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HOLMES TREMOR IN ASSOCIATION WITH BILATERAL HYPERTROPHIC OLIVARY DEGENERATION AND PALATAL TREMOR

CHRONOLOGICAL CONSIDERATIONS

Case report

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ABSTRACT - Hypertrophic olivary degeneration (HOD) is a rare type of neuronal degeneration involving the dento-rubro-olivary pathway and presents clinically as palatal tremor. We present a 48 year old male patient who developed Holmes' tremor and bilateral HOD five months after brainstem hemorrhage. The severe rest tremor was refractory to pharmacotherapy and botulinum toxin injections, but was markedly reduced after thalamotomy. Magnetic resonance imaging permitted visualization of HOD, which appeared as a characteristic high signal intensity in the inferior olivary nuclei on T2- and proton-density-weighted images. Enlargement of the inferior olivary nuclei was also noted. Palatal tremor was absent in that moment and appears about two months later. The delayed-onset between insult and tremor following structural lesions of the brain suggest that compensatory or secondary changes in nervous system function must contribute to tremor genesis. The literature and imaging findings of this uncommon condition are reviewed.

KEY WORDS: rubral tremor, midbrain tremor, Holmes' tremor, myorhythmia, palatal myoclonus.

Tremor de Holmes em associação com degeneração olivar hipertrófica bilateral e tremor palatal: considerações cronológicas. Relato de caso

RESUMO - Degeneração olivar hipertrófica (DOH) é um tipo raro de degeneração neuronal envolvendo o trato dento-rubro-olivar e se apresenta clinicamente como tremor palatal. Relatamos o caso de um homem de 48 anos que desenvolveu tremor de Holmes e DOH bilateral cinco meses após hemorragia em tronco encefálico. O intenso tremor de repouso foi refratário a farmacoterapia e injeções de toxina botulínica, mas foi enormemente reduzido após talamotomia. Ressonância magnética permitiu a visualização da DOH, que apareceu como um sinal intenso característico na oliva inferior em imagens ponderadas em T2 e densidade de prótons. Aumento do complexo olivar inferior também foi percebido. O tremor palatal era ausente naquele momento e apareceu cerca de dois meses depois. O início tardio do tremor após a lesão estrutural sugere que alterações compensatórias ou secundárias no sistema nervoso devem contribuir para a gênese do tremor. A literatura e os achados radiológicos dessa patologia incomum são revisados.

PALAVRAS-CHAVE: tremor rubral, tremor mesencefálico, tremor de Holmes, miorritmia, mioclonus palatal.

A variety of conditions including cerebral hemorrhage have been associated with an unusual combination of 2 to 5-Hz rest, postural, and kinetic tremor of an upper extremity. This tremor has been nominated rubral or midbrain tremor, Holmes' tremor, or myorhythmia. The traditional terms rubral or midbrain tremor has been discarded because of cases showing lesions outside these classical locations were described[1,2]. Furthermore, experimental lesions of the red nucleus do not induce a persistent tremor[3]. Myorhythmia is an old term that has been used with very different meanings. In order to avoid definitions

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that include topographic relations, the term Holmes' tremor has been proposed and accepted, because Holmes (1904) provided one of the early descriptions of this tremor[4]. The following criteria have been proposed to define Holmes tremor[5]: a. Both resting and intentional tremor must be present. Many patients also have postural tremor. The tremor rhythm is often not so regular as for other tremors, giving the impression of jerky movements; b. Frequency must be slow, usually bellow 4.5 Hz; c. If the date of the lesion is know, a variable delay (usually 2 weeks to 2 years) between the lesion and the first occurrence of the tremor is typical.

