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REVIEW ARTICLE

Paroxysmal nonepileptic events in childhood and adolescence

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Abstract

Objective: this article aims to describe paroxysmal nonepileptic events (PNEs) in childhood and adolescence, emphasizing semiology and clinical aspects to facilitate the diagnosis, pointing out differences in relation to epileptic events (EEs) and highlighting general treatment guidelines. **Method:** a non-systematic review of the literature was conducted, focusing on research regarding semiology, clinical features and treatment. Diagnostic manuals were also consulted. **Results:** PNEs can be categorized in: physiological events – including hypoxic events, sleep disorders, movement disorders and migraine related disorders – and psychogenic nonepileptic events (mainly conversion disorder; factitious disorder, malingering and panic disorder are also discussed). Around 15% of the patients referred to epilepsy centers actually present PNEs. A significant number of these events does not need treatment and presents spontaneous remission. **Conclusion:** physicians should be able to identify PNEs, avoiding an incorrect epilepsy diagnosis and its implications, such as unnecessary tests and iatrogenic pharmacotherapy, as well as negative psychosocial consequences for both the patient and the family.

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INTRODUCTION

Epilepsy may be present in up to 0.5% of the pediatric population.[1] It is a chronic condition that requires longitudinal follow-up. During an epileptic seizure, the clinical event (whether motor, behavioral, or sensory) is the result of abnormal electrical activity in the brain. Definitive diagnosis is difficult, and distinction between epileptic and non-epileptic events is fundamental to avoid unnecessary investigations, family anxiety, and inappropriate use of antiepileptic drugs, which is associated with the risk of side effects.[2] Inappropriate action can lead to iatrogenic pharmacological and psychosocial effects that can cause limitations, stigma, and prejudice to the individual, which are still associated with epilepsy. There may be potential increase in morbidity and mortality.

Paroxysmal non-epileptic events (PNEs) are characterized by clinical episodes similar to those of epileptic events (EEs), but are not accompanied by abnormal electrical discharges in the brain. They involve motor activity, sensory changes, emotional changes, or impairment of consciousness. The pediatrician, family physician, neurologist, and pediatric psychiatrist should be aware of PNEs, including emergency services.

A significant proportion of patients referred to epilepsy clinics present with PNEs at a rate of 15% (12%–16%).[3,4] A review of 887 pediatric patients treated in an epilepsy monitoring unit, assessed by clinical history and video-electroencephalography (VEEG), found a 15.9% rate of non-epileptic events.[3] Another study that also used VEEG found a 12.4% rate of PNEs in a sample of 765 children who presented paroxysmal events.[4] It should be noted that studies have shown that 30%–35% of children diagnosed with epilepsy are misdiagnosed.[1,5] Even for specialists, correct diagnosis may not be completely clear. A recent study involving neurologists, neuropsychologists, psychiatrists, and neurology residents found a diagnostic accuracy of 75% for paroxysmal events, with clinical experience as a determinant factor for the correct identification of these events.[6]

Among factors that contribute to incorrect diagnosis are inadequate clinical history, consideration of traditional but unreliable warning signs, incorrect interpretation of test results (particularly EEG results), and the perception that clinical evolution could worsen if intervention is delayed.[7] To avoid damage from a misdiagnosis, strategies such as recognizing the possibility of misdiagnosis and adopting the practice of reviewing and reconsidering previously established diagnoses are recommended.[7]

Non-epileptic events can be classified as **physiological** or **psychogenic**. Physiological PNEs are associated with organic causes[2] and can be classified into hypoxic–ischemic phenomena, sleep disorders, movement disorders, and migraine-associated disorders. Psychogenic PNEs, on the other hand, are associated with psychological factors.[8] This category includes conversion disorder (and differentiation from factitious disorder and simulation), with panic disorder as a differential diagnosis.

PHYSIOLOGICAL NON-EPILEPTIC EVENTS

Hypoxic–ischemic phenomena

Notable among hypoxic–ischemic phenomena are syncope and shortness of breath.

