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Clinical case

Holmes Tremors in a 60-year-old Woman Following Primary Brainstem hemorrhage (PBH) Responsive to Standard Dose of Trihexyphenidyl: A case report and literature review

Tremblements de Holmes post Hematome du tronc cérébral répondant à une dose standard de trihexyphenidyl chez une patiente de 60 ans

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Résumé

Introduction : le tremblement de Holmes, connu autrefois sous le nom de tremblement rubral ou mésencéphalique, est un phénomène rare et atypique, se manifestant par un tremblement de repos irrégulier associé à un tremblement d'action souvent exacerbé par la posture. Les lésions vasculaires ou traumatiques affectant le circuit cérébello-thalamocortical et le triangle de Guillain-Mollaret en sont les principales causes. À l'heure actuelle, il n'existe pas de protocole thérapeutique fondé sur des essais cliniques randomisés, et la réponse aux traitements proposés varie considérablement. Les traitements médicamenteux de première ligne proposés incluent la lévodopa, le lévétiracétam et le trihexyphénidyle, ce dernier étant souvent prescrit à des doses élevées. Nous présentons un cas de tremblement de Holmes compliquant un hématome ponto-mésencéphalique avec une réponse favorable au trihexyphénidyle à une dose standard.

Cas clinique : patiente âgée de 60 ans ayant présenté un AVC hémorragique du tronc cérébral par micro angiopathie hypertensive, révélé par un trouble de la vigilance d'installation brutale avec une évolution favorable. Vingt-six jours après cet événement, des tremblements de Holmes dans la région brachiofaciale droite ont été observés. Le traitement par trihexyphénidyle a été initié à des doses standards, atteignant progressivement 12 mg répartis en trois prises, ce qui a conduit à une disparition presque complète des tremblements et, à 3 mois, la patiente a gardé juste une dysarthrie séquellaire.

Conclusion : L'administration de trihexyphénidyle représentait un choix délicat en raison du trouble de la vigilance préexistant et de l'âge avancé de la patiente. Néanmoins, sans utiliser des doses excessives, les tremblements ont cessé, soulignant ainsi la nécessité de mener des études à grande échelle pour établir des protocoles de traitement adaptés tout en personnalisant le choix thérapeutique pour chaque patient.

Mots-clés : Tremblement de Holmes, Hématome du tronc cérébral, trihexyphénidyle, sujet âgé, rapport de cas.

Abstract

Introduction: The Holmes tremor, once known as rubral or mesencephalic tremor, is an uncommon and atypical condition that presents as an irregular resting tremor, often accompanied by an action tremor that worsens with certain postures. This phenomenon is primarily caused by vascular or traumatic injuries that impact the cerebellothalamocortical pathway and the Guillain-Mollaret triangle. Currently, there is no therapeutic protocol based on randomized clinical trials, and the efficacy of the proposed treatments varies significantly. First-line pharmacological treatments include levodopa, levetiracetam, and trihexyphenidyl, the latter frequently prescribed at high doses. We present a case of Holmes tremor associated with a pontine-mesencephalic hematoma, which showed a favorable response to standard-dose trihexyphenidyl.

Clinical case: A 60-year-old patient presented with a hemorrhagic stroke in the brainstem secondary to hypertensive microangiopathy, characterized by a sudden disturbance in consciousness and a favorable outcome. After twenty-six days, Holmes tremors were observed in the right brachiofacial area. The patient was started on trihexyphenidyl at standard doses, which were gradually increased to a total of 12 mg taken in three doses, resulting in nearly complete resolution of the tremors. At the three-month follow-up, the patient exhibited only mild dysarthria as a residual effect.

Conclusion: The choice to administer trihexyphenidyl was particularly challenging due to the patient's pre-existing vigilance issues and her advanced age. Nonetheless, by refraining from high doses, the tremors were resolved, underscoring the necessity for comprehensive studies to formulate effective treatment protocols and to personalize therapeutic decisions for each individual patient

Keywords: Holmes tremor, primary brainstem hemorrhage (PBH), Trihexyphenidyl, elderly patient, case report.