The anatomy of this tremor is complex and incompletely understood, but there has been broad agreement that the tremor follows interruption of the dentate projections pathways, particularly in the region of the superior cerebellar peduncle and red nucleus[6]. Symptomatic palatal tremor, also known as symptomatic palatal myoclonus, is a clinically, pathologically, and anatomically well defined movement disorder characterized as a stereotypic 1-3 Hz palatal contractions that commonly appears after a disruption of the so-called Guillain-Mollaret triangle (the dentatoolivary tract)[7-9]. Symptomatic palatal tremor is correlated with hypertrophic olivary degeneration (HOD), an unusual form of transneuronal degeneration affecting the inferior olivary nuclei[7,9].

We report a patient with brainstem hemorrhage who first presented magnetic resonance imaging (MRI) evidence of bilateral HOD, then a palatal myoclonus.

CASE

A 48-year-old man suddenly developed dysarthria, dizziness, diplopia, and ataxia. Two hour after the onset, the patient was admitted to the intensive care unit of "Santa Casa de Misericórdia de Porto Alegre". On admission his blood pressure was 180/120 with normal regular pulses and general examination. He was drowsy and dysarthric, with the speech not intelligible, but correctly responsive to verbal commands. Neurological examination demonstrated right-predominant miosis, left nuclear facial nerve palsy, horizontal gaze paralysis to the left with nystagmus

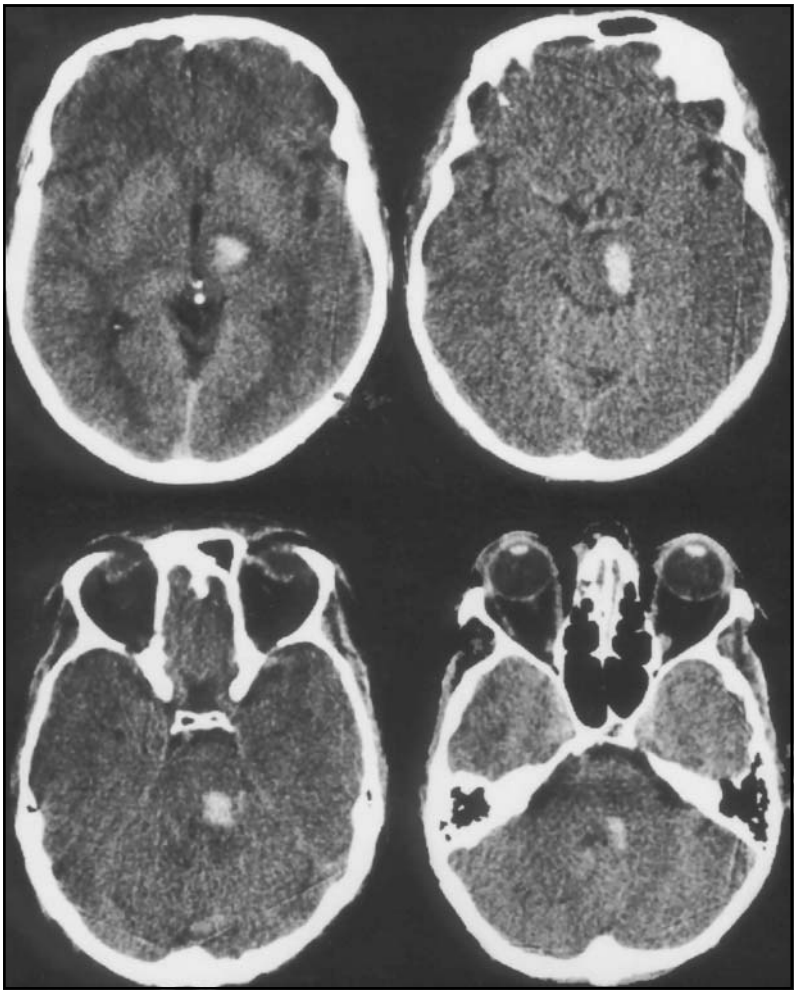

Fig 1. CT scan demonstrated a large hemorrhage area in the brain steam.