Syncope is a sudden and transient loss of consciousness and postural tonus, with rapid and complete recovery.[9] Incomplete cases with partial impairment of consciousness are called pre-syncope. Syncope is a symptom, not a disease, and has several causes. It is related to inadequate supply of oxygen to the central nervous system (cerebral hypoperfusion). In 75%–80% of cases, syncope is neurocardiogenic, also called vasovagal or reflex syncope, which occurs in 1%–3% of consultations in pediatric emergency services.[9] Another less common type is syncope with cardiovascular causes, such as arrhythmias and cardiac structural alterations.[10,11] Additionally, there are other diseases that manifest as clinical syncope, but the mechanisms differ from those of cerebral hypoperfusion. In these cases, psychogenic causes should be considered (conversion and anxiety), along with simulation, neurological causes (epilepsy and vertigo), cataplexy, metabolic disorders (such as hypoglycemia and electrolyte disturbances), and poisoning.[9,10] Dehydration and side effects of drugs should also be considered.

In vasovagal syncope, episodes are usually accompanied by prodromes such as dizziness, nausea, sweating, abdominal pain, and pallor. Additional factors may include orthostatic stress (such as standing on a bus) or painful or unpleasant emotional stimulation (for example, high ambient temperature, blood collection, or vaccination).[10] Events may also be related to mobilization of the neck, such as stretching, turning the head, or shaving; in these cases, the mechanism is hypersensitivity of the carotid sinus. Another particular type of syncope is situational, with specific triggering factors involving the Valsalva maneuver, such as coughing, evacuation, urination, sneezing, and weight lifting.[10]

In comparison with EEs, the following are not common in syncope: tongue biting, urinary incontinence, occurrence in supine position, crying as prodrome, or directing the gaze and head to the side.[11] EEG performed during recordings of syncopal events usually shows generalized cerebral suffering.

Although clinical presentation is very important to distinguish syncope from EEs, some tests may be required. Intercritical EEG has very limited value for the diagnosis of syncope and should not be carried out initially. Electrocardiography (ECG) and Holter monitoring may be useful to rule out cardiac arrhythmia. The tilt test, performed in children aged >6 years who present with two or more episodes (or one serious episode), can cause vasovagal syncope and provide support for diagnosis. In this test, in addition to the observation of the

clinical condition, hemodynamic parameters such as blood pressure and heart rate are also assessed.

The Calgary score, both in its traditional version and modified version, can also help in the differential diagnosis between syncope and EEs. This consists of a set of nine questions related to medical history, triggering factors, circumstances, and symptoms during an episode of transient loss of consciousness. A score of ≥1 suggests EE.[12]

Treatment of syncope should address the identified mechanism and related causes. For vasovagal-type syncope, treatment includes teaching the patient general behaviors such as increasing liquid and salt intake, placing the head between the legs or laying down, as well as avoiding/preventing triggering factors. In recurrent cases, drugs such as beta-adrenergic inhibitors, fludrocortisone, serotonin reuptake inhibitors, alpha-adrenergic stimulants (including methylphenidate), and anticholinergics can be used.[9, 10] Pacemakers can be considered in refractory cases.[9]

Although they are distinct clinical entities, syncope and EEs may coexist in the same patient. A recent study found the presence of syncope in 37% of patients with epilepsy.[13] The two diagnoses may overlap because of associated or independent physiopathological mechanisms. For example, temporal crisis can lead to asystole, causing cardiac syncope. On the other hand, an episode of syncope may trigger a seizure, even in patients without epilepsy.[13]

Breath-holding spells most often begin between 6 and 12 months of age, generally occurring up to 3 or 4 years of age.[14] The trigger is often a situation of annoyance, fear, shock, or mild trauma. The child cries, and at the end of an exhale, is unable to relax, with apnea and cyanosis occurring. There are two clinical entities: the cyanotic and pallid forms. One type generally predominates. The cyanotic form is more common, and episodes always occur after an emotional trigger: frustration, fear, or anger. The pallid form occurs suddenly after an unpleasant stimulus, such as a mild trauma.[14,15] Breath-holding spells can progress to loss of consciousness, global hypotonia, opisthotonos, and clonic movements, often confused with seizures. Investigation should look for anemia and cardiac abnormalities,[15,16] especially if seizures occur without obvious stimulus and there is a family history of syncope or sudden death. Treatment is based on guidelines for care during crisis episodes and iron supplementation, if recommended. Occasionally, more specific drug treatment may be recommended. Piracetam can be used as it is safe and has good response.[17] In severe cases of the pallid form, atropine and scopolamine may be indicated. More recent reports have described cases with satisfactory response to levetiracetam, fluoxetine, glycopyrrolate, and theophylline.[16] The physician should also be attentive to generalized tonic or tonic–clonic seizures after breath-holding spells. In these cases, specific medications are indicated, and combined treatment with scopolamine and piracetam may be an option. The use of antiepileptics is controversial.[15]

