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Steroid-responsive intracranial germinoma presenting as Holmes' tremor: Importance of a tissue diagnosis

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Abstract

Holmes' tremor (rubral or midbrain outflow tremor) refers to a hyperkinetic movement disorder characterized by mild resting and more severe postural and action tremor often with associated brainstem symptoms, dystonia and cerebellar deficits. This syndrome should prompt lesional evaluation with neuroimaging focused on the dorsal midbrain, cerebellar outflow tracts, and thalamus. Herein we report a 26-year-old previously healthy male who presented with 4 years of progressive horizontal diplopia, right Parinaud syndrome, and appendicular ataxia. Neuroimaging revealed a right dorsal midbrain enhancing lesion which completely resolved with intravenous methylprednisolone prompting a diagnosis of neuroinflammatory syndrome. Subsequent clinical and radiographic evaluations, however, revealed steadily progressive left dorsal midbrain syndrome with an expansile enhancing lesion which culminated 4 years from symptom onset with a right upper extremity low-frequency rest, postural and action tremor, ataxic dysarthria, and mild right dystonia with dysidiadochokinesia. Uncomplicated brainstem biopsy confirmed intracranial germinoma and the patient underwent definitive radiation therapy with dramatic radiographic response and partial clinical improvement. This case, which to our knowledge is only the second report of intracranial germinoma presenting as Holmes' tremor, highlights the critical importance of definitive tissue diagnosis in the evaluation of lesional brainstem pathology presenting as Holmes' tremor. Steroid responsiveness can be seen in non-inflammatory pathology including intracranial germinoma. Prompt evaluation and appropriate treatment are important as Holmes' tremor responds poorly to symptomatic therapies and response to radiation therapy is favorable for germinomas.

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Conflicts of Interest/Disclosures

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Keywords

Behçet's disease; Germinoma; Holmes tremor; Multiple sclerosis; Rubral tremor

1. Introduction

Holmes' tremor phenomenologically refers to a syndrome characterized by a proximal resting, postural and action tremor often associated with dystonia and cerebellar findings. While etiologies vary, a structural lesion in the dorsal midbrain is common.

2. Case report

A right-handed 26-year-old otherwise healthy man presented for evaluation of chronic progressive neurologic symptoms of 4 years duration. In October 2010, he first suffered gradual onset of horizontal diplopia. Examination showed a right Parinaud syndrome and mild appendicular ataxia. MRI revealed an enhancing lesion in the right midbrain (Fig. 1A, B). Evaluation included an acellular lumbar puncture with normal protein and glucose, normal immunoglobulin G index, unremarkable cytology, but presence of oligoclonal bands. Multiple sclerosis was diagnosed and high-dose intravenous methylprednisolone (MP; 1000 mg/day for 3 days) was initiated followed by interferon beta-1a (44 mcg thrice weekly).

Surveillance imaging confirmed radiographic resolution which was felt to strongly support a neuroinflammatory etiology (Fig. 1C). In 2011, a new enhancing focus in the opposite dorsal midbrain was discovered (Fig. 1D). He was re-treated with MP but now without improvement. Additional history revealed prior episodes of recurrent oral aphthae, and Behçet's disease was diagnosed. Azathioprine (150 mg/day) and prednisolone (60 mg/day) were begun. Despite this therapy, by September 2013 examination showed a left Horner's syndrome, lower right facial weakness, impaired right hemibody thermal sensation, and bilateral Babinski signs.

Serial neuroimaging revealed gradual progression of the left midbrain lesion with local mass effect (Fig. 1E, F). Cerebrospinal fluid (CSF) showed four white blood cells/mm³, normal glucose, slightly elevated protein, and unremarkable cytology. Infectious workup and systemic autoantibodies (anti-neutrophil cytoplasmic antibody, anti-nuclear antibody, anti-cardiolipins, neuromyelitis optica autoantibodies, and angiotensin-converting enzyme) were negative. Serum human chorionic gonadotropin was normal but alpha-fetoprotein was slightly elevated (7.3 ng/mL, normal <6 ng/mL). MR spectroscopy and brain positron emission tomography were unrevealing. Neoplasm was thought unlikely due to the slow rate of progression and steroid responsiveness. Infliximab (400 mg intravenously every 2 weeks) was begun but symptoms progressed.

In March 2014, referral was made to our facility at which time he reported 3 months of progressive proximal right arm tremor and chronic horizontal diplopia described as "slowness of eye movements" with lateral gaze. Neurologic examination showed ataxic dysarthria and a coarse, low-frequency right upper extremity rest, postural, and action tremor

predominating in the proximal musculature with mild right hand dystonia and dysidiadochokinesia (Supp. Video 1).

Repeat MRI revealed substantial increase in the left dorsal mid-brain enhancing lesion (Fig. 1G). Stereotactic biopsy was safely performed and pathology revealed intracranial germinoma (Fig. 2). He was treated with radiation therapy (6000 cGy) and marked radiographic improvement was observed (Fig. 1H) with subjective improvement in the resting more than postural or action tremor (Supp. Video 2).

