

Rubral Tremor After Thalamic Infarction in Childhood

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The occurrence of tremor after thalamic lesions is well known. Delayed rubral tremor secondary to bilateral thalamic infarction is a rare finding and has not been reported previously in childhood. We present two children with a combined resting-postural-kinetic tremor caused by bithalamic infarction. The first child was a male 14 months of age, and the second was a male 9 years of age. These children come from unrelated families. On hospital admission of the first patient, generalized seizures and routine electroencephalogram (EEG) findings with diffuse spike-wave discharges predominantly over the left frontal area were clinically observed, leading to the initial diagnosis of epilepsia partialis continua. However, clinical observation and video-EEG monitoring of the movements revealed nonepileptiform accompaniments, favoring the diagnosis of rubral tremor. In the second patient, EEG revealed no paroxysmal activity and was within normal limits for age. In both patients, cranial magnetic resonance imaging revealed ischemic lesions in thalami bilaterally but failed to reveal any mesencephalic lesion. These patients demonstrate that thalamic infarction can cause rubral tremor in childhood.

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Tan H, Turanli G, Ay H, Saatci I. Rubral tremor after thalamic infarction in childhood. *Pediatr Neurol* 2001;25: 409-412.

Introduction

Tremor is the most common movement disorder. Most patients with tremor have Parkinson's disease or essential tremor. The remaining types of tremor, consisting of

different idiopathic forms that are caused by brain trauma or multiple sclerosis, are uncommon but often give rise to severe disability [1]. The term "rubral tremor" (also called Holmes' tremor or midbrain tremor) is used to describe a tremor that is revealed at rest and becomes pronounced on goal-directed movement [2,3]. The appearance of tremor after thalamic lesions is well known but infrequent [4,5]. A computer-based scanning of the National Library of Medicine revealed that an association between medial bithalamic infarction and isolated rubral tremor has not been described previously, although thalamic infarction in children (particularly in infancy) has occasionally been reported [6,7]. Therefore we report two children with isolated rubral tremor associated with thalamic infarction.

Case Reports

Patient 1

A male patient 14 months of age was admitted to the hospital because of high fever and restlessness. He had a 1-year history of Wilms' tumor, for which a right nephrectomy had been performed 9 months previously. Follow-up abdominal ultrasound scan 3 months postoperatively revealed a left renal mass, 1-2 cm in size. The patient underwent a course of chemotherapy, receiving the last dose 1 week before admission.

On admission, the patient was febrile with a temperature of 39.2°C. His pulse was 72/minute, and respiratory rate was 32/minute. Neurologic and physical examinations were otherwise normal. Hematologic and blood chemistry values were in normal limits except for a marked neutropenia (2000 WBC/mm³). An extensive microbiologic analysis, including culture and microscopic examinations of blood, urine, and cerebrospinal fluid, failed to reveal any source of infection. The patient responded well to antibiotic treatment.

On the third day of admission, a low-amplitude resting tremor in all limbs was observed. The tremor was more apparent in the distal parts of the upper limbs and the amplitude increased on attempts to reach a target. The following day, additional involuntary movements on the right side of the body, predominantly in the face, neck, and arm, appeared. The amplitude of these 3-Hz clonic movements increased progressively and resulted in abduction and adduction of the right arm at the shoulder joint in the resting position. Neurologic examination revealed synchronous, low-amplitude involuntary movements involving the tongue and the proximal right lower extremity muscles. The movements tended to disappear during sleep, and increased in amplitude on awakening and in response to verbal, tactile, and noxious stimuli.

Phenobarbital therapy (5 mg/kg/day) was introduced on the sixth day of admission after two successive afebrile generalized seizures recorded at the time of the abnormal movements. While the movements continued, eight-channel electroencephalogram (EEG) recording revealed bilateral synchronous 3.5-4-Hz spike-and-wave discharges of higher amplitude in the left frontal area. Three-hour video-EEG monitoring revealed the same localized abnormality. A causal relationship between these EEG abnormalities and the tremor-like movements was difficult to establish.

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Received January 22, 2001; accepted June 22, 2001.

