Non epileptic paroxysmal events in childhood

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Abstract

Non epileptic paroxysmal events are recurrent movement disorders with acute onset and ending, which may mimic epilepsy. The duration, place, timing of the attacks, and state of consciousness may confuse pediatricians about the diagnosis of epilepsy and non epileptic paroxysmal events. The key point in the diagnosis is taking an accurate and detailed history. Wrong diagnosis can give rise to anxiety of both the family and the child, interruptions in the child’s education, limitations in career planning, and irreversible damages in the long term. The diagnosis can prevent unnecessary drug use and psychological damage. This review aims to discuss the clinical findings, treatment, and differential diagnoses of non epileptic paroxysmal events, and to increase awareness about non epileptic paroxysmal events among pediatricians. (Turk Pediatri Ars 2017; 52: 59-65)

Keywords: Childhood, epilepsy, non-epileptic event

Introduction

Nonepileptic paroxysmal events of childhood constitute a complex condition including recurrent intermittent motor movements, behavioral changes and somatic symptoms (1). They may be associated with different signs and symptoms including fainting, loss of consciousness, headache, vomiting, dizziness, abdominal pain, irregular breathing, sleep disorders, and emotional and psychiatric problems. These repetitive movements with sudden onset and ending, which last for seconds or minutes, may occur at any age and most importantly, may be misdiagnosed as epilepsy and treated unnecessarily. In nonepileptic paroxysmal events (NEPE), changes of electroencephalogram (EEG) are not observed during the event. Sometimes, the duration, location, type and time of occurrence of the episodes and consciousness state may bring physicians to question between the diagnoses of epilepsy and NEPE. In this case, differential diagnosis is possible with visualization of episodes by video recording and simultaneous evaluation of EEG (1, 2).

In Europe, the prevalence of epilepsy in children has been estimated as 4-5%. In a study conducted in Denmark, it was found that 39% of children who were diagnosed as having epilepsy were misdiagnosed, and approximately 47% of these diagnoses consisted of NEPEs (3). A misdiagnosis affects the patient’s family life, education, and many economic factors. Absenteeism of the child and workforce loss of the parents, psychological damage in the child and parents, and limitations in the child’s choice of career and profession lead to irreversible damage. Therefore, it is crucial that physicians evaluate each finding very carefully for an accurate diagnosis. The most common NEPEs by ages are shown in Table 1. The aim of this review was to discuss the clinical findings, therapeutic approaches, and differential diagnosis of NEPEs and increase awareness among pediatricians.

Clinical approach

The clinical approach in childhood NEPE is substantially complex. The most important step in the diagnosis is a detailed history. In particular, the age of onset of the movement is one of the most important questions that should be asked in the differential diagnosis. The frequency of the movement, changes observed since onset,
remote or recent diseases in the past, drug use, history of delivery and pregnancy, motor-mental developmental process since infancy, and familial history should be carefully examined. Online viewing techniques with the advancement in technology and mobile phones, tablets, cameras and digital cameras carried by parents have markedly increased the rate of accurate diagnoses in these patients. Images belonging to the patient being monitored sometimes prevent many unnecessary techniques and use of drugs. In this disease group, the most important differential diagnosis is epilepsy and video-EEG is the most important investigation for differentiation of paroxysmal movement and epilepsy (2, 4). Table 2 shows NEPE and the epileptic conditions that are most commonly confused with NEPE.

Neonatal period

Jitteriness
Jitteriness is the most common movement disorder in the neonatal period. The most important features that differentiate this movement, which is composed of recurrent tremors in the extremities, include increase of movement with stimuli and stopping of the movement with slight flexion of the extremity. Eye movements and autonomic changes (hypertension, apnea) do not accompany jitteriness; presence of these changes suggests epileptic episodes. Jitteriness may be physiologic (benign) or may occur pathologically as a result of hypoglycemia, hypocalcemia, hypoxic ischemic encephalopathy, intracranial hemorrhage, sepsis, hypothermia, hyperthyroidism and drug withdrawal reactions (5).