3. Discussion

Holmes' tremor (also known as midbrain, outflow, or rubral tremor) is characterized by an irregular low-frequency unilateral proximal tremor which unlike other syndromes involves rest, postural, and kinetic components. This syndrome classically results from lesions in the dorsal midbrain and is thought to result from disruption of both nigrostriatal and cerebello-thalamo-cortical circuitry [1]. While anatomic imaging has revealed damage to the superior cerebellar peduncle, cases incorporating dopamine transport imaging have also revealed reduced striatal dopaminergic uptake. Ultimately, isolated damage to either pathway may be insufficient to result in the genesis of this syndrome and combined dysfunction may be necessary [1].

Causative lesions in Holmes' tremor include multiple sclerosis [2], brainstem hemorrhage [3], ischemia, trauma [4], abscess, vascular malformations, and even neuroleptic or paraneoplastic disorders. To our knowledge, the current patient is only the second report of Holmes' tremor secondary to intracranial germinoma [5]. In the current patient, a neuroinflammatory diagnosis was entertained despite atypical imaging findings and lack of convincing CSF results. Initial steroid responsiveness was considered highly suggestive of an inflammatory etiology; however, steroid responsiveness is well recognized in non-inflammatory neoplastic conditions including cerebral lymphoma and rarely with intracranial germinomas [6,7]. While the mechanism of steroid responsiveness has not been elucidated, these lesions are frequently associated with diffuse lymphocytic infiltrates which may account for the perceived steroid effect, though as in this case, durable responses are not seen [6]. In cases where diagnostic uncertainty remains following non-invasive testing, intracranial biopsy is warranted and should be pursued.

Rapid diagnostic evaluation is critical since treatment of the underlying cause is the mainstay of therapy. In general, response to pharmacologic interventions in Holmes' tremor is frequently unsatisfactory [3]. Biopsy of the causative lesion is mandatory in cases of diagnostic uncertainty so as to guide appropriate therapy. In the only prior report of Holmes' tremor in a patient with intracranial germinoma, pharmacologic interventions and low-dose radiation (15 Gy) were not effective and thalamotomy was pursued [5]. In such treatment refractory cases, recent literature also supports deep brain stimulation for symptomatic management [4]. In the current patient, radiographic response was dramatic and partial symptomatic improvement was observed.

4. Conclusion

Holmes' tremor, though an uncommon manifestation of primary brain tumors, is important to recognize and rapidly treat. Prompt lesional evaluation should be performed and if diagnostic uncertainty remains, intracranial biopsy should be safely pursued. While steroid responsiveness is seen with inflammatory central nervous system pathology, it can also occur in intracranial neoplasms, including intracranial germinoma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Seidel S, Kasprian G, Leutmezer F, et al. Disruption of nigrostriatal and cerebellothalamic pathways in dopamine-responsive Holmes' tremor. *J Neurol Neurosurg Psychiatry*. 2008; 80:921–3. [PubMed: 18450789]
2. Kock M, Mostert J, Heersema D, et al. Tremor in multiple sclerosis. *J Neurol*. 2007; 254:133–45. [PubMed: 17318714]
3. Raina GB, Velez M, Pardal MF, et al. Holmes tremor secondary to brainstem hemorrhage responsive to levodopa: report of 2 cases. *Clin Neuropharmacol*. 2007; 30:95–100. [PubMed: 17414941]
4. 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. *Neurosurgery*. 2005; 56:E445. [PubMed: 15794849]
5. Kim MC, Son BC, Miyagi Y, et al. Vim thalamotomy for Holmes' tremor secondary to midbrain tumour. *J Neurol Neurosurg Psychiatry*. 2002; 73:453–5. [PubMed: 12235320]
6. Mascalchi M, Roncaroli F, Salvi F, et al. Transient regression of an intracranial germ cell tumour after intravenous steroid administration: a case report. *J Neurol Neurosurg Psychiatry*. 1998; 64:670–2. [PubMed: 9598688]
7. Koizumi H, Oka H, Utsuki S, et al. Primary germinoma arising from the midbrain. *Acta Neurochir*. 2006; 148:1197–200. [PubMed: 17039305]

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.jocn.2014.11.013>.

Fig. 1.

Serial radiographic findings in intracranial germinoma presenting as Holmes' tremor. MRI progression is seen on axial T1-weighted gadolinium enhanced sequences (A, E, F), coronal T1-weighted gadolinium enhanced sequences (D, G, H), and axial fluid attenuated inversion recovery (B) and coronal T2-weighted sequences (C). These studies show a homogeneously enhancing lesion with surrounding edema in the right dorsal midbrain first appearing in October 2010 (A, B) which resolved on follow-up imaging (C). New left dorsal midbrain enhancing nodule was present in November 2011 (D) which gradually progressed through December 2012 and June 2013 (E, F) culminating in a large enhancing lesion extending from the diencephalon to the dentate nucleus of the left cerebellum (G) which nearly resolved following radiation therapy (H).

Fig. 2.

Histopathologic findings of intracranial germinoma (original magnification $\times 160$). Histologically, nests of large tumor cells with prominent nucleoli sat amongst a population of small reactive lymphocytes (A, hematoxylin and eosin). Tumor cells were immunoreactive for octamer-binding transcription factor 4 (B) and c-kit, and negative for alpha-fetoprotein and human chorionic gonadotropin. No non-germinomatous germ cell tumor component was identified (This figure is available in colour at www.sciencedirect.com).