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Tremor and Other Hyperkinetic Movements

New Observations Letters

Reversible Holmes Tremor due to Middle Cerebral Artery Giant Aneurysm

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Abstract

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In 1904, Gordon Holmes first described a peculiar tremor that now bears his name. The tremor Holmes depicted was present at rest (except during complete relaxation) and was exacerbated by both voluntarily maintaining postures and movements. Holmes tremor (HT) is a symptomatic, mostly unilateral, low-frequency (<5 Hz) tremor. Depending on the extent of the underlying lesion, HT is usually associated with other neurological manifestations such as sensorimotor deficits, bradykinesia, muscle tone alterations, ophthalmoparesis, and ataxia.[1] Several thalamic or midbrain lesions may produce HT including stroke,[2] arteriovenous malformations,[3] traumatic injuries,[4] inflammatory or infective diseases,[5] and tumors.[2] Although previously known as "rubral tremor," HT is the preferred nomenclature nowadays by experts considering that single lesions of the red nucleus are insufficient to generate persistent tremor. Indeed, the generation of HT requires a dysfunction of both dopaminergic and non-dopaminergic circuitries. In particular, the resting and postural components may be triggered by nigrostriatal damage,[6] while the action components may be due to the involvement of dentato-rubro and cerebello-thalamic tracts.[3,7] Typically, HT develops months after the lesion, probably requiring concomitant degeneration and aberrant regeneration of involved circuits. HT pathogenesis is complex and different in each case. Consequently, the functional neuroimaging of basal ganglia Dopamine Transporter scan (DaT-scan), Single-Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) gives inconsistent results,[6,8] and the response to symptomatic drugs, L-dopa, and Deep Brain Stimulation (DBS) of different targets such as Ventral Intermediate Nucleus (VIM), SubThalamic Nucleus (STN), Globus Pallidus Internus (GPI), prelemniscal radiations is variable and almost unpredictable.[2,9] Almost all recounted cases have complex clinical syndromes, and a complete clinical recovery has never been reported.

A 40-year-old man presented with a 6-month history of mild but worsening tremor of variable intensity. The patient had a focal, irregular, rest and action tremor of middle amplitude and low frequency (about 4 Hz), limited to his right arm with oscillatory motion around the elbow. It was present inconsistently at rest, particularly during emotional activation, and enhanced by posture maintenance. It was evoked by various positions and tasks. Particularly, the tremor was present during fine motor skills such as writing, and it was increased by drinking and shaving, showing a minimal intentional component. The patient also reported slight loss in manual dexterity in his right hand. A minimal hypokinesia was present in the patient's right arm (Video 1). The neurological examination was otherwise normal and did not show bradykinesia or muscle tone alteration. There was no history of neurodegenerative disease in his family.

Nevertheless, two of his first-degree relatives had previously died from a ruptured cerebral aneurysm. The patient underwent brain magnetic resonance imaging (MRI) that revealed a space-occupying lesion resembling an onion bulb. The lesion, a giant left middle cerebral artery bifurcation aneurysm with almost complete thrombosis, was compressing the left diencephalon, involving the thalamus, basal ganglia, and left upper mesencephalon at the level of *substantia nigra* and red nucleus (Figure 1). Due to the clear etiology of the tremor, the DaT-scan imaging was avoided and the patient underwent surgery. The total excision of the aneurysm led to an almost complete disappearance of the tremor at the first neurological check, 1 month after surgery. The patient was followed clinically every year, and at the last follow-up (12 years after surgery), the patient maintained a virtually normal neurological examination. Currently, the tremor is no longer detectable, except for a minimal postural tremor manifesting in his right arm only during isometric effort and at certain positions (Video 1). The patient also describes a minimal subjective loss of movement fluidity in his right hand.

