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Case Report

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Holmes Tremor in A Case of AIDS with Toxoplasma Abscess: Is A Common Result of Different Pathogenetic Mechanisms?

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Abstract

Holmes tremor is a low-frequency tremor clinic that predominantly affects proximal extremities during rest, posture, and action. It is generally associated with lesions located in the mesencephalon or thalamus. It is thought that the clinic is formed in similar phenomenology but as a result of different physiopathologic events. It is known that weeks, months, or even years pass from the underlying cause for the duration of symptoms. In this article, it is aimed to present a case of Holmes tremor, developing approximately nine months after HIV-related toxoplasmic abscess located in the mesencephalon and the thalamus and to discuss these rare associations with the literature.

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1. Introduction

Holmes tremor is a rare, unilateral, low-frequency tremor that dominates the proximal extremity and is observed during rest, posture and action. The amplitude of tremor may be low at rest, but it increases during posture and reaches its highest level during movement (Holmes, 1904). The clinical picture is be due to various etiologies such as ischemia, vascular malformation, tumor or demyelinating disease located in mesencephalon or thalamus. The clinic is mostly unilateral and prominent in upper extremity, and sometimes accompanied by ipsilateral dystonia (Deuschl et al., 1996; Deuschl et al., 1998). Clinical signs appear weeks, months or even years after the primary lesion. Cerebellothalamic and nigrostriatal system degeneration or structural and functional impairment due to interruption of pallidothalamic pathways is involved in the pathogenesis (Kim et al.,2009; Deuschl & Bergman, 2002). The primary goal of treatment is to eliminate the underlying cause. If additional treatment is required, levodopa, dopamine agonists, clonazepam, propranolol, amantadine, valproate or levetiracetam can be preferred (Raina et al., 2016, ; SchreudFerlazzo et al., 2008). Surgery is recommended in resistant cases who do not respond to medical treatment. It has been reported that stereotaxic thalamotomy and deep brain stimulation to the thalamic ventral intermediolateral (VIM) nucleus are beneficial in terms of dystonia in addition to tremor (Yuk et al., 2019). Holmes tremor cases with brain abscess due to HIV-related opportunistic toxoplasma infection are extremely rare in the literature (Lekoubou et al., 2010).

In this article, it is aimed to discuss the clinical features, etiologies and treatment methods in the light of the literature in a patient who was diagnosed with Holmes tremor nine months after the diagnosis of brainstem abscess with AIDS.

2. Case Report

41-year-old female patient was admitted to the Neurology department with weakness in the right half of the body and facial asymmetry nine months ago. In the first examination with magnetic resonans imaging (MRI), there were two abcesses; first one is a 12x15x18 mm lesion which appears to be central hypointense in T2-weighted and FLAIR sequences and whose periphery appears to be hyperintense in T1-weighted sequences at the left thalamus, internal capsule and also the mesencephalon tegmentum. The second one was smaller than 1 cm and located at adjacent to the anterior horn of the lateral ventricle on the right (Figure 1).

There were HIV and toxoplasma Ig G positivity in laboratory tests. She was diagnosed with opportunistic toxoplasma-induced brainstem abscess secondary to human immunodeficiency virus (HIV) infection. After the antiparasitic (Trimethoprim-sulfamethaxazole, azithromycin) and antiviral treatment (dolutegravir, tenofovir disoproxil/emtricitabine), she was discharged with a partial neurological recovery. After 3 months, he went to the ophthalmologist because of poor vision. She was diagnosed with cytomegalovirus retinitis and valganciclovir was added to the treatment. At the end of the fifth month, she presented with gradually increased involuntary movements in the right arm.

In neurological examination, there was dystonic posture in the right hand with low-frequency tremor observed during rest and posture in the right upper extremity, with additional sequelaes as right hemiparesis, central facial paralysis and 0.3 / 0.6 vision. Neuroimaging showed the same lesions with the difference of markedly reduced edema effect (Figure 2).

