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A Report of a Patient with Hyperekplexia

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Abstract

Introduction: Hyperekplexia, or startle disease, is a rare neurological disorder characterized by excessive startle responses to noise or touch stimulation that can cause serious injury from frequent falls**.** The disease is characterized by a triad of generalized stiffness while the patient is awake, nocturnal myoclonus, and an exaggerated startle re**fl**ex. Hereby, an interesting case of hyperekplexia with comorbidities is reported that was misdiagnosed as epilepsy for some years.

Methods: Our patient was a 16-year-old right handed boy with frequent falls, without loss of consciousness that caused serious head trauma. He had exaggerated myoclonic jerks with tactile and auditory stimuli. Also, he had nocturnal attacks including a startle myoclonic jerk followed by sudden stiffening of the limbs and trunk with vocalization that lasted about 3 seconds without loss of awareness. There was a positive family history of jerky movements in his mother only when she was sleeping. He had a posttraumatic encephalomalacia in the right frontotemproparietal region due to one of his falls 10 years ago. He was diagnosed with epilepsy and was treated with valproate with no success. After total antiepileptic discontinuation and 10 days of video-EEG monitoring, no interictal epileptifrom finding was recorded. The attacks were not accompanied with ictal activity on EEG. Hyperekplexia may be misdiagnosed with startle epilepsy. The preservation of consciousness and absence of epileptiform discharges on EEG can be helpful for differentiating hyperekplexia from startle epilepsy. Startle epilepsy is often resistant to treatment; however, hyperekplexia usually responds well to clonazepam.

Keywords: Hyperekplexia, Video-EEG Monitoring, Carbamazepine

Introduction

Hyperekplexia, the familial startle ailment, was introduced by Kirstein and Silfverskiold in 1958. Hereditary hyperekplexia (HPX) is specified by generalized stiffness at birth that declines throughout the first years of life; it is an excessive startle reaction to unanticipated (especially auditory) stimuli, and a short period of generalized stiffness after the startle reaction during which voluntary movements are infeasible. It is correlated with severe damages and ambulation loss from successive falls provided that generalized stiffness episodes are not treated. In many children, excessive head-retraction reflex (HRR) including the head development accompanied by flexor spasms of neck muscles and limbs derived via tapping the nose tip is detectable. The outcomes involve movements of periodic limb in hypnagogic and sleep myoclonus. Generally, intellect is normal. Moderate intellectual disability may happen (1). Commonly, the hereditary hyperekplexia is induced by gene coding mutations for the repressive glycine receptor alpha-1 subunit (GLRA1) on chromosome 5 (2).

Case presentation

Our patient was a 16-year-old right handed boy with normal mental development. The patient had jerky movements since he was one month old. Later on, he experienced frequent

falls without loss of consciousness that caused serious head trauma and jaw dislocation. He had exaggerated myoclonic jerks with tactile and auditory stimuli. Also, he had nocturnal attacks. Although there was no history of absence seizure or clear generalized tonic clonic seizures; the patient was diagnosed with genetic generalized epilepsy. The attacks occurred several times per day despite using antiepileptic drugs (Valporate, Phenobarbital, Primidone, and Carbamazepine). At the age of six, one of his falls resulted in a severe head trauma with intraparenchymal hemorrhage in the right frontotemproparietal region. Later, this encephalomalatic lesion (Image 1) gave rise to a hypothesis, stating that the attacks might be refractory focal seizures (given that the patient was conscious during the nocturnal attacks); he was referred for epilepsy surgery evaluation. The patient is the product of a normal gestation and delivery with appositive parental consanguinity. There was a history of hypnic jerks and obsessive compulsive disorder (OCD) in his mother. His systemic exam was within normal limits except for the recent surgery on jaw dislocation and multiple cranial scares. The neurologic exam was normal. During alertness and sleep, there was a clear startle reflex with exaggerated myoclonic jerks with tactile and auditory stimuli and a positive HRR test. Other routine lab data were also within normal limits. The 10-day video-EEG monitoring after total antiepileptic discontinuation revealed no interictal epileptiform. The background activity and sleep patterns were appropriate. There was a focal delta slowing in the right parietotemporal region (T6, P4) which was consistent with the existing lesion. Several habitual attacks were recorded; the sleep myoclonus occurred during K complex without accompanying epileptiform discharges. The startle myoclonus during consciousness state was reproducible and without a proceeding EEG change. During sleep, irrespective of external stimuli (auditory and tactile), there was a startle myoclonic jerk followed by sudden stiffening of the limbs and the trunk accompanied by vocalization. The event lasted about 3 seconds, and he was totally aware during the attack. Postictally, he was conscious and oriented immediately. There was no EEG ictal pattern accompanying the attacks. (Fig.1, Film 1) The patient was diagnosed with hyperekplexia, thus 2 mg/day clonazepam and 400 mg/day carbamazepine were prescribed. His attacks diminished dramatically. Although, there were still occasional startle jerks (2-4/month), they did not cause falling. Genetic test was performed that a homozygous whole exon deletion was detected in exon 9 of GLRA1 gene. The genotype of the patient is consistent with the autosomal recessive inheritance of the disease.