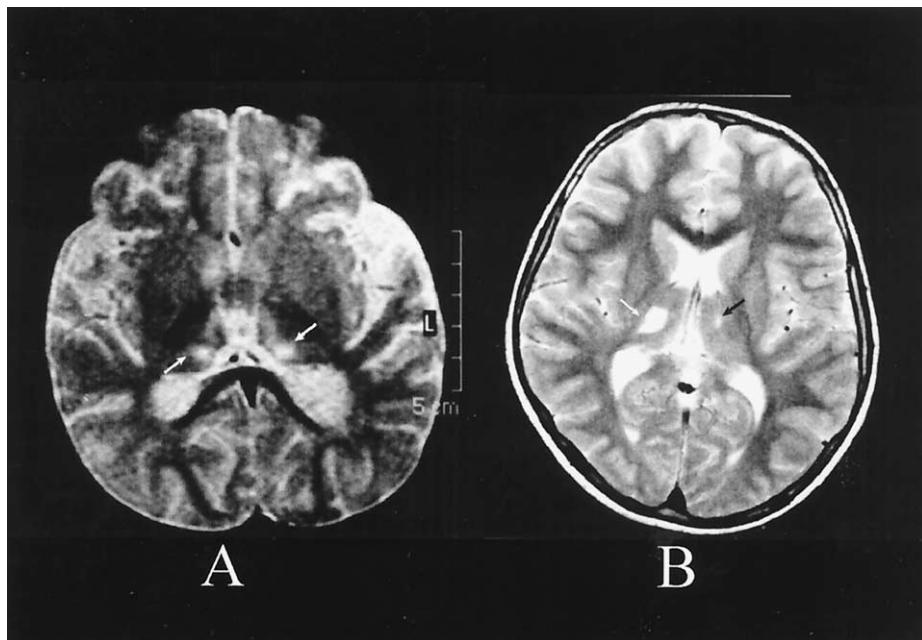


Figure 1. (A) T_2 -weighted axial image ($TR/TE = 3,000/80$ ms) indicating hyperintense lesions in the thalami bilaterally, representing ischemic lesions (arrows). Observe the atrophy with enlarged subarachnoid space and the ventricles. (B) T_2 -weighted axial image ($TR/TE = 3,000/80$ ms) of the 6-month follow-up MRI revealing right thalamic chronic infarct with central cystic change (white arrow). Also, observe the small left thalamic lesion (black arrow), possibly ischemic in origin.

Diazepam infusion during EEG monitoring obliterated completely the spike-wave discharges, although the amplitude of persisting involuntary movements remained the same. We were not able to perform a combined EEG-electromyogram (EMG) registration to demonstrate the possibility of a fixed temporal relationship between the tremor and EEG activity. We concluded that the paroxysmal activity was not related to tremors, because the tremors persisted after suppression of discharges with diazepam. Although computed tomography (CT) of the brain was normal, cranial magnetic resonance imaging (MRI) examination revealed bilateral, symmetric, poorly defined lesions in the medial aspects of the thalami, hyperintense on T_2 - and isointense on T_1 -weighted images, with no mass effect or apparent contrast enhancement. The involuntary movements did not improve with phenytoin (5 mg/kg/day) and clonazepam (0.01 mg/kg/day) treatment, and both drugs were discontinued. Treatment then changed to valproic acid (20 mg/kg) and benzotropine (0.05 mg/kg), with marked improvement in both involuntary movements and EEG abnormalities within few days. One month after discharge, neurologic examination indicated no evidence of tremor. Repeat MRI revealed that the thalamic lesions were more well defined (Fig 1A).

Patient 2

A male 9 years of age, whose family history was unremarkable, was admitted to our hospital. Six months ago he developed sudden weakness on his left side just after falling from an altitude of 2 meters, when, on admittance to a different hospital, he was found to have left hemiparesis and hemisensory loss. His weakness gradually improved, but 3 months later he noticed the gradual onset of fine tremulous movement in his left arm. This involuntary movement gradually worsened, and tremor appeared in his left leg.

On admission, his general condition was normal. Neurologic examination revealed him to be alert and oriented. Visual acuity was normal. The other cranial nerves were intact. Deep tendon reflexes were symmetrically normal, and the plantar response was flexor bilaterally. His gait was not ataxic. Apart from the tremor, the neurologic findings were normal. Tremor of the left upper extremity was present principally during sustained posture, becoming clear during intentional voluntary movements. The tremor subsided during sleep. Laboratory examination findings were normal for blood cell count, acanthocytosis, red blood cell morphology, routine serum chemistries, and erythrocyte sedimentation rate, immunologic tests for autoimmune disorders, and urinalysis. Serum

ceruloplasmin and copper levels were normal. Urine blood amino acid profile, proteins C, S, and antithrombin III, blood homocysteine level, C-reactive protein, and thyroid function tests were normal. Antinuclear antibody, anti-DNA, antiphospholipid, and anticardiolipin antibodies, and factor II and V Leiden mutations were negative. Electrocardiography and echocardiography were both normal. We performed a video-EEG test for the second patient, which was negative for a pathologic discharge with a background activity consistent with his age. MRI revealed an apparent right thalamic infarct with a minimal left thalamic involvement (Fig 1B). No abnormality was present in the brainstem, cerebellum, or basal ganglia. The selective cerebral angiogram did not reveal any abnormality. Surface EMG indicated rhythmic grouping discharges of approximately 4.5 Hz in the left forearm and hand at rest, and this was rubral tremor frequency. The resting tremor component responded to levodopa/carbidopa, whereas the kinetic component improved partially.