Sleep Disorders

Sleep disorders should be considered in the differential diagnosis between PNEs and EEs. Considering the third edition of the International Classification of Sleep Disorders (ICSD-3),[18] three groups deserve mention: excessive daytime sleepiness disorders, parasomnias, and sleep-related movement disorders.

Notable among **excessive daytime sleepiness disorders** is type 1 **narcolepsy** (also called narcolepsy-cataplexy). The central feature of this disorder is excessive daytime sleepiness associated with at least one of two criteria: 1) cataplexy, associated with an average latency of ≤8 min in the multiple sleep latency test in addition to two or more early episodes of REM sleep (sleep-onset REM period); and 2) hypocretin-1 concentration of ≤110 pg/mL in the spinal fluid or less than 1/3 of the average values obtained in normal patients. Excess sleepiness is manifested by episodes of uncontrollable need to sleep or by short-lasting attacks of sleepiness repeated throughout the day.[18] The pathophysiology of this disorder involves a deficiency in the transmission of hypocretin (a neurotransmitting neuropeptide produced in the hypothalamus) that causes an instability in sleep–wakefulness regulation, with rapid transitions between the two states.[19] **Cataplexy**, which can be associated with narcolepsy, is considered a dissociative manifestation of REM sleep and consists of sudden and transient loss of muscle tonus during waking hours.[20] Episodes generally last from a few seconds to 2 min.[18] When this phenomenon occurs, with the patient falling to the ground, a differential diagnosis of atonic seizures must be considered. In cataplexy, however, there is no loss of consciousness, memory, vision, or hearing, and recovery is very fast. Episodes are generally triggered by excitement, anxiety, fear, joy, laughter, or anger. Besides these episodes triggered by emotions, children with narcolepsy may also present generalized hypotonia or reduced muscular tonus in the face, without a triggering emotional factor. This can lead to an unstable gait as well as a typical facial appearance with drooping eyelids, open mouth, and protruding tongue (cataplexy face). Positive motor phenomena such as myoclonus can also occur in seizures. Narcolepsy typically occurs after 10 years of age. Initial bimodal distribution has been described, with a peak at 15 years and another at 35 years.[18] Treatment of the disorder is symptomatic. For excessive daytime sleepiness, dopamine-releasing agents and stimulants, such as modafinil, methylphenidate, and dextroamphetamines, are used. For cataplexy, tricyclic antidepressants and selective serotonin reuptake inhibitors are therapeutic options.[21] Recent research has shown the effectiveness of sodium oxybate.[21]

Parasomnias are unwanted physical events or experiences that occur when falling asleep, during sleep, or while awakening. They involve complex movements, behaviors, emotions, perceptions, dreams, and autonomic activity. Even though non-REM sleep, REM sleep, and wakefulness are relatively stable and have their own neurophysiological characteristics, they can coexist, which leads to manifestations

of parasomnias.[18,22]

Non-REM sleep parasomnias (called arousal disorders, in which there is a mixture of elements of wakefulness and non-REM sleep) include confusional arousals, night terrors, and sleepwalking. These three conditions occur during the transition from slow-wave sleep (N3) to more superficial stages during the first third of the night, with sleep deprivation and fever as possible triggering factors. In addition, the age of onset is generally 2–10 years (with the exception of sleepwalking, which tends to start at 5 years); the episodes last 10–20 min, and frequency varies from 3 to 4 times per week to 1 or 2 times per month. The episodes spontaneously end and the child falls back to sleep and has complete or partial amnesia with regard to the episode.[23]