Discussion

Hyperekplexia is known by exaggerated startle reflex and neonatal hypertonia. Hyperreflexia and hypertonicity are transient and naturally diminish after the first year of life. Muscle stiffness and hypertonicity result in the delayed development of early motor milestones. The patients may accept ambulation in their early childhood delayed because of the fear of frequent falls from exaggerated startle reflex that usually persists into adult life. Hyperekplexia children, around the age of five, usually face episodic nocturnal

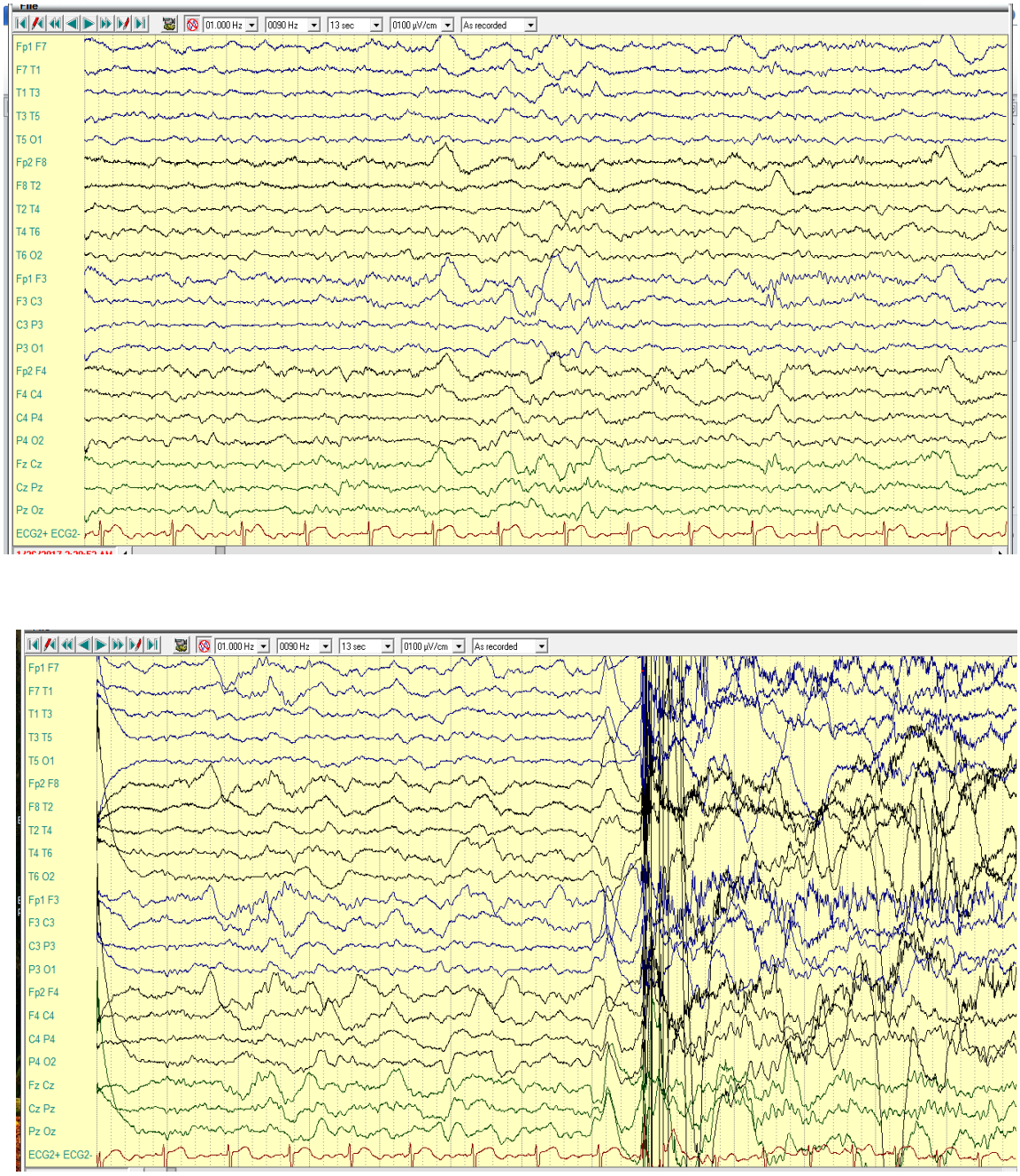
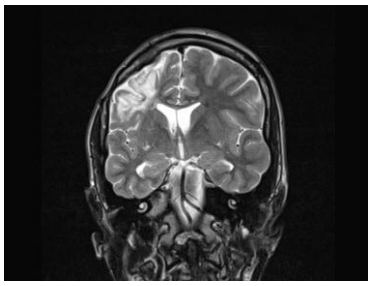
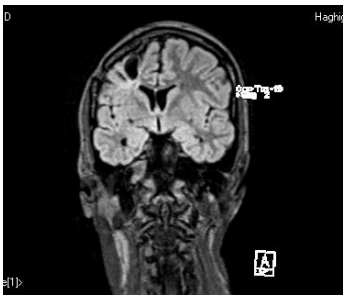