Introduction

The contemporary definition of Holmes tremors (HT) is based on the criteria established by the International Movement Disorder Society (MDS) in 1998 and revised in 2018[1]. This definition aligns closely with Holmes's original description, which characterizes HT as a syndrome that includes resting, postural, and intention tremors, typically arising from rhythmic muscle contractions at both proximal and distal levels, with a frequency of less than 5 Hz[1]. This condition has been referred to by several names, such as rubral tremor, mesencephalic tremor, thalamic tremor, post-traumatic tremor, or complex tremor[2]. Between 1904 and 2016, a mere 155 patients were documented, suggesting that this tremor is quite rare[3]. The predominant causes are often vascular and traumatic injuries affecting the cerebellothalamocortical circuit and the Guillain-Mollaret triangle[2].

The variability in response to the proposed treatments is significant, and there are no randomized clinical trials to guide therapeutic decisions[4]. Most available options are based on limited case studies[5]. Recent research indicates that medical treatment should be considered the first-line therapy, although deep brain stimulation shows much more promising results[4]. Carbidopa or levodopa is effective in approximately 50% of patients with HT[1], [3], [6]. Other first-line treatments include levetiracetam and central anticholinergics, particularly trihexyphenidyl[4], [7]. In this regard, trihexyphenidyl (Artane) is often prescribed at high doses, reaching up to 38 mg per day[7]. However, the use of these pharmacological classes presents challenges for elderly patients with impaired alertness

This report details an uncommon instance of Holmes tremor in a 60-year-old female patient after a spontaneous brainstern hemorrhage. Due to impaired alertness, treatment selection required careful consideration. The administration of trihexyphenidyl at a standard dose of 12 mg, led to a marked clinical enhancement.

Clinical case

A 60-year-old right-handed female with a history of hypertension for eight years and irregular medical follow-ups. She was admitted to our neurology service during the late subacute phase, 12 days following the onset of her initial symptoms, due to a spontaneous intracerebral hemorrhage in the ponto-mesencephalic region (Figure 1), which was marked by a sudden deterioration in her consciousness. The initial neurological examination indicated a stage I coma (Glasgow Coma Scale score of 12/15) and a right-sided flaccid hemiplegia. The ICH prognostic score was assessed at 2.

After a 14-day hospital stay, roughly 26 days post-symptom onset, the patient developed tremors affecting the neck, chin, submental region, lips, and soft palate, with occasional involvement of the eyelids and extension to the proximal right arm. These tremors, which were slow and of considerable amplitude, sometimes lessened and disappeared entirely during sleep. The diagnosis of Holmes tremor was made. Treatment with trihexyphenidyl was initiated, starting at a dosage of 6 mg in two divided doses, but no improvement was observed after 72 hours. The dosage was subsequently increased to 10 mg in three daily doses, resulting in the resolution of tremors in the eyelids and the proximal right arm. An increase to 12 mg in three daily doses led to a near-complete resolution of the tremors within three weeks, leaving only mild tremors in the lips and palate, along with a slight residual dysphonia after three months.