With the diagnosis of Holmes tremor, levetiresetam was started by dose titration in addition to the current antiviral treatment in order to avoid of aggravation of liver dysfunction. Significant improvement in tremor was observed in the third month of clinical follow-up. However, Clonazepam was added to the treatment by planning dose titration due to the continuation of dystonia and it had to be discontinued due to intolerance. Thereupon, she was directed to a center aiming to completely eliminate the functional loss caused by tremor and dystonia to apply deep brain stimulation in addition to other medical treatment options. During the period, she was diagnosed with inflammatory breast cancer with axillary lymph node and mandibular bone metastasis after a palpable mass

in the left breast and decided to give priority to oncological treatment. In the sixth month of the neurological follow-up, a significant regression was observed in the abscess lesion in the mesencephalon and thalamus in neuroimaging performed for oncological treatment (Figure 3). She has been following up in our neurology, infectious diseases and oncology outpatient clinics.

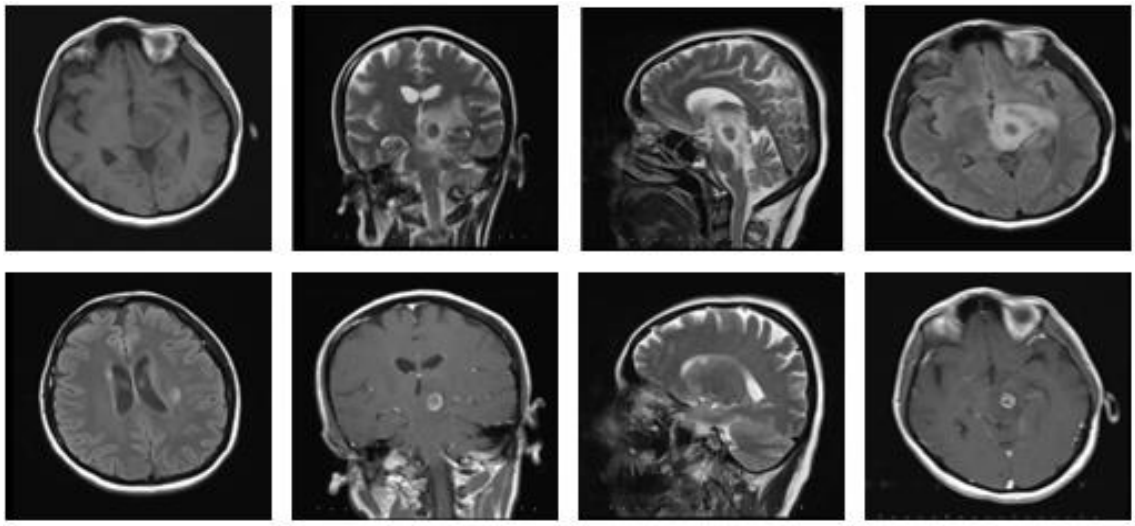

Figure 1. T1A iso-hypointense, central hypointense and peripherally hyperintense in T2A and FLAIR sequences, peripheral enhancing abscess lesion at left thalamus, capsule interna and mesencephalon causing mass effect with intense edema and a second abscess lesion at adjacent to the anterior horn of the lateral ventricle on the right.