Although mild, isolated, and primarily action related, the herein reported tremor shows the main characteristics of HT according to the current consensus statement on the classification of tremors.[10] Indeed, our patient has a rest, postural, and intention tremor of the right arm at low frequency (<5 Hz). Moreover, the tremor resulted secondary to an acquired lesion in the vicinity of the red nucleus. This unique and mild HT case caused by a rare lesion widens the spectrum of conditions causing HT. Indeed, giant aneurysms have never been reported as a possible cause of HT. Gross and Sibon had reported two similar cases of middle cerebral artery giant aneurysm causing "hemiparkinsonism" characterized by lateralized pyramidal and extrapyramidal signs and tremor.[11,12] Bostantjopoulou also described a case of hemiparkinsonism due to a similar aneurysm, where the tremor was predominantly present at rest.[13] In these cases, the tremor was part of an obvious parkinsonian syndrome, which lacks in our case. Moreover, HT usually occurs with other localizing signs, and it has always been reported as part of severe or complex motor syndromes. Compared with other recounted cases of HT, our case showed an almost isolated and focal tremor syndrome. Thus, we emphasize that HT may also present as a pure, focal, rest and action tremor suggesting a meso-diencephalic lesion rather than an incipient Parkinson's disease or an essential tremor. Therefore, it is crucial to recognize this syndrome and look for a possible lesion in the aforementioned anatomical region. Additionally, our HT case is relatively mild and reversible due to the gradually compressive and non-destructive nature of the lesion; the very slow growth of the aneurysm probably only caused a dysfunction of the nigro-striatal and dentato-rubro-thalamic pathways. In spite of a concomitant compression of the left cerebral peduncle, pyramidal signs were minimal consisting of a slight loss of manual dexterity in patient's right hand. The pyramidal tract was probably dislocated but not damaged by the aneurysm. The patient was cured by surgery: we emphasize the reversible nature of HT in peculiar cases.

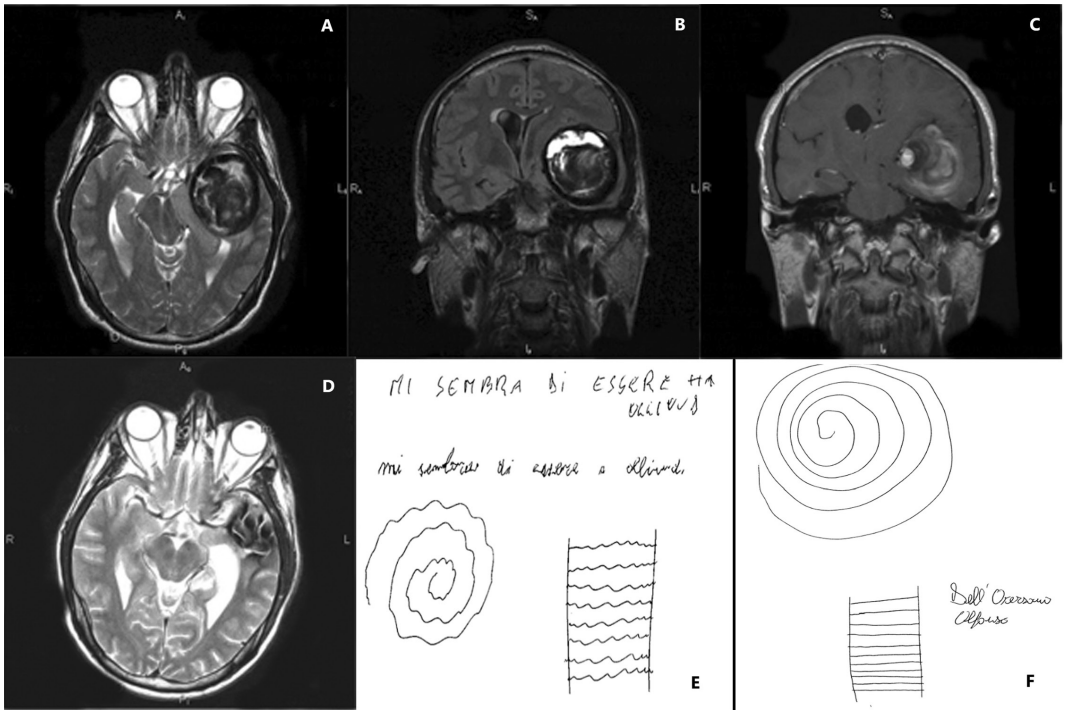

Figure 1. **Patient's MRI and graphic test.** (A–C) MRI shows the giant aneurysm compressing *substantia nigra*, red nucleus, basal ganglia, and thalamus. (C) Gadolinium enhancement of the residual open component of the aneurysm. (D) Complete removal of the aneurysm. (E and F) Patient's graphic tests before and after surgery.

Video 1. **Tremor Clinical Features: This Video Shows the Clinical Manifestations of the Tremor Prior to the Surgical Excision of the Aneurysm Compared to the Clinical Picture Following the Surgery and Lasting up to 12 Years (Last Follow-up)**. In sequence, it shows postural tremor, postural tremor during isometric effort (handgrip), movement fluidity in pronation/supination test, and kinetic tremor during fine motor skills (graphic tests).

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