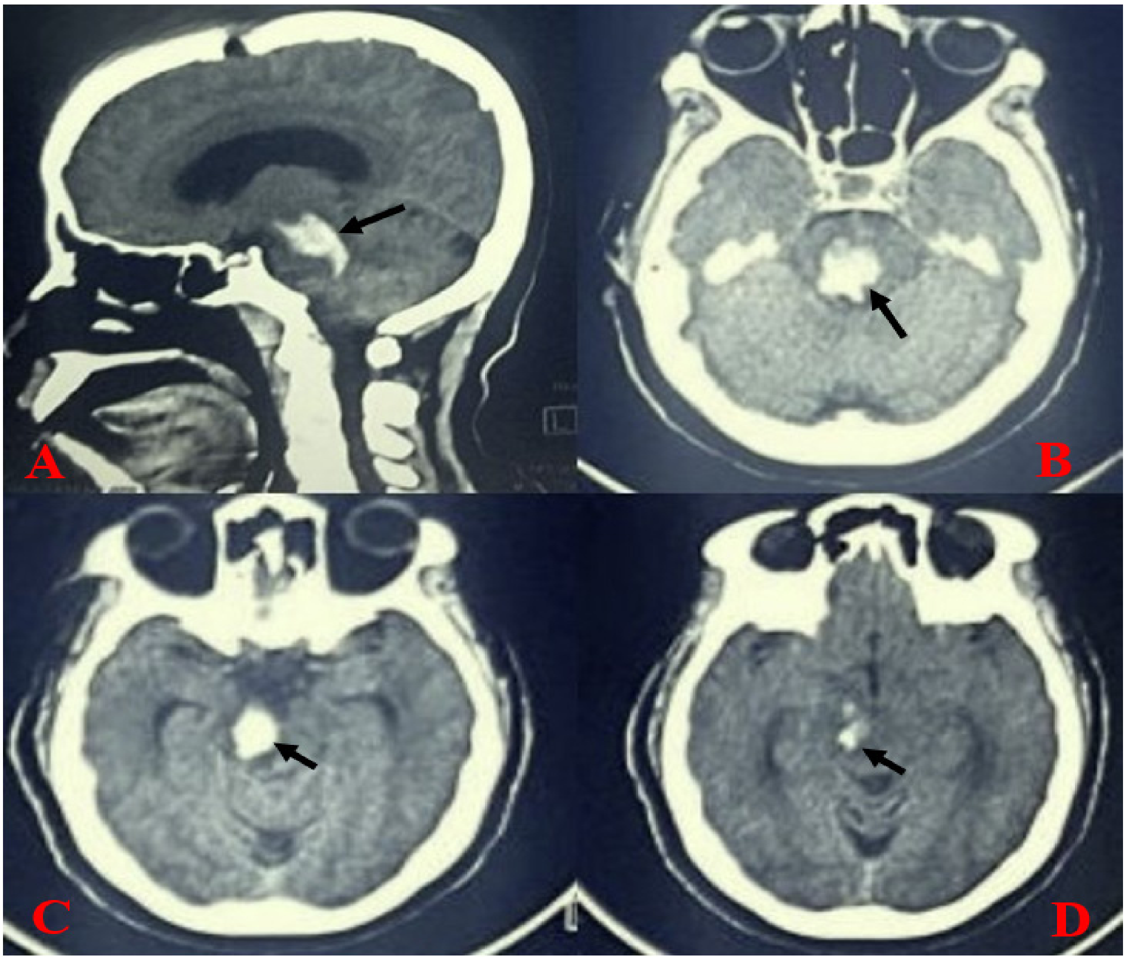

Figure 1 Cranioencephalic Computed Tomography Four Days after Symptom Onset

Cranio-encephalic CT with mid-sagittal (A), pontine axial (B), and midbrain sections (C, D), revealed spontaneous Brainstern hyperdensity, highly suggestive of intracerebral hemorrhage involving the pons, right middle and superior cerebellar peduncles, midbrain (including red nuclei, locus coeruleus and right cerebral peduncle)

Discussion

Tremor is the most commonly observed movement disorder in clinical practice and can be defined as an involuntary, rhythmic oscillatory movement that can affect nearly any part of the body [8]. The traditional classification of tremors is based on their occurrence at rest or during action. Action tremors are further divided into kinetic, postural, and terminal (or intention) tremors. Gordon Holmes was the first to describe an atypical tremor characterized by an irregular, low-frequency resting tremor (less than 4.5 Hz) accompanied by pronounced action tremors, typically exacerbated by posture. The contemporary definition of Holmes tremor (HT) is based on criteria established by the International Movement Disorder Society (MDS) in 1998 and revised in 2018[1]. Unlike other tremor types, proximal muscles are often affected. There is limited literature on Holmes tremor, which may be attributed to misdiagnosis, placing HT in another tremor category, or the lack of reported isolated cases[6]. From 1904 to 2016, only 155 patients were documented, indicating that this tremor is rare[3]. This report concerning a 60-year-old woman following a hemorrhagic stroke in the brainstem represents the first documented case of Holmes tremor in Côte d'Ivoire.