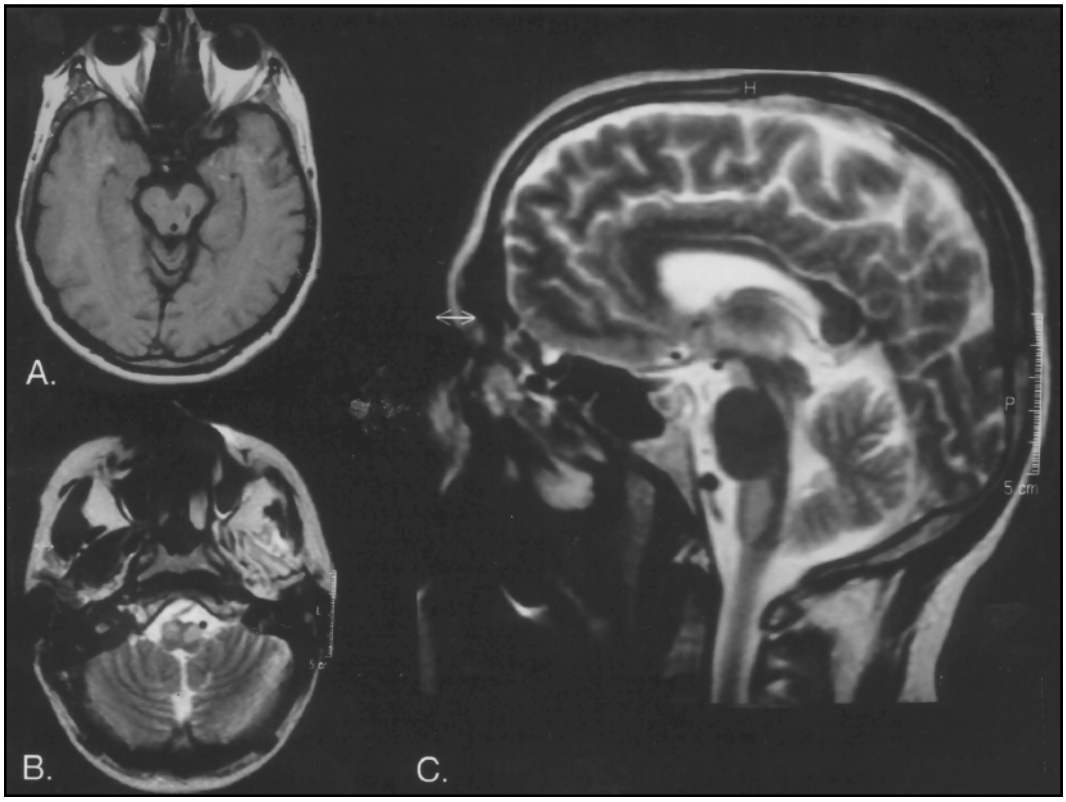

Fig 2. MRI 5 months after the hemorrhage: T1-weighted axial image (A) shows a residual tuft in the midbrain. Axial and sagital images (B and C) shows increased signal intensification in the area of the olives on T2, greatest in the left. Enlargement of the inferior olivary nuclei was also noted.

of the abducting eye. Adduction of the left eye was impaired. Upward and downward gaze was mildly limited on both sides. Partial ptosis was observed in the left eyelid. The patient was quite ataxic and with right hemiparesis (upper extremity more severely affected than the lower extremity). Sitting was difficult without support. Heel-to-heel test showed both dysmetria and incoordination on the left side.

Computed tomographic scan showed a hemorrhage extending throughout the length of the pontine tegmentum and midbrain to the thalamus (Fig 1). Blood chemical examination was normal. The patient's condition slowly improved in the following months.