Discussion

Rubral tremor is a rare type of tremor, with 2-5-Hz resting, postural, and kinetic components. Characteristically, it presents at rest, becomes more pronounced during maintenance of a fixed posture and further increases in amplitude with intentional voluntary movements [3,8].

The two patients described here demonstrated rubral tremor as a manifestation of thalamic infarction confirmed by MRI. Because extensive investigations toward the etiology of cerebrovascular accident were negative, the cause of lesion in the first patient was considered to be nephroblastoma and chemotherapy. However, an acute insult resulting from neutropenic fever could not be ruled out. In the second case, the lesion was considered to be caused by trauma. Stroke may develop in the course of malignancies, especially those of solid tumors and lymphomas, and even the first symptom of either may be stroke. The pathophysiology is considered to be the result of low-grade disseminated intravascular coagulation and

secondary fibrinolysis, with the balance shifted toward clotting. Chemotherapy is believed to cause stroke by creating microangiopathy [9]. Trauma results in infarction in the area of the basal ganglia by causing stretch in perforating branches of middle cerebral artery [10]. The tremor that was seen in our cases has many features of rubral tremor, as described in the literature [11]. There is no exact consensus regarding the definition of rubral tremor. Some authors consider that this entity is actually a cerebellar tremor associated with parkinsonian tremor [3]. The rest tremor component is considered to result from involvement of the ascending nigrostriatal pathway, whereas the kinetic component occurs in lesions involving dentatorubrothalamic fibers [12].

The "Guillain-Mollaret triangle," considered to be responsible for occurrence of rubral tremor, consists of three corners, namely the red nucleus, inferior olfactory nucleus (via the central tegmental tract), and contralateral dentate nucleus [13]. The so-called rubral, or midbrain, tremor is primarily caused by red nuclear lesions, however, red nucleus involvement is not necessary for its development [14]. It is caused by a combination of damage to the brachium conjunctivum and nigrostriatal pathways in the vicinity of the red nucleus [7]. Vascular insults involving medial or posterior regions of the thalamus, thalamosubthalamic area, and mesencephalon have also been reported to be associated with rubral tremor [15].

The delay in onset has been reported as the most striking feature of rubral tremor. Although varying, the time interval between the date of the lesion and the appearance of tremor usually ranges from 2 weeks to 2 years [16]. Although the date of the lesion was not known in our first patient, the MRI findings were in favor of chronic infarction. Regarding the second patient, tremor typically arose clinically 3 months after the trauma. Although the reason for this delay is not known precisely, the proposed mechanism is the reorganization process after deafferentation [17].

In both patients, lesions were demonstrated to involve the thalamus bilaterally. However, the second patient had contralateral clinical findings related to right thalamic lesion with minimal left involvement. No abnormality was present in the brainstem, cerebellum, or basal ganglia in either of our patients. In a recent review of published reports, Lee and Marsden [18] found no isolated tremor among 62 patients with movement disorders caused by a lesion in the thalamic or subthalamic region. There were 11 patients with 2-5-Hz resting, postural, and intention tremors in addition to dystonia. Lesions were secondary to stroke in approximately one-half of the cases. Ghika et al. [19] reported three adult patients with rubral-like tremor syndrome caused by thalamic infarction in the territory of the posterior choroidal artery. They examined another 54 patients with thalamic infarcts of other territories and found no abnormal movements. The impact of this specific territory has also been supported by two other cases with rubral tremor secondary to posteromedially located tha-

lamic hemorrhage. There was no disturbance of consciousness or other signs of midbrain damage characteristic of this location at the time involuntary movements began. This raised the possibility that the stroke might have occurred days before the onset of the tremor [3].

Clinical confusion may occur regarding the differentiation of rubral tremor from epilepsia partialis continua. Clonic-like movements at rest usually raise the suspicion of an epileptic origin. Coexistence of generalized seizures and lateralizing epileptiform activity in EEG may lead an erroneous diagnosis of epilepsia partialis continua. In our patient, the persistence of movements after EEG had returned to normal background activity favored a rubral tremor. Moreover, the presence of postural and kinetic components, stimulus sensitivity, impersistence into sleep, and clinical response to anticholinergic treatment were atypical for epilepsia partialis continua [20].

In conclusion, these cases demonstrate that thalamic infarction can be the cause of isolated rubral tremor in infancy and childhood. The frequent occurrence of accompanying seizures caused by high susceptibility to metabolic alterations and the delay in onset of the tremor may lead to clinical confusion in the diagnosis of rubral tremor. Therefore, an extensive laboratory evaluation, such as video-EEG monitoring and MRI, along with neurologic examination, should be performed in all children suspected to have rubral tremor.

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