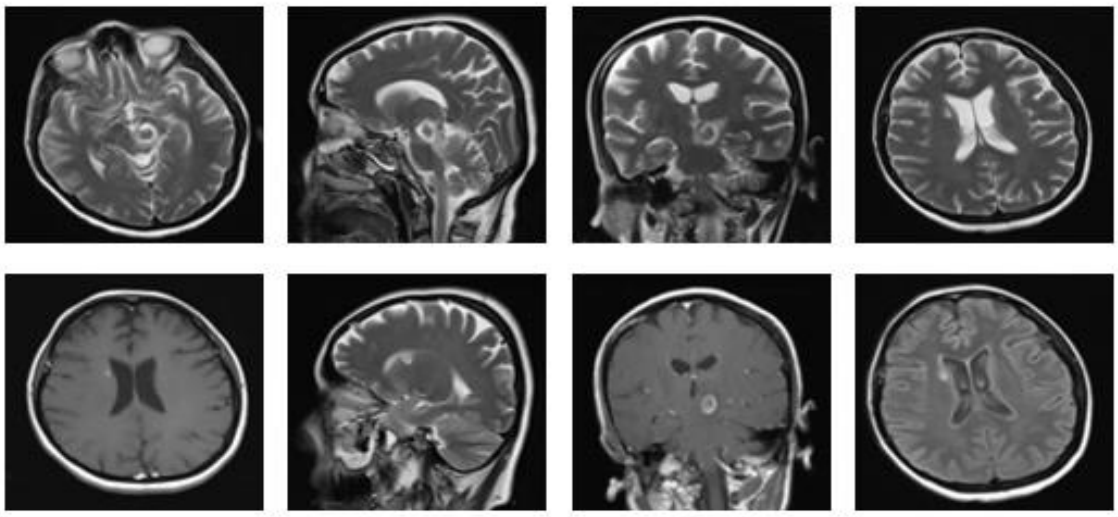

Figure 2. Abscess lesion preserving its size but with markedly reduced edema effect.

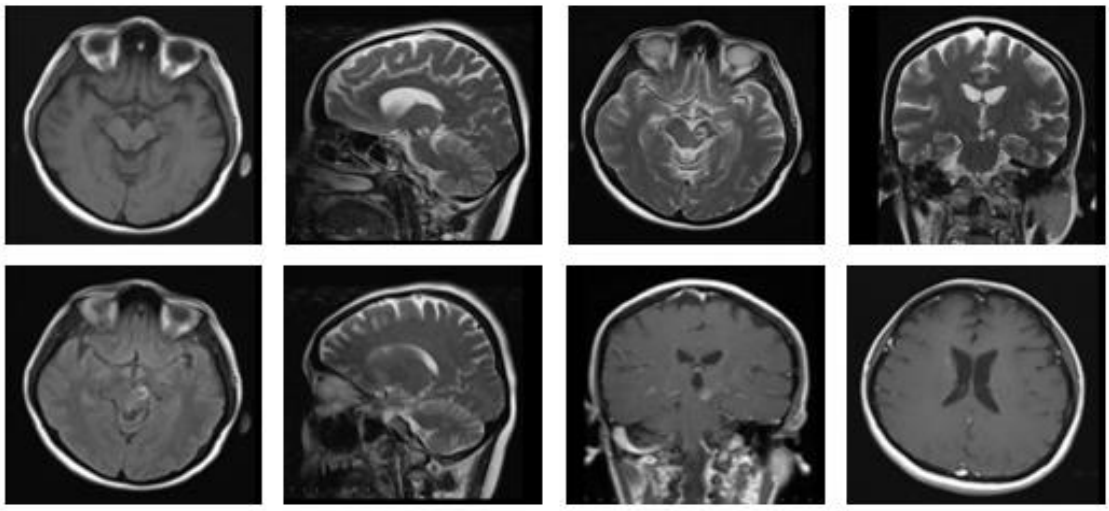

Figure 3. Reduction in size of both abscess lesions and marked reduction in peripheral edema and partial enhancement.

3. Discussion

Gordon Holmes first described this tremor in 1904 and named the cases by associating with the location of the lesion such as mesencephalon tremor, thalamic tremor or rubral tremor (Holmes, 1904). In 1997, it was decided to use the name 'Holmes tremor' in the diagnosis with the criteria defined at the Tremor Symposium held in Germany.

According to the criteria, Holmes tremor has a clinic that occurs at rest and during action, with a low frequency (usually below 4.5 Hz), after a latent period of four weeks to two years from the causative lesion (Deuschl et al., 1996; Deuschl et al., 1998).

Cerebellothalamic and nigrostriatal system dysfunction is held responsible for the physiopathology of the combination of resting and kinetic tremor (Kim et al.,2009). Mesencephalon tegmentum and thalamus are affected together as a rare form of involvement in presented case.

It is known that occurence of tremor needs time, at least four weeks, after the hemiparesis caused by the involvement of the corticospinal tract. As stated in the diagnostic criteria, the latent period between four weeks and two years suggests that tremor may be the result of a secondary degeneration process. The presence of cases with similarly located lesions but no tremor suggests that this secondary degeneration does not always develop or regenerates before clinical manifestation (Lekoubou et al., 2010; Ling et al., 2022).

