Clinical Reasoning: A Three-Year-Old Boy With Abnormal Movements During Sleep

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Abstract:

We report a case of a three-year-old boy who presented with abnormal movements which initially occurred only during sleep. Three years later, he went on to develop hyperkinetic movements during the daytime while awake. There was a strong family history of various paroxysmal neurological disorders. In this report, we discuss the clinical approach, differential diagnosis, investigation and treatment options for nocturnal hyperkinetic movements and paroxysmal movement disorders.

Key Words: Paroxysmal dyskinesia, Sleep-related movement disorders.

Section 1

A three-year-old patient presented with a chief complaint of nocturnal hyperkinetic movements. Pregnancy and developmental history were unremarkable, and the patient was unmedicated. Medical history was only remarkable for a history of mild head trauma at age two. There was no consanguinity, but there was a history of epilepsy on the father's side of the family.

The abnormal movements occurred almost every night (sometimes multiple times per night) two or three hours after falling asleep. They consisted of large amplitude and low frequency non-rhythmic movements lasting for a few seconds. While the phenomenology of the movements varied somewhat, rotating and twisting movements involving the upper more than lower limbs were the predominant features (see video 1). These movements would alternate between sides of the body from one episode to another, with the left side
being more frequently involved. No triggering factors (besides sleep) were noted. These movements were not preceded by apparent arousals or physiological body movements. The patient did not wake up during the episodes or recall them. The patient, who lived in a remote region, was referred at this time to our pediatric neurology reference center for assessment.

Questions for consideration:

1. Based on the patient's presenting symptoms, what is your differential diagnosis?
2. What diagnostic testing would you recommend for this patient?

Section 2

Epilepsy was the first diagnosis considered. Following an unremarkable routine EEG, the patient was further investigated by prolonged video-EEG monitoring. It captured multiple typical episodes of abnormal nocturnal movements (as described above) without interictal or ictal epileptiform abnormalities. Sleep-related hypermotor epilepsy (SHE, previously known as nocturnal frontal lobe epilepsy) presents with seizures predominantly during non-REM sleep, that are usually brief, frequent, with bilateral tonic posturing or gross proximal limb movements and preserved consciousness. Ictal EEG is frequently normal or obscured by abundant movement artifacts. (1, 2). We also considered in our differential diagnosis paroxysmal hypnogenic dyskinesia (PHD), which many experts believe to be a form of sleep-related hypermotor epilepsy (SHE). (2-4) No specific diagnosis was given at this time. Epilepsy was felt to be unlikely in the absence of stereotyped episodes. MRI was performed early in the investigation to rule out any
structural abnormality and was unremarkable. Given the patient's normal neurological exam and absence of daytime impairment, a watchful waiting approach was decided upon.

At age 6, our patient began to present dystonic posturing during the day, lasting a few seconds and predominantly affecting his arms, particularly his left side. The symptoms were often triggered by sudden movements, such as getting up from a chair. These episodes could occur several times per week. His neurological exam between episodes remained normal. At this point, the family history was reassessed. His father was diagnosed with epilepsy but also had paroxysmal hyperkinetic movements occurring during the day from a young age, for which he had never sought out a specific diagnosis. Moreover, on the father's side of the family, several members have tics, epilepsy, epilepsy and dystonic movements or paroxysmal dystonic movements alone. (Figure 1)

Our patients' short-lasting episodes of dystonic posturing preceded by sudden movements, were suggestive of paroxysmal kinesigenic dyskinesia (PKD). However, the nocturnal episodes are less characteristic and lead to a reconsideration of epilepsy. Therefore, we repeated routine EEG, which was once again normal.

Most hyperkinetic movement disorders are diminished or absent during sleep. However, there are several exceptions that are worth considering in this patient. In particular, ADCY5-related movement disorder (ADCY5-RMD) should be considered in a child presenting with hyperkinetic movements, especially if they occur at night. However,
ADCY5-RMD usually is associated with a daytime mixed hyperkinetic movement disorder, superimposed with paroxysmal worsening and significant functional impairment. (5) Other examples of movement disorders that can occur during sleep include periodic limb movement of sleep (PLMS), sleep-related rhythmic movement disorder, and tics. (6) However our patients’ movements were not suggestive of any of those diagnoses.

Wilson's disease may present initially with fluctuating dystonia before progressing to more classical clinical manifestations. (4) We thus performed a workup for Wilson's disease, including urinary copper, ceruloplasmin and liver function tests which were unrevealing.

GLUT-1 deficiency may also present with paroxysmal movement disorders. However, these are usually exercise induced and frequently presents with other neurological symptoms, including seizure, developmental delay, and other movement disorders. (7)

Our patients’ symptoms during the attacks sometimes alternated between sides with a preserved consciousness, which may suggest alternating hemiplegia of childhood (AHC). Dystonia and other movement disorders can accompany these attacks. However, AHC attacks usually last a few minutes to hours, and intellectual impairment is present. (4)
Question for consideration:

1. Which additional tests would help establish the diagnosis?

Section 3.