Hyperekplexia
Hyperekplexia is a sudden, exaggerated startle response that occurs as a result of unexpected stimuli. Noises and tactile, visual and vestibular stimuli are the most common stimuli that cause this exaggerated response. Following stimulus, fear and shrinkage in the face, flexion of the head and shoulders, adduction of the arms, flexion of the trunk and legs, and finally loss of tonus may be expected. If hyperekplexia prevents the patient’s normal activities and leads to apnea, frequent falls and injuries, it is considered pathologic. Patients benefit from low-dose benzodiazepine, valproic acid, and levatiracetam (6, 7). This condition occurs most commonly as a result of glycine receptor alpha-1 subunit gene mutation (GLRA1) in the brain and spinal nerves. It is an autosomal domi-

Table 1. Common non-epileptic paroxysmal events by age

<table>
<thead>
<tr>
<th>Newborn</th>
<th>Infancy and game age</th>
<th>Adolescent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jitteriness</td>
<td>Breath-holding spells</td>
<td>Syncope</td>
</tr>
<tr>
<td>Hyperekplexia</td>
<td>Shuddering attacks</td>
<td>Sleep disorders</td>
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<tr>
<td>Benign sleep myoclonus</td>
<td>Stereotypes</td>
<td>Psychogenic crises</td>
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<tr>
<td></td>
<td>Benign paroxysmal torticollis</td>
<td>Tics</td>
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<tr>
<td></td>
<td>Benign paroxysmal tonic upward gaze</td>
<td>Migraine</td>
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<tr>
<td></td>
<td>Benign paroxysmal vertigo</td>
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<td></td>
<td>Sleep disorders</td>
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<td></td>
<td>Masturbation</td>
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<td>Spasmus nutans</td>
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<td>Sandifer syndrome</td>
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<td>Tics</td>
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</tbody>
</table>

Table 2. Non epileptic paroxysmal events and the epileptic conditions that they imitate

<table>
<thead>
<tr>
<th>NEPE</th>
<th>Imitating epileptic condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope</td>
<td>Generalized tonic-clonic seizure, focal seizures, absence seizures, drop attacks, myoclonic seizures</td>
</tr>
<tr>
<td>Breath-holding spell</td>
<td>Tonic spasms</td>
</tr>
<tr>
<td>Sandifer syndrome</td>
<td>Tonic spasms, infantile spasm</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Frontal lobe seizures, rolandic seizure</td>
</tr>
<tr>
<td>Benign sleep myoclonus</td>
<td>Myoclonic seizure, focal seizures</td>
</tr>
<tr>
<td>Pseudo-crisis</td>
<td>Status epilepticus, non-convulsive status, tonic clonic seizures, absence seizures, focal seizures</td>
</tr>
<tr>
<td>Migraine</td>
<td>Occipital lobe seizures, temporal lob seizures</td>
</tr>
</tbody>
</table>

Nepe: Non epileptic paroxysmal events
nantly inherited disorder. The other genes found include SLC6A5, GLRB, GPHN, and ARHGEF9. Neonatal epilepsy, myoclonic seizures, neonatal tetany, phenothiazine intoxication, and cerebral palsy must be definitely considered in the differential diagnosis (8).

Hereditary hyperekplexia (Startle disease) occurs in the neonatal period. The most common finding is a sudden startle response with tactile stimulation on the tip of the nose. In these patients, long-term generalized contraction including the whole body (extremities, trunk and face) may be observed in cases in which the stimuli persists, and increase during functions that require effort including crying and defecation (Stiff-baby syndrome). Laryngospasm and cardiorespiratory failure, which occur as a result of this condition, increase the risk of sudden infant death. These generalized contractions may be confused with tonic epileptic seizures. In addition, the diagnosis is important in terms of acute treatment because postural maneuvers of the trunk and extremities (flexion of the head and feet) in place of antiepileptic drugs stop the episode (6-8).

**Benign sleep myoclonus**

Benign sleep myoclonus is characterized by repetitive, high-frequency myoclonic jerks in the arms and legs, which last for seconds or minutes, especially while falling asleep following feeding in the neonatal period. It occurs with an incidence of approximately 0.8-3/1000 in term and near-term babies. Its differential diagnosis with myoclonic seizures and focal seizures is important. It may be symmetric or generalized, or myoclonic episodes involving a single extremity may be observed. If the child wakes up, the episode is over; the most important feature is that it is not observed outside of sleep. These episodes usually disappear spontaneously when the child is 4-6 months old. It is thought that it is caused by immaturity of the neuronal structure providing motor control during sleep and genetic factors. Treatment is unnecessary. Antiepileptic drugs may sometimes increase sleep myoclonus (8).