Although various causes have been reported in the etiology, cerebrovascular disease, trauma, vascular malformation and multiple sclerosis play the most common role (Deuschl et al., 2002). Focal lesions caused by HIV-associated opportunistic toxoplasma infection are a rare cause of Holmes tremor. The first disease to be considered in the presence of central system involvement in HIV-positive cases is toxoplasma encephalitis. The most important risk factors include female gender, highly immunocompromised (CD4 + T lymphocyte count <100 / mm^3) and no primary prophylaxis. It is associated with a poor prognosis, with 40% having worsening AIDS status and 23% mortality after one year (San-Andrés et al., 2003). Typically, similar to presented case, it is characterized by multiple lesions with peripheral enhancement and edema effect.

Differential diagnoses include primary central nervous system lymphoma, cryptococcal meningitis, progressive multifocal leukoencephalopathy (PML), and cytomagalovirus (CMV) infection (Siddiqi & Koralnik, 2015). There are a very limited number of HIV-toxoplasma related Holmes tremor cases in the literature. Deep white matter localized lesions have been described in the left upper brain stem and frontal lobe for the first case (Koppel & Daras, 1990). Subsequently, five more HIV-associated toxoplasma abscess cases with similar localization, mostly unilaterally involved, were reported. These six cases were compiled and discussed from various sides; one of the striking features of this article is the emphasis that the main source of Holmes tremor is HIV-related primary neuronal damage, rather than toxoplasma-induced lesion (Lekoubou et al., 2010). The hypothesis put forward by DaTSCAN SPECT studies in the literature is supported by the presence of a single HIV-toxoplasma-related Holmes tremor case in which presynaptic dopaminergic nigrostriatal system involvement was shown, and there was no significant involvement difference in other cases (Yuk et al., 2019).

The first goal of Holmes tremor treatment is to eliminate the underlying cause. However, there may be cases that do not improve despite the appropriate treatment of the etiological factor. It is possible to encounter cases where surgical treatment is not possible due to the location and characteristics of cavernoma or mass lesions, which are among the common causes. In the light of the pathophysiology mentioned above, different agents such as levodopa, dopamine agonists, amantadine have been tried and responded in some cases.

However, the efficacy of carbamazepine, valproic acid, clonazepam and levetiracetam has been demonstrated and put into use in cases where no response was obtained (Raina et al., 2016,; SchreudFerlazzo et al., 2008).

Among the medical treatment options, levetiracetam has an important place due to its good tolerability characteristics such as low side effect profile, no difficulty in titration and renal elimination (SchreudFerlazzo et al., 2008).

Considering the continuity of multiple drug use and the possibility of hepatotoxicity in our case, levetiracetam, an agent that undergoes renal elimination, was preferred. The improvement observed in the follow-up of the patient from the first month onwards reached a level where she was able to fulfill her activities of daily living and self-care at the end of the third month. However, complete recovery was never achieved despite dose titration. In cases where there is still no response despite symptomatic medical treatment, invasive treatment options such as deep brain stimulation can be applied in addition to medical treatment (Garos et al., 2010). Thereupon, any other options could be used because of hepatic disfunctions releated to HIV infection therapies and deep brain stimulation had been recommended to the patient but this option had to be postponed due to the intervening breast cancer treatment process and the effect of deep brain stimulation could not be observed.

4. Conclusion

Holmes tremor; It still maintains its place as a very interestig subject with its etiological diversity of the same phenomenology and the areas waiting to be clarified in its physiopathology. Our case; It has been found worth sharing with its extremely rare etiology, rich imaging findings in emergency department, and aspects contributing to the primary neuronal injury hypothesis proposed for the Holmes tremor pathophysiology.

Ethical Statement

Since this is a case report, ethical approval was not obtained. However, signed informed consent was obtained from the patient.

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Presentation Information

This study was presented as a poster presentation at 59th National Neurology Congress in 2023.

Conflicts of Interest

The author declare no conflicts of interest regarding this study. Any institution or organization providing funding for this research did not have any role in the design, data collection, analysis, interpretation, or publication to influence or distort the findings.

Author Contributions

The entirety of the all process of the article belongs to the author.

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