In **confusional arousals**, the child sits up in bed crying or moaning and does not respond to comforting from parents. Patients may also repeat expressions like "no" or "go away." In general, there are no autonomic symptoms or motor stereotypies. In **night terrors**, the child wakes up suddenly and screams intensely, is agitated and appears terrified, and also presents autonomic phenomena such as sweating, tachycardia, and facial flushing. The child does not recognize parents and is inconsolable. In **sleepwalking,** the behaviors are more complex, such as walking, eating, opening and closing drawers, and touching objects. Some patients become agitated and even expose themselves to risks or get hurt. There may be autonomic symptoms, such as sweating and facial flushing.[23]

Differential diagnoses of non-REM sleep parasomnias include partial complex seizures and frontal lobe seizures. In comparison to sleep disorders, epileptic seizures are generally shorter in duration (between 30 s and 5 min), tend to occur several times throughout the night (and not preferentially during the first third of sleep), and may be associated with daytime sleepiness.[23] Episodes of parasomnias are benign and tend to decrease with time. There is no need for pharmaceutical treatment if seizures are sporadic. Low-dose benzodiazepines can be used in frequent and prolonged seizures.[23] Behavioral and cognitive–behavioral strategies may be useful in treatment. Examples include guidance for the patient and family, adequate sleep time, protection of the environment, and planned awakening before the time at which episodes habitually occur.[24]

Notable among **REM sleep parasomnias** are REM sleep behavioral disorder, isolated and recurrent sleep paralysis, and nightmares. **REM sleep behavior disorder** is characterized by repeated episodes of vocalization and/or complex motor behaviors that occur during REM sleep. Polysomnography demonstrates REM sleep without atonia. The eyes remain closed during the episodes, and the individual exhibits motor activity related to the context of the dream; patients do not respond to the environment and there may be violent behavior. This disorder most commonly affects adult individuals aged >50 years, but it can also occur in childhood. In these cases, it may be associated with narcolepsy, brainstem pathologies, or the use of antidepressants. Benzodiazepines can be used for treatment.[18,23]

Recurrent isolated sleep paralysis consists of episodes in which the patient is unable to move the trunk or limbs while remaining conscious; these episodes last from seconds to minutes, without a diagnosis of narcolepsy. It can occur when falling asleep or when waking up and may be associated with hallucinations.[18] It is common in adolescents and young adults, and sleep deprivation may be a trigger.[23] Differential diagnosis should include partial seizures, atonic seizures, and periodic paralysis with or without hypokalemia.[18] Recurring episodes may be treated with medications to suppress REM sleep. The use of tricyclics, clonidine, and clonazepam is described in the literature,[23] as well as selective serotonin reuptake inhibitors.[25]

Nightmare disorder entails repeated dreams with disturbing content, typically during the last third of the night. Nightmares generally lead to awakening and are remembered. They cause significant suffering or damage to the individual's quality of life. There may be mood changes, resistance to sleep, cognitive impairment, negative impact on the family, behavioral problems, excessive daytime sleepiness, fatigue, and problems in school and relationships. In children, this disorder is often associated with psychosocial stressors. Nightmares are common from 3 years of age and reach a peak incidence at 6–10 years. It is important to note that occasional occurrence of these phenomena without damage is not synonymous with the disorder.[18] Psychotherapy has shown positive results.[24]

Another group that should be addressed is **sleep--related movement disorders.** This category includes restless leg syndrome, periodic limb movement disorder, sleep-related bruxism, rhythmic sleep movement disorder, and benign myoclonus. These disorders involve alterations in simple and stereotyped movements, unlike parasomnias, which (as described above) involve more complex movements.