To explore the presence of an underlying sleep disorder, the patient had a polysomnographic study with full-montage EEG and additional surface EMG electrodes on the flexor digitorum superficialis muscles. No abnormal movements were observed during the polysomnographic study and EEG was unremarkable.

Because of the consideration of PKD, we tested for and found a mutation in the PRRT2 gene. (8) Therefore, a diagnosis of PKD was confirmed. PRRT2 mutations were also confirmed in two distant relatives with isolated dystonia and combined dystonia and epilepsy, respectively (see figure 1). Genetic testing is currently pending in several other relatives.

Questions for consideration:

1. How would you manage this patient at this point?
2. What is the typical course of the disease?

Section 4.

PKD typically responds well to antiepileptic medications, especially sodium-channel blockers. There is up to a 90% response rate with carbamazepine and phenytoin. (3, 4) Our patient was started on carbamazepine. There was a complete resolution of symptoms
occurring day and night, apparently confirming that the sleep-related movements were also dyskinesias related to PKD. Figure 2 summarises the patients’ longitudinal clinical history, investigations, and treatment. Attacks usually peak in intensity after several years and remain stable or decrease over time. Remission is possible and occurs most often during the third decade of life. Up to 27% of patients become symptom-free. (3, 4)

Discussion
Paroxysmal dyskinesias are a heterogeneous group of rare diseases presenting recurrent episodes of hyperkinetic movements. The movements are usually dystonic, but chorea, ballistic movements, unspecified dyskinesias, or a combination can occur. Consciousness is preserved during episodes. These disorders are generally categorized according to the trigger and duration of the episodes. This includes PKD, paroxysmal non-kinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia and PHD. (3, 4)

The nature of PHD is somewhat controversial. It is no longer considered a paroxysmal movement disorder in most classifications. (9) It corresponds to involuntary movements during non-REM sleep stage N2. They usually last 30 to 45 seconds. (3) However, authors often argue that this disorder represents SHE because of the semiology (particularly when strictly stereotyped), and it responds well to antiepileptics. (3, 10) Genetic studies show nicotinic receptor mutation (as in autosomal dominant nocturnal frontal lobe epilepsy) in many of these patients. (2) The EEG is often normal or obscured
by movement artifacts, but the extreme stereotypy of the episodes allows for the diagnosis of epilepsy. (2)

Our patient’s nocturnal episodes were brief, with large-amplitude limb movements that could alternate sides. Video-EEG monitoring revealed no epileptiform abnormalities in the presence of multiple episodes of abnormal movements, which were not stereotyped. The non-stereotyped nature of the movements was reassuring against an epileptic nature in our patient's case. Thus, leaving non-epileptic PHD as the most likely diagnosis.

Interestingly our patient eventually developed daytime episodes typical of classical PKD. PKD usually affects more males than females and begins during childhood. It is triggered by sudden motion, and the hyperkinetic movements only last a few seconds to a few minutes. (3) The movements can affect arms or legs, be unilateral or bilateral, and alternate from side to side. (3) A refractory period usually lasts 5-20 minutes after the attack. There could be multiple daily attacks, which usually decrease in frequency with age. (4) It has been described that PKD can occur during sleep or during arousals from NREM sleep, often preceded by dreaming or physiologic nocturnal movements (like turning), which was not the case for our patient, who remained sleeping and unconscious before, during and after the movements. (11, 12)

Most cases of PKD are inherited in an autosomal dominant pattern. The genetic anomaly is most often found on the PRRT2 gene on chromosome 16. (8) It is now well known that PRRT2 mutations can present with other phenotypes, such as familial infantile
convulsions with paroxysmal choreoathetosis, benign familial infantile seizures, ataxia, typical migraines, and hemiplegic migraines. PRRT2 mutations have been identified in patients with nocturnal dyskinesias, though these appear to occur during arousals from NREM sleep rather than during sleep and were not associated with daytime dyskinesias. (8, 13) Moreover, to our knowledge PHD as an initial presentation progressing towards a more classical PKD phenotype has not been reported. This report highlights that not all cases of PHD are related to SHE and may represent the initial manifestation of PKD. Hence, we may consider genetic testing for PRRT2 mutations in children with unexplained non-stereotyped sleep-related movements.

WNL-2023-002441_vid1 --- http://links.lww.com/WNL/D200
References


Abbreviations by order of appearance

EEG: Electroencephalogram
SHE: Sleep-hypermotor epilepsy
PHD: Paroxysmal hypnogenic dyskinesia
MRI: Magnetic resonance imaging
PKD: Paroxysmal kinesigenic dyskinesia
RMD: related movement disorder
PLMS: periodic limb movement of sleep
AHC: Alternating hemiplegia of childhood
Figures and Video

Figures 1: Pedigree demonstrating an autosomal dominant inheritance pattern with incomplete penetrance and variable expressivity.

*PRRT2* denotes that the individual has a confirmed mutation.
Figure 2: Clinical timeline

The arrow represents the timeline from age three to nine. The main clinical symptoms, investigations, and treatments are represented below the arrow.

Video 1: Sleep-related hyperkinetic movements.
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