Five months after the hemorrhage a tremor arose in the right hand and gradually increased in amplitude to affect the entire limb. Examination in that period revealed a coarse flexion-extension tremor at the fingers, wrist, and elbow, most prominent distally with a frequency of ~ 3-5 Hz measured clinically. The tremor was present at rest, increased with posture, and further amplified during intentional movements. The tremor nearly incessant during wakefulness was exhausting and incapacitating. During sleep it disappeared. On that moment there was no palatal tremor. The patient was capable of standing with help but incapable of walking. Ocular abnormalities included left internuclear ophtalmoplegia. Speech was dysarthric and hardly intelligible. Magnetic resonance imaging (MRI) permits visualization of HOD, which appears as a characteristic signal-enhancing lesion in proton-density and T2-weighted images. The signal was higher in the side of the lesion (Fig 2). On returning 4 weeks later the neurological examination had not changed. Two months later the patient presented with palatal tremor. The patient had not noticed the palatal tremor.

Pharmacotherapy was attempted with clonazepan, levodopa, trihexyphenidyl, valproic acid, propranolol without effect. A mild improvement of the tremor amplitude was obtained with botulinum toxin type A injections. The tremor was markedly reduced after left thalamothomy.

DISCUSSION

We present a patient who developed Holmes' tremor and MRI evidence of HOD five months after brain stem hemorrhage. Palatal tremor was not present in this moment and appears about two months later. There are some noteworthy characteristics in this patient: (1) difference in timing of appearance of Holmes tremor and palatal tremor, (2) correlation of appearance of palatal tremor and the morphologic change of the olives, (3) the bilateral olivary involvement.

Holmes' tremor usually begins weeks to months after brainstem stroke, so compensatory or secon-

dary changes in nervous system function must contribute to tremor genesis. The delayed-onset between insult and tremor following structural lesions of the brain are well described but poorly understood. The occurrence indicates brain plasticity or irritative etiology. Exactly how it occurs and why it occurs in some cases and not others remains a mystery.

The pathophysiologic basis of Holmes' tremor is not clear. It seems generally accepted that this Holmes' tremor involves different lesions centered to the brainstem, cerebellum, and thalamus[10]. However, lesions of the fibber tracts in other regions may cause a similar clinical phenomenon. Isolated lesions in the red nucleus are not tremorogenic. The lesions causing Holmes tremor are frequently located in the area of the substantia nigra and nigrostriatal fibers, suggesting dopaminergic denervation as possibly contributory[11]. In six patients with a contralateral tremor following a peduncular lesion was found a marked decrease of [18F]-fluorodopa uptake in the striatum ipsilateral to the lesion without significant changes in the D2-specific binding[11]. These results indicate an important involvement of the nigral dopaminergic system in peduncular tremors that appears to be independent of postsynaptic dopamine receptors.

Stereotactic lesions performed in monkeys in the parvicellular red nucleus, brachium conjunctivum decussation and ventromedial mesencephalon (substantia nigra) demonstrated that damage to all three areas was necessary for sustained tremor[3]. These findings confirm clinic-pathologic observations in humans. A combination of damage to the red nucleus and neighboring cerebello-thalamic, cerebello-olivary, and nigrostriatal fibers tracts are required [3]. The peculiar mixture of rest, postural and kinetic tremor follows logically from this combination of pathology. Although attention has focused on the dentatorubral and dentatothalamic tract that forms the ascending limb of the dentate projection, components of the descending limb have also been implicated[6]. In particular, clinical evidence of a role for the rubroolivary tract is supported by experimental evidence of a rubroolivocerebellorubral loop[6].