Fig 1. a) Sleep EEG that show delta slowing of right frontotempropariatal region. b) EEG record of myoclonic event that did not show any epileptic EEG activity at onset



a



b

Image 1. a) T2 coronal view of brain MRI that show extensive gliosis of frontopariatal region. b) FLAIR coronal view of brain MRI that show posttraumatic encephalomalacia and gliosis of frontopariatal region

clonic limb jerking. Every stage takes several minutes. Compared with the upper extremities, the lower extremities are involved more seriously. This nocturnal clonic jerking does not respond to antiepileptic drugs and is not epileptic (3). An adult neurologist has to know the pediatric manifestations of this situation, since pediatric patients with hyperekplexia can be carried well to adult clinics in adolescence. Other affected members can be hardly identified since in the same family minor and major forms of hyperekplexia can coexist. The major form of hyperekplexia is related to exaggerated startle and falls occurring in generalized hypertonia in the first year of life. However, hypnic jerks and exaggerated startle are the mere characteristics of the minor form. Neurological assessment in adults is often quite normal (4). The abnormal startle reaction is triggered commonly through unexpected or loud noises and involves unexpected stiffness and fall with arms by two sides and with no loss of consciousness. The hyperekplexia patients' intelligence is normal or mildly impaired. Critical mental disorder or seizure is not a disease characteristic. The sporadic patients usually have these atypical properties and do not possess usual genetic mutations of the illness (5). The atypical features propose various genetic or non-genetic etiologies, including brainstem tumor, infarction, multiple sclerosis, or infection (6). Diagnosing hyperekplexia is not hard; however, it can be misdiagnosed as epilepsy, spastic quadriplegia, or cerebellar impairment because of nocturnal clonic limb jerking, tonic spasm during the attack, hypertonicity, and unsteady gait (7). So, nose tapping should be involved in the regular examination when affected individuals face episodic tonic flexion, hyperreflexia, and infantile hypertonicity (8). The genetic examination of hyperekplexia is done merely in laboratories. Microscopic or gross pathology of nervous system has not been identified in the hyperekplexia (9). Electromyography (EMG) reflex assessments which record the reaction of limb and head muscles to tactile and acoustic stimulants show shorter latency, greater sensitivity, greater muscle response domain, and lower habituation in hyperekplexia in comparison to normal individuals (10). The initial response to the stimulants is seen in the sternocleidomastoid muscle, showing a brainstem origin of the reflex (10). The initial physiological disorder in congenital hyperekplexia is a lowered threshold and elevated excitability in pontomedullary reticular neurons causing broad enhanced gain of vestigial withdrawal reflexes. The recordings of Electroencephalography (EEG) during tonic spasm were normal and sometimes non-specific waves and spikes were observed (3). Hyperekplexia is a treatable ailment. Clonazepam can be used for

treatment. Patients often need high clonazepam doses (0.1– 0.2 mg/kg/day) without losing effectiveness with time (11). In case of wrong diagnosis of the disease as seizure, the treatment will be ineffective since benzodiazepines are not the commonly used anticonvulsants. Other medications like valproic acid (12) and clobazam (13) have beentested; however, their effectiveness has not been proved. There are also other medications which have different outcomes including phenytoin, piracetam, carbamazepine, diazepam, and phenobarbital (1). In the present case, the focal slowing in the right central and temporal region was compatible with the existing MRI lesion (posttraumatic encephalomalacia). All the same, there was no interictal epileptiform discharge despite sleep deprivation and complete AED discontinuation, and there was no EEG ictal activity. The possibility of a bilateral asymmetric tonic seizure without loss of awareness typically originating from the mesial frontal SSMA area was really far-fetched, and no supporting evidence was found. The events were most likely exaggerated startle response. With respect to the positive family history of myoclonus and startle in his mother and parental consanguinity, a diagnosis of hyperekplexia was the best option.

Conclusion

Hyperekplexia can have more dramatic feature compared with startle myocloni which can lead to misdiagnosis and mismanagement. Video-EEG monitoring and HRR test are useful in distinguishing this disease from different epilepsies.

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Ethical issues

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Authors' contributions

All authors equally contributed to the writing and revision of this paper.

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