Akgun Y, Ozek M et al. Deep brain stimulation for Holmes' tremor related to a thalamic abscess. Childs Nerv Syst 2008; 24:1057–1062.
27. Puschmann A, Wszolek ZK. Diagnosis and treatment of common forms of tremor. Semin Neurol 2011 31(1): 65–77.
28. Raina GB, Velez M, Pardal MF et al. Holmes tremor secondary to brainstem hemorrhage responsive to levodopa: report of 2 cases. Clin Neuropharmacol 2007;30(2): 95-100.
29. Remy P, de Recondo A, Defer G et al. Peduncular 'rubral' tremor and dopaminergic denervation: a PET study. Neurology 1995;45:472-477.
30. Rieder CR, Reboucas RG, Ferreira MP. Holmes tremor in association with bilateral hypertrophic olivary degeneration and palatal tremor: chronological considerations. Case report. Arq Neuropsiquiatr 2003;61:473-477.
31. Romanelli P, Bronte-Stewart H, Courtney T, et al. Possible necessity for deep brain stimulation of both the ventralis intermedius and subthalamic nuclei to resolve Holmes tremor. case report. J Neurosurg 2003;99:566-571
32. Samie MR, Selhorst JB, Koller WC. Post-traumatic midbrain tremors. Neurology1990;40:62-66.
33. Seidel S, Kasprian G, Leutmezer F et al. Disruption of nigrostriatal and cerebellothalamic pathways in dopamine responsive Holmes' tremor. J Neurol Neurosurg Psych 2009;80: 921-923.
34. Steinke W, Sacco RL, Mohr JP et al. Thalamic stroke. Presentation and prognosis of infarcts and hemorrhages. Arch Neurol 1992;49(7):703-710.
35. Strecker K, Scheneider JP, Sabri O, Wegner F. Responsiveness to a dopamine agent in Holmes tremor case report. Eur J Neurol 2007; 14: 9–10.
36. Striano P, Elefante A, Coppola A et al. Dramatic response to levetiracetam in post-ischaemic Holmes' tremor. J Neurol Neurosurg Psychiatry 2007;78:438-439.
37. Suda S, Yamazaki M, Katsura K et al. Dramatic response to zonisamide of post-subarachnoidhemorrhage Holmes' tremor. J Neurol 2012; 259:185–187.
38. Walker M, Kim H, Samii A. Holmes-like tremor of the lower extremity following brainstem hemorrhage. Mov Disord 2007;22:272–274.
39. Weng YH1, Kao PF, Tsai CH, Yen TC, Lu CS. Dopamine deficiency in rubral tremor caused by midbrain hemangioma: case report. Chang Gung Med J 2000;23(8):485-891.
40. Woo JH, Hong BJ, Kim JS et al. Holmes tremor after brainstem hemorrhage, treated with levodopa. Ann Rehabil Med 2013; 37: 591–594.

41. Velez M, Cosentino C, Torres L. Levodopa-responsive rubral (Holmes') tremor. Mov Disord 2002; 17: 741–742.
42. Yang YW1, Chang FC, Tsai CH, Wu JC, Lu CS, Kuo CC, Lu MK, Chen WL, Lee CC. Clinical and magnetic resonance imaging manifestations of Holmes tremor. Acta Neurol Taiwan 2005;14(1):9-15.
43. Yuill GM. Suppression of "rubral" tremor with levodopa. Br Med J 1980;281:1428-1430.
44. Zakaria R1, Vajramani G, Westmoreland L, Fletcher N, Eldridge P, Alusi S, Osman-Farah J. Tremor reduction and quality of life after deep brain stimulation for multiple sclerosis-associated tremor. Acta Neurochir (Wien) 2013;155(12):2359-2364.
45. Zeuner KE, Deuschl G. An update on tremors. Curr Opin Neurol 2012;25:475-482.

ABSTRACT

We present a patient who experienced ischemic stroke within the posterolateral part of left hypothalamus with subsequent severe burning pain localized in right upper limb, predominantly within the hand and thalamic tremor which occurred 4 months after stroke. The patient was treated for pain with tricyclic and heterocyclic antidepressants, opioid analgesics including morphine, benzodiazepines, non-narcotic analgesics, carbamazepine and gabapentine, without major effect. Levodopa and other dopaminergic agents were used to alleviate the thalamic tremor. After 2 years of ineffective treatment the patient was offered implantation of electrodes to the periventricular grey matter (PVG)/ periaqueductal grey matter (PAG) as well as implantation an electrode to ventroposterolateral thalamic nucleus (VPL). Deep brain stimulation (DBS) of the sensory thalamus and the periventricular/ periaqueductal grey area complex may be applied for treatment of intractable neuropathic pain syndrome. Soon after starting simultaneous PAG/PVG and PVL stimulation we observed significant alleviation of the patient's thalamic tremor and severe burning pain in the hand, and the effect persisted over subsequent months. In this article we present current knowledge on possible etiology of the Holmes tremor, as well as current therapeutic options for this rare type if movement disorder.

STRESZCZENIE

W artykule prezentujemy przypadek pacjenta, u którego doszło do udaru niedokrwiennego w zakresie tylno-boczne części lewego wzgórza, z następowym ostrym piekącym bólem w zakresie prawej kończyny górnej, zlokalizowanym głownie w obrębie dłoni, jak również drżeniem wzgórzowym, które pojawiło się 4 miesiące po udarze. Pacjent był leczony trój cyklicznymi i heterocyklicznymi lekami przeciwdepresyjnymi, lekami przeciwbólowymi z grupy opioidów z uwzględnieniem morfiny, benzodiazepinami, nienarkotycznymi lekami przeciwbólowymi, karbamazepiną oraz gabapentyną, bez zadowalającego efektu przeciwbólowego. W

celu zmniejszenia nasilenia drżenia wzgórzowego zastosowano lewodopę, jak również inne leki dopaminergiczne. Po 2 latach nieskutecznego leczenia zachowawczego, choremu zaproponowano implantację elektrod do istoty szarej okołowodociągowej (PAG) i okołokomorowej (PVG), jak również do jądra brzuszno-tylnego wzgórza (VPL). Głęboka stymulacja (DBS) jąder czuciowych wzgórza i istoty szarej okołowodociągowej/okołokomorowej mogą być stosowane w leczeniu uporczywego bólu neuropatycznego. Wkrótce po rozpoczęciu stymulacji PAG/PVG oraz VPL zaobserwowaliśmy znaczną redukcję drżenia wzgórzowego u pacjenta, jak również zmniejszenie nasilenia piekącego bólu w zakresie dłoni, a efekt ten utrzymywał się w kolejnych miesiącach. W poniższym artykule prezentujemy aktualny stan wiedzy na temat możliwej etiologii drżenia Holmesa, jak również aktualnie dostępnych opcji terapeutycznych w tym rzadkim typie zaburzeń ruchowych.

Artykuł zawiera 23618 znaków ze spacjami