Knowledge of the components of the triangle of Guillain and Mollaret is essential for understanding how lesions affecting the triangle can influence the inferior olivary nuclei. The triangle is composed of the contralateral dentate nucleus, the ipsilateral red nucleus and the ipsilateral inferior olivary nucleus. One of the main sources of fibers to the red nucleus is the dentate nucleus, but there are also fibers coming from the emboliform and the globose nuclei. The efferent from the dentate ascend through the superior cerebellar peduncle, or brachium conjunctivum, decussate in the caudal midbrain, and then enter the colateral red nucleus. The rostral third of the red nucleus (the parvicellular part) is the end point of the dentaterubral pathway, where they have asymmetric synapses. The parvicellular part of the red nucleus sends uncrossed fibers through the central tegmental tract to the dorsal lamella of the principal inferior olivary nucleus. The inferior olivary nucleus is a highly developed complex, being the major source of climbing fibers to the cerebellum. These fibers have powerful excitatory synapses on Purkinje cell dendrites. The triangle is completed by inferior olivary nucleus efferents crossing the midline, forming the largest component of the inferior cerebellar peduncle (corpus restiform), and terminating on the original dentate nucleus, as well as in all parts of the cerebellum[8]. This is a bi-directional pathway, a coupled system likely to be of a feedback function, because there are also projections from the dentate nuclei to the contralateral caudal inferior olivary nuclei. The inferior olive tends to possess a slow, rhythmic, spontaneus activity[12].

HOD is not a primary lesion but, rather, develops as a lesion of the Guillain- Mollaret triangle. MRI may currently be the only procedure capable of confirming the diagnosis. MRI showed high signal intensity in the inferior olivary nuclei on T2- and proton-density-weighted images. Enlargement of the inferior olivary nuclei was also noted[8,13]. HOD occurs after interruption of the monosynaptic dentatoolivary tract. The pathology and time course of HOD are microscopically well characterized. The neuronal hypertrophy begins at 3 weeks, neuronal and glial hypertrophy peak at 8-9 months, pseudohypertrophy (neuronal dissolution and gemistocytic astrocytes) occurs thereafter, gradually leading to olivary atrophic degeneration[13,14]. MRI permits antemortem visualization of HOD, which appears as a characteristic signal-enhancing lesion in proton-density and T2-weighted images[6,8,15]. Although virtually all patients who develop palatal myoclonus after a brain insult will have HOD, not all patients with HOD develop palatal myoclonus[6].

Palatal tremor is a rhythmic involuntary movement that appears mainly in the soft palate. Palatal tremor is separated into two distinct clinical entities, symptomatic palatal tremor and essential palatal tremor arising from different pathophysiological mechanisms. Symptomatic palatal tremor is thought to arise from a lesion of the brainstem or cerebellum

within the Guillain-Mollaret triangle[7-9]. Clinically, however, essential and symptomatic palatal tremors behave differently. Patients with symptomatic palatal tremor usually have symptoms of considerable cerebellar or brain stem dysfunction associated with an acute lesion within the triangle of Guillain and Mollaret, such as results from ischemic injury or hemorrhage. Patients with essential palatal tremor have no focal lesion but the palatal tremor can produce a self-audible clicking sensation due to activation of the levator veli palatini muscle innervated by the ninth cranial nerve.

There have been few cases describing the development of palatal tremor some time after the appearance of Holmes tremor[16]. Although the imaging features have been well described, the temporal course of hypertrophy and T2 signal increase in the inferior olivary nucleus has not been fully characterized. The data from the MR images indicate that increased olivary signal on T2-weighted images first appeared 1 month after the inciting lesion and persisted for at least 3 to 4 years. Olivary hypertrophy initially appeared on imaging studies obtained 6 months after the acute event, and resolved by 3 to 4 years[8,17].

Although it is an anatomic triangle, symptomatic palatal tremor and HOD are associated with lesions of the first two limbs of the triangle, but not with lesions involving olivodentate fibers, since it is olivary deafferentation that is thought to be the source of the ensuing hypertrophic degenerative changes[8].