**Infancy and school-age period**

**Breath-holding spells**

Breath-holding spells occur between the ages of 6 months and 5 years in children. Its frequency is 5%. The spells are clinically observed in two forms as cyanotic form and pallid form. The frequency of the episodes is variable; they may occur a few times a day or every 3-4 months.

*pallid breath-holding spells*; the child screams briefly, usually following minor injuries, seeing blood or drawing of blood and painful stimuli (falling, hitting the head). Afterwards, hypotonia, loss of consciousness, and pale skin occur. The reason is sudden bradycardia caused by a vagal response. The episodes usually last for a period of less than 60 seconds. When the child wakes, he/she is tired and wishes to rest. The episode is substantially severe in children with anemia. Treatment is usually unnecessary. The children are healthy between episodes. The prognosis is always favorable.

**Cyanotic breath-holding spells**; 65% of breath-holding spells are cyanotic. A stimulant factor (pain, anger or fear) may trigger the episode. Prolongation of expiration during crying may result in apnea. At the time of breath-holding, the skin color starts to change. This period may result in inspiration or cyanosis may deepen, and secondary hypoxia may be added. Loss of tonus and rarely myoclonic jerks may accompany. A postictal period may be observed depending on the severity of the episode. During severe episodes, generalized hypertonia and opisthotonus posture may be observed. The child should be positioned on their side at the time of breath-holding in order to prevent aspiration. Giving psychological support to the family is beneficial. If anemia is present, iron treatment should be given. Antiepileptics are not used for treatment of breath-holding spells (9).

**Shuddering attacks**

Shuddering attack is an NEPE that initiates with rapid tremor of the head and shapes with continuance of this movement in the shoulder and trunk. The attacks last only for 1-2 seconds and they are benign movements that recur frequently (sometimes 100 times a day). Nursing, eating, and urination may initiate the attacks. They occur at the age of 4-6 months and disappear spontaneously at the age of 6-8 years. Treatment is unnecessary (10).

**Stereotypes**

Stereotypes are recurrent, simple movement groups that can be stopped voluntarily. They most commonly occur as recurrent movements in patients with mental retardation and autism. These ritual movements including clapping, shaking arms, and shaking the head do not involve complex movement series and complex motor movements. Stereotypes may be unilateral or bilateral. They are usually concentrated in the upper extremities and do not occur in the lower extremities. Generally, a stimulating impulse is not needed for the onset of the movements. However, they markedly increase during periods of stress. They can be stopped with initiation of another activity or distraction of the child (11).
Benign paroxysmal tonic upward gaze
Benign paroxysmal tonic upward gaze consists of a clinical picture of chronic and recurrent ataxia associated with upward deviation of the eyes with a constant or variable period. The clinical picture of ataxia may not be noticed in all patients. The attacks last for a short period. The age of onset ranges between 1 month and 2 years. In children with a normal neurologic development, it is expected to recover spontaneously in 1-2 years from onset. If neurologic findings including ataxia, developmental delay, intellectual failure, and delay in speech accompany, spontaneous recovery may not be observed in these patients who should be screened with further imaging and diagnostic methods (12).

Benign paroxysmal vertigo
The International Headache Society (IHS) identified benign paroxysmal vertigo (BPV), benign paroxysmal torticollis, cyclic vomiting, and abdominal migraine as periodic syndromes of childhood and stated that these conditions were precursors of migraine (13). Benign paroxysmal vertigo comprises episodes of dizziness that occur suddenly and last for a few minutes with an onset during infancy. The attacks usually occur at ages of 1-2 years after the child starts walking, and may last up to the age of 6 years. Nausea, vomiting, and paleness may be prominent. The child is awake, suddenly becomes panicked, as if frightened, and does not want to move until the event ends. If the child is urged to walk during this period, he/she is unbalanced. While young children cry in panic, older children try to describe the event. In the beginning, the episodes occur every day or every 2-3 months. The frequency decreases with age. Neurologic examination before and after the episode is normal. Electroencephalogram and magnetic resonance imaging (MRI) are normal. Although some studies emphasized that peripheral vestibular dysfunction and central vestibular pathology may cause BPV in the etiology, a definite cause could not be found. However, it has been emphasized that these patients have a genetic predisposition and are diagnosed as having migraine more frequently in advanced periods of life compared with the normal population. If vertigo episodes are short, treatment is not recommended. It has been reported that some patients benefited from cyproheptadine and diphenhydramine treatment if vertigo episodes were long and frequent (14).