The current understanding of the pathophysiology of HT is still largely theoretical [3], [5]. It is commonly believed that the development and progression of HT require multiple brain lesions that impact the dopaminergic nigrostriatal system, the cerebellar-thalamic-cortical pathway and the dentate-rubro-olivary pathway are necessary for the onset and advancement of HT [3], [5]. This condition has been labeled with various terms that refer to the lesion's location, including rubral tremor, mesencephalic tremor, thalamic tremor, post-traumatic tremor, and complex tremor [2]. Nevertheless, these designations can be misleading due to their clinico-neuroanatomical associations, as Holmes tremor may result from lesions affecting a range of cortical and subcortical structures [9], [10]. Therefore, "Holmes tremor" is the term most frequently favored [4], [11]. Identified mechanisms of lesions include vascular injuries, whether ischemic or hemorrhagic, traumatic brain injuries, as well as inflammatory demyelinating diseases, neoplasms, and paraneoplastic disorders [12], [13], [14]. Additionally, environmental toxins and viral infections should also important factors to consider[12], [13], [14]. Genetic factors have been identified in Holmes tremor, particularly recent mutations in the PNPLA6 gene, which are responsible for cerebellar degeneration [12]. This gene is essential for the production of the membrane protein known as neuropathy target esterase (NTE), which plays a critical role in neural tube formation during embryonic development [5]. Previous studies have shown that vascular mechanisms are the most common, with ischemic or hemorrhagic vascular lesions accounting for approximately 48 to 55% of HT cases, followed by traumatic brain injuries, which represent about 17 to 20% of cases [5]. In this case, the HT was associated with a hypertensive Brainstem hemorrhage.

The manifestations of Holmes Tremor typically arise between four weeks and two years following a neurological injury. Due to the involvement of various networks and structures within the central nervous system (CNS), Holmes Tremor is often linked with additional clinical symptoms such as bradykinesia, spasticity, dystonias, choreoathetotic movements, ataxia, and ophthalmoplegia. In our case, symptoms emerged approximately 26 days post-stroke, without any accompanying motor disorders. The onset delay of these symptoms is attributed to abnormal synaptic rearrangements and deviant sprouting of collateral axons, which occur pathologically after neuronal damage. Normally, damaged synapses undergo degeneration, followed by reinnervation and rearrangement to restore healthy neuronal connections. In the case of Holmes Tremor, it is believed that these neuronal connections are reestablished in a disordered manner or that the connectivity between the restored neurons is impaired, leading to a reduction in neurotransmitter release. However, the mechanisms explaining the delayed onset of Holmes Tremor symptoms remain only partially understood.

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The challenge of correlating Homes Tremor (HT) with a specific neuroanatomical location or a distinct network through imaging techniques remains significant [17]. This difficulty can be partly attributed to the extensive nature of the pathological systems involved in tremor. Increasingly, multimodal neuroimaging approaches, which encompass functional connectivity, functional MRI, and nuclear medicine, are being employed to investigate the pathological network associated with HT [3]. Recent studies have identified a common brain network in individuals with HT, which includes the following structures: the red nucleus, the internal globus pallidus (GPi), the posterior oral ventral nucleus (VOP), the pulvinar nucleus, the pontomedullary junction, the cerebellar cortex, the cerebellar vermis in lobule VI, and the cerebellar cortex in lobule X [5], [17].

The effectiveness of various treatment options is quite diverse, and there is a lack of randomized clinical trials to guide therapeutic choices [4]. Most available treatments are derived from limited case series [5]. Deep brain stimulation (DBS), which focuses on the ventral intermediate thalamic nucleus (VIM), the internal globus pallidus (GPi), and the subthalamic nucleus (STN), has proven to be more effective than medication-based treatments ($p = 0.025$) [4], [5], [17], [18]. Recent studies suggest that medical treatment should be considered as the first line of approach [4]. Carbidopa or levodopa is effective in approximately 50% of patients with HT [1], [3], [6]. Other first-line therapeutic options include levetiracetam and anticholinergics, such as trihexyphenidy[4], [7]. (Figure 2)

Anticholinergic agents inhibit muscarinic receptors both peripherally and centrally. They counteract the hyperactivity of cholinergic interneurons in the striatum, which is a consequence of decreased dopaminergic inhibitory tone [19], [20]. Due to their effectiveness in managing tremors associated with Parkinson's disease, these medications are also employed to treat HT, often at higher doses [5]. In a documented case, Li-Min Liou reported administering up to 38 mg of Trihexyphenidyl in a single dose to a 22-year-old patient with HT due to a left thalamic cavernoma [7]. In our case, we opted for standard doses not exceeding 12 mg per day, divided into three administrations, as the patient already displayed a disturbance in alertness. This condition limited our ability to increase the Trihexyphenidyl dosage due to the potential side effects in older adults, particularly the risk of cognitive decline and confusion [20] [19]. Furthermore, it is advisable to monitor the plasma concentration of these medications when administered outside the standard therapeutic range, which is not feasible in our working conditions [7], [20], [21]. It is noteworthy that there is a lack of guidance from randomized clinical regarding the use of anticholinergics in patients with HT, although these medications are suggested based on observational studies [4]. Any therapeutic choice in this context should be guided by a balance between efficacy and tolerability[22].