HOD usually occurs unilaterally and ipsilateral to the lesion if the lesion is in the brain stem or contralateral to the lesion if the lesion is in the cerebellum as identified on MRI. There have been only rare reported cases in which a unilateral lesion resulted in bilateral HOD. Bilateral HOD after a right cerebellar artery infarct that occurred during craniotomy was reported[18]. The reason for this is unclear. A midline lesion, however, if located in the brachium conjunctivum, may result in bilateral HOD if there is involvement of both the right and left dentato-olivary fibers as they cross. The patient we described incurred bilateral HOD from a left brain stem hemorrhage located near the decussation of these fibers. The limb tremor and increased signal on T2- and proton density–weighted images were observed at approximately 5 month after ictus but that palatal tremor was not observed until 7 months after ictus. Differences on the time of appearance of tremor suggest that responsible neuronal circuitries subserving abnormal rhythmic excitation of motoneurons in the brainstem may develop with different time courses after the stroke. It is feasible that the palatal tremor could develop only after certain central nervous system pathophysiological changes had developed which correlated with the observed hypertrophy of the inferior olive on MRI.

REFERENCES

1. Mossuto-Agatiello L, Puccetti G, Castellano AE. "Rubral" tremor after thalamic haemorrhage. J Neurol 1993;241:27-30.
2. Martinez Perez-Balsa A, Marti-Masso JF, Lopez de Munain A, Ruibal M, Ruiz J. "Rubral" tremor after vascular thalamic lesions. Rev Neurol 1998;26:80-84.
3. Ohye C, Shibazaki T, Hirai T, et al. A special role of the parvocellular red nucleus in lesion-induced spontaneous tremor in monkeys. Behav Brain Res 1988;28:241-243.
4. Holmes G. On certain tremors in organic cerebral lesions. Brain 1904;27:327-375.
5. Deuschl G, Krack P. Tremors: Differential diagnosis, neurophysiology, and pharmacology. In Jankovic J, Tolosa E (eds). Parkinson's disease and movement disorders. 3. Ed. Baltimore: Williams & Wilkins, 1998:419-452.
6. Shepherd GM, Tauboll E, Bakke SJ, Nyberg-Hansen R. Midbrain tremor and hypertrophic olivary degeneration after pontine hemorrhage. Mov Disord 1997;12:432-437.
7. Deuschl G, Mischke G, Schenck E, Schulte-Mönting J, Lücking CH. Symptomatic and essential rhythmic palatal myoclonus. Brain 1990;113:1645-1672.
8. Goyal M, Versnick E, Tuite P, et al. Hypertrophic olivary degeneration: metaanalysis of the temporal evolution of MR findings. Am J Neuroradiol 2000;21:1073-1077.
9. Yanagisawa T, Sugihara H, Shibahara K, Kamo T, Fujisawa K, Murayama M. Natural course of combined limb and palatal tremor caused by cerebellar-brain stem infarction. Mov Disord 1999;14:851-854.
10. Vidailhet M, Jedynak CP, Pollak P, Agid Y. Pathology of symptomatic tremors. Mov Disord 1998;13:49-54.
11. Remy P, Recondo A, Defer G, et al. Peduncular "rubral" tremor and dopaminergic denervation: a PET study. Neurology 1995;45:472-477.
12. Armstrong, DM. Functional significance of the inferior olive. Physiol Rev 1974;54:358-417.
13. Goto N, Kaneko M. Olivary enlargement: chronological and morphometric analyses. Acta Neuropathol 1981;54:275-282.
14. Goto N, Kakimi S, Kaneko M. Olivary enlargement: stage of initial astrocytic changes. Clin Neuropathol 1988;7:39-43
15. Sperling M, Herrmann C Jr. Syndrome of palatal myoclonus and progressive ataxia: two cases with magnetic resonance imaging. Neurology 1985;35:1212-1214.
16. Masucci EF, Kurtzke JF, Saini N. Myorhythmia: a widespread movement disorder: clinicopathological correlations. Brain 1984;107:53-79.
17. Yokota T, Hirashima F, Furukawa T, Tsukagoshi H, Yoshikawa H. MRI findings of inferior olives in palatal myoclonus. J Neurol 1989;236:115-116.
18. Uchino A, Hasuo K, Uchida K, et al. Olivary degeneration after cerebellar or brain stem haemorrhage: MRI. Neuroradiology 1993;35:335-338.