Benign paroxysmal torticollis
Benign paroxysmal torticollis is a movement disorder characterized by recurrent episodes with an onset at the age of 2-8 months in infancy. Typically, it disappears at the age of 3-5 years. Episodes may last for 1-2 hours or for days (15). The child keeps his/her head turned to one direction; vomiting and paleness may accompany. It is notable that the period and frequency of the episodes decrease as the age gets older. In these patients, benign paroxysmal vertigo, cyclic vomiting syndrome, abdominal migraine and migraine develop more frequently in the advanced period compared with the normal population. Treatment is not routine because the episodes end spontaneously. If the episodes are frequent and painful, cyproheptadine and diphenhydramine are the first-line drugs to be selected. In the differential diagnosis, posterior cranial fossa pathologies should be absolutely excluded. Therefore, imaging should be performed (11).

Parasomnias
Parasomnias are sleep disorders that occur during the first 1/3 of night sleep and involve unwanted behavior and movements. The sleep disorders that are most commonly confused with epileptic seizures are parasomnias. These occur most commonly at the age of 4-12 years. Stress, restlessness, and infections are thought to be triggering factors. Confusional arousal, night terrors, and sleepwalking are the most common parasomnias in childhood (16).

Confusional arousal; this is characterized by sudden awakening during the night in the non-REM phase of sleep, prolonged confusion, and sometimes complex behaviors. This is the most common type of parasomnia observed in children. Approximately 20% of children are affected. The patient is not aware of what he/she experiences at the time of awakening. Differential diagnosis with epileptic attacks is imperative (17).

Night terror; night terrors occur in the non-REM phase of sleep and are characterized by screaming, cold sweat, and hallucinations, approximately 1.5-2 hours after falling asleep. It most commonly occurs in boys aged 4-6 years. It typically occurs once a night. The child does not recognize his/her parents at the time of the crisis and does not remember anything the next day. It may last a few minutes or longer than expected. It occurs commonly in young children and disappears at the school age. For a differential diagnosis, night-long sleep-video recordings are used when necessary (18).

Sleepwalking; sleepwalking occurs in the non-REM phase of sleep. The child walks during sleep. When he/she is awakened, a short period of confusion is observed. It is observed commonly, especially in adolescence. Episodes occur 1.5-2 hours after falling asleep and may last for 5-10 minutes. One should watch for environmental factors because the child may involuntarily harm him-
self/herself during an episode. In some patients, respiratory tract problems have been identified (obstructive sleep apnea) and it has been observed that the frequency and time of sleepwalking decrease when these problems are treated. Differential diagnosis especially with frontal lobe seizures should be performed (19).

**REM sleep disorders**; REM sleep disorders are characterized by sleep-related motor and behavioral changes. Motor and behavioral movements including laughing, speaking, groaning, and kicking observed during this period may be confused with epileptic episodes (20). Video EEG is the most important test that should be performed in the differential diagnosis.

**Masturbation**
Masturbation is defined as self-stimulating pleasure behaviors of the child. It occurs between the ages of 3 months and 5 years. It may be observed in both sexes, but is more frequent in girls. The patients press their legs by stretching them while sitting or lying, their breathing speeds up, flushing occurs, and the hands are usually not on the genital region in contrast to what is expected. The event lasts for a few minutes and may be interrupted by intervention. It may recur 15-20 times a day. When causes including urinary tract infections, vulvovaginitis, and diaper dermatitis cause pruritus, the child accidentally finds out that they feel pleasure during movements they perform to eliminate irritation. In these patients, the most important differential diagnosis is epilepsy. Video EEG history is definitely necessary to exclude the diagnosis of epilepsy in suspected patients. It is observed more commonly in children with lack of love and interest and with mental retardation. It is eliminated with behavioral treatment (21, 22).