Other pharmacological agents, including clonazepam, bromocriptine, amantadine, or botulinum toxin injections, can be regarded as second-line options [4]. For patients suffering from central nervous system toxoplasmosis, notable improvement in HT has been documented with the use of antiparasitic therapy alongside corticosteroids, suggesting that targeting the root cause may help reverse network dysfunction prior to irreversible neuronal damage [23]. Although our study did not involve a specific etiological treatment, the gradual absorption of the hematoma might contribute to a clinical enhancement of the tremor.

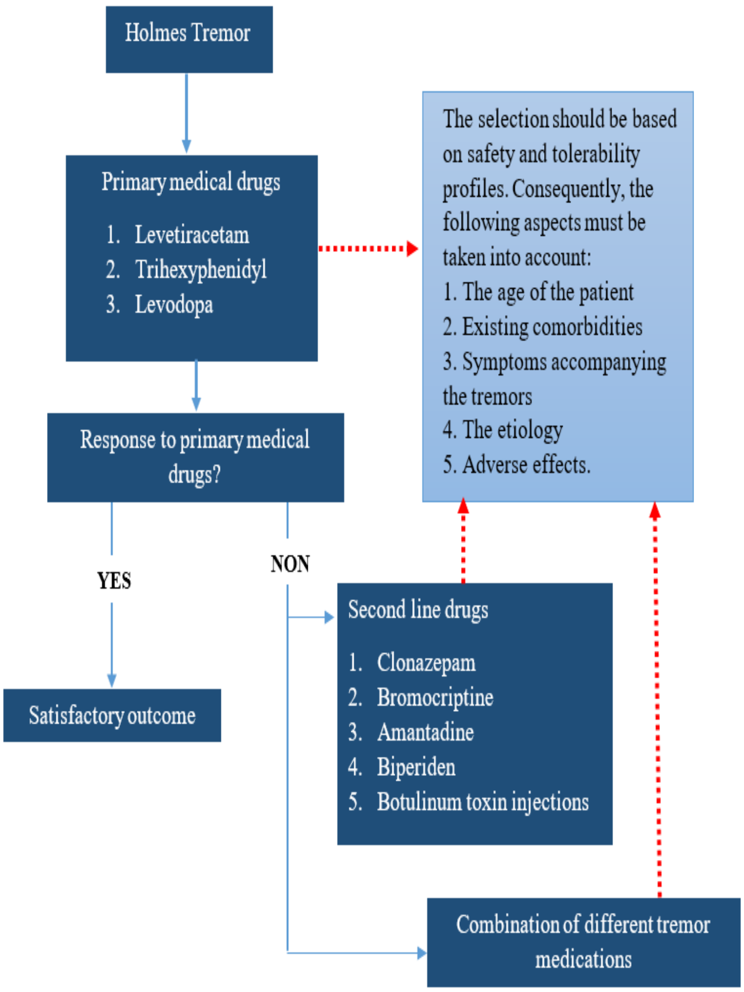

Figure 2. A potential algorithm for the treatment of Holmes Tremor on the basis of the limited evidence available to date (adapted from reference 4 and 22).

Legend: A proposed algorithm for the treatment of Holmes Tremor, based on the limited information available so far [4]. In this regard, Wang advocates for the initiation of medical therapy for HT with one of the following first-line agents: levetiracetam, trihexyphenidyl, or levodopa. Second-line treatments may include clonazepam, bromocriptine, amantadine, biperiden, or botulinum toxin injections. Depending on the patient's response to therapy and their tolerance, various combinations of treatments could be considered.

Conclusion

In an elderly individual with Holmes tremors and compromised vigilance due to a brainstem hematoma, the use of an anticholinergic at a typical dosage resulted in favorable outcomes after four weeks, without any significant adverse effects. The variability in therapeutic responses seen in Holmes tremors underscores the need for large-scale studies to develop treatment guidelines tailored to the underlying causes and clinical-radiological presentations.

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Conflict of interest : None

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