**Spasmus nutans**
Spasmus nutans is a rare, idiopathic paroxysmal disorder that consists of nod, nystagmus, and torticollis. It occurs in the first year of life and recovery occurs at the age of 3-6 years (23). Spasmus nutans may be associated with arachnoid cyst, optic nerve hypoplasia, diencephalic syndrome, subacute necrotizing encephalopathy (Leigh disease) and intracranial tumors. In addition, it is known that it is associated with retinal diseases (acromatopsia, cone and rod dystrophy, night blindness, and Bardet-Biedl syndrome) (24).

**Sandifer syndrome**
Sandifer syndrome is a movement disorder that comprises gastroesophageal reflux, spasm in the head, neck, and trunk, and abnormal posture. It occurs in early childhood and neurologic development is normal in most patients. These movements, which are confused with dystonia, include retrocollis, opisthotonic posture, and slanting of the head on one side (25). In this syndrome, which occurs intermittently, crying and these tonic movements may be confused with epileptic seizures (26). Patients with Sandifer syndrome may have hiatal hernia. Antireflux treatment should always be given and surgical treatment (fundoplication) should be performed if medical treatment is considered insufficient (25).

**Adolescence**

**Syncope**
Paroxysmal consciousness disorders with vascular, cardiac or neurologic origin characterized by sudden loss of consciousness, loss of tonus, falling, and spontaneous recovery in a short time are called syncope. The frequency in the first two decades is about 15% (27). Dizziness, blackout, malaise, paleness, nausea, cold sweat, palpitation, blurred vision, and hearing loss may be present before the attack. Syncope can be classified as neurally-mediated syncope (vasovagal, carotid sinus hypersensitivity, glossopharyngeal syncope), cardio- genic syncope, (arrhythmias, heart diseases, vascular problems) and non-cardiogenic syncope (orthostatic hypotension, neurological, metabolic, endocrine, psychogenic, and drug-related syncope) (28).

**a. Vasovagal syncope**
Vasovagal syncope is the most common form of syncope in children. It constitutes approximately half of syncope attacks. The mechanism involves sudden loss of vasomotor tonus and as a result, systemic hypotension, bradycardia, and asystole. Hypotension and paradoxic bradycardia are present. History of standing without moving for a long period before the attack (e.g., ceremonies, choirs) is obtained. In addition, emotional factors including hunger, pain, anxiety, seeing blood, crowded environment, fear, and fatigue have a stimulatory effect. The autonomous nervous system induced by the vagus nerve leads to a reduction in heart rate and blood supply in the central nervous system. Before syncope, the most common symptoms include blackout, malaise, and nausea, which last approximately 10 seconds. In addition, sweating, increased salivary secretion, blurred vision, and tachycardia may also be expected. Following prodromal symptoms, loss of consciousness and decreased muscle tonus in the whole body, loss of posture, and falling down are observed. The patient's face is pale, the pulse is weak, the heart rate is reduced, the skin is sweaty, the pupils are enlarged, and the whole body is flaccid. Rarely, abnormal movements including contraction in the extremities...
and sometimes even enuresis may occur during syncope. It is difficult to differentiate such syncope attacks from epileptic seizure. A typical syncope lasts for a few minutes and the child rapidly regains consciousness. In an epileptic seizure, blurred consciousness and stupor mostly continue in the postictal period (28, 29).

b. Cardiovascular syncope
Cardiovascular syncope is more frequent at young ages compared with vascular syncope. It is observed considerably rarely in childhood and its frequency among the syncopes ranges between 2% and 6% (30). Cardiovascular syncope mostly occurs during lying, performing physical exercise or following physical exercise in patients with known cardiac disease. It may be observed in any condition in which cardiac output is reduced in association with bradycardia or tachyarrhythmia. Aortic stenosis, hypertrophic cardiomyopathy, coronary artery anomalies, arrhythmias (Wolf-Parkinson-White syndrome, congenital AV block, long QT syndrome), postoperative conduction problems, myocarditis, Marfan syndrome, hypertension, and aortic dissection are cardiovascular causes that may lead to syncope (28). In these patients, echocardiography and 24-hour rhythm Holter recording are the most important diagnostic tools.

c. Cerebrovascular syncope
Conditions that affect the brain vessels in childhood including vertebrobasilar artery failure, subclavian steal syndrome, migraine, Moyamoya disease, and Takayasu disease are the causes of cerebrovascular syncope (29).

d. Orthostatic hypotension
Orthostatic hypotension is observed in tall adolescents with asthenic body type. It is more common in men. It occurs as a result of sudden reduction in the blood pressure and increased cardiac beats at the time of sudden standing or during prolonged standing. In children who stand rapidly, a blood shift occurs in the lower extremities. Under normal conditions, the orthostatic reflex is activated when cardiac output and blood pressure are reduced, the sympathetic system is activated, and the efficiency of the parasympathetic system is reduced. This regulates cardiac output, blood pressure, and brain circulation. In orthostatic hypotension, a reduction in the brain blood supply leads to syncope when one stands rapidly. A systolic blood pressure lower than 90 mm Hg or a reduction more than 20 mm Hg suggests orthostatic hypotension. Anemia, excessive sweating, blood loss, conditions that may cause hypovolemia (diarrhea, dehydration), drugs that may affect the orthostatic reflex (phenothiazines, sedatives, nitrates, antidepressants, antihypertensive drugs, calcium channel blockers) may lead to orthostatic syncope (28, 30).

Psychogenic non-epileptic crises
Psychogenic non-epileptic crisis is a movement disorder that occurs as a result of internal (recalling the past, emotions) and external (history, places, persons) triggering factors, and is generally observed in adolescence. It is characterized by prolonged drowsing and asynchronous loss of tonus in the hands and feet following unresponsiveness to stimuli. Frequently, injury does not occur during falling. Seizure types are not compatible with each other. In contrast to epileptic seizures, the eyes are usually closed. Enuresis and en coupresis are not observed. Some patients who have had epileptic seizure before may mimic a seizure with the aim of secondary gain. It is very difficult to make the diagnosis in these patients and some may be followed up in epilepsy centers with a diagnosis of resistant epilepsy. Patients should definitely be evaluated by a child psychiatrist in terms of underlying triggering emotional factors. In the differential diagnosis, Video-EEG is the most important diagnostic tool (4).

Tics
Tics are repetitive movements that may occur from time to time or persistently, may be preventable, affect one or more muscle groups, and may be voluntarily controlled, albeit for a short time. It is vital to differentiate the motor part from epileptic seizures. Tics are not episodic-like seizures and recur many times during the day. Loss of consciousness and postictal period are absent. They occur most commonly at ages of 5-10 years. The decision for treatment is given by evaluating the frequency of the tics, presence of single or multiple tics, and with a neurologic examination of the patient (22).

Migraine
Migraine is the most commonly observed paroxysmal neurologic disease in childhood. Although its etiology has not been elucidated fully, vascular, hormonal, chemical, and neuronal theories are being contemplated. Complicated migraine is migraine in which transient neurologic findings are present during headache. This group in particular is frequently confused with epilepsy. Studies showed that EEG findings were present, especially in the occipital lobe areas in patients with migraine. Variability in findings including nausea, headache, tinnitus, visual symptoms, and somnolence may cause physicians to be torn between the diagnoses of epilepsy and migraine. Making the diagnosis based on the order of the signs, the time of the event, the consciousness of the patient at the end of the event, neurologic findings and general status, the frequency of recurrence, triggering factors (stress, sleeplessness, hunger, foods), response to drugs (antiepileptics, non-steroid anti-inflammatory drugs), imaging methods (MRI, com-
puterized tomography (CT) and EEG findings is the most accurate way for these two diseases (31).

In conclusion, an accurate and detailed history is the most important step in NEPE. Long-term video-EEG monitoring is the most important test, both to see the images and to make the distinction from epileptic attacks. Images from day-to-day devices smart phones, tablets, and cameras have increased the rate of diagnosis in these conditions. An accurate and early diagnosis prevents unnecessary drug use and tests. A wrong diagnosis may cause the child to change their life style, career plans, and choice of profession, which is a cause of anxiety for both the child and family in the long term. Appropriate communication with the family is the best way to reduce this anxiety.

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