Restless leg syndrome is a disorder characterized by the need to move the legs when resting and is usually associated with an unpleasant sensation. Symptoms worsen at the end of the day and are relieved by movement. The arms can also be involved.[18] Diagnosis is clinical. There is an association with iron deficiency, and serum ferritin is consequently required. Treatment involves iron supplementation when indicated. In moderate and severe cases, dopaminergic agents, gabapentin, pregabalin, clonidine, and benzodiazepines can be used.[26]

Periodic limb movement disorder is characterized by simple, repetitive, and stereotyped limb movements during sleep. It is more frequent in the legs, with extension of the hallux and flexion of the ankle and knee (and sometimes the hip). For diagnosis in children, more than five movements per hour should occur (more than 15 in adults) and sleep or other areas of the patient's life are generally compromised.[18] Symptoms improve with the use of dopaminergic agents and benzodiazepines.[18] Pregabalin and gabapentin may be considered.[26] There are reports of an association between movements of the lower and upper limbs, forming a complex pattern, with

the need for partial differentiation from partial EC.[27]

Bruxism is a contraction of the temporal muscles during sleep that causes energetic closure of the upper and lower jaws, producing a noise. This can cause wear of the dental enamel, dental or jaw pain, and headache. Episodes last 8–10 up to 40 s. The most effective treatment is protection of the teeth. There is no proof of effective use of medications.[28]

Rhythmic sleep movement disorder involves repetitive movements of the large muscle groups, with negative consequences for the patient.[18] *Jactatio capitis noturna*, *jactatio corporio nocturna,* and *rhythmie du sommeil* are other names for this disorder. It is very common in small children of around 9 months of age, and its prevalence decreases until the age of 5 years. The disorder originates in the early stages of sleep (non-REM) and the movements are repeated at an average of one per second (0.5–2 seconds) and may last from a few seconds to 30 min. There may be an association with intellectual disability. There are three main types of movements: head banging (rhythmic front-to-back movements of the head: striking the pillow or the head of the bed are the most frequent), head rolling (turning the head laterally when the child is supine), and body rocking (with hands on the knees, the child moves forward and backward rhythmically). In addition to these three types, other movements include rocking the body and legs alone. There may also be a combination of movements and vocalizations**.** Care involves instructions to avoid physical damage, and symptoms generally recede between 3 and 4 years of age.[18,23,29]

Another frequent clinical entity is **benign sleep myoclonus**, characterized by symmetric or asymmetric myoclonic contractions involving the upper and lower limbs, trunk, or entire body. They are predominant during the onset of sleep (non-REM sleep). The condition is benign with favorable evolution.[18,23,29] Onset occurs in the neonatal period, during the first weeks of life, with symptoms resolving within weeks to months (median of 2 months). The event occurs exclusively during sleep, is not associated with autonomic disorders, and ceases when the child awakens. EEG and neurological test results are normal.[30] Swinging the body or repeated auditory stimuli can be triggering factors.[31]

Movement Disorders

Other physiological PNEs are movement disorders, mainly including tic disorder, dystonia, self-stimulation, *spasmus nutans*, opsoclonus, tremors (chills), benign paroxysmal torticollis, essential tremor, stereotypies, paroxysmal dyskinesias, and gastro-esophageal reflux.[2,32]

Tic disorder involves sudden, rapid, recurrent, and non-rhythmic movements or vocalizations.[33] Tics do not occur during sleep and can be suppressed by the patient to a certain degree, although they may be experienced as uncontrollable. They may be of the simple motor type (affects one muscle or muscle group), complex motor type (with the involvement of several muscle groups), or phonic type (vocals, with the expression of vocalizations, simple noises, or articulated language: echolalia, palilalia, or coprolalia). This disorder predominantly affects boys and onset usually occurs at 4–8 years. The peak of severity occurs at 10–12 years, with a decline during adolescence.[34] In most cases, this disorder is transient, lasting less than a year. If duration is longer, it is considered persistent or chronic. The disorder can involve motor or vocal tics alone. However, if there is a combination of multiple motor tics and one or more vocal tics, even at different times, this characterizes **Tourette syndrome**.[33] This may be associated with obsessive–compulsive behavior, hyperactivity, inattention, and learning difficulties.[33] Tics are much more frequent than myoclonic seizures, with which they are confused. Myoclonic seizures are faster, cannot be suppressed, and are not accompanied by a premonitory sensation; they can also occur during sleep.[33] Treatment involves psychoeducation, behavioral therapy, and pharmacological intervention when necessary. Clonidine, sulpiride, baclofen, topiramate, and typical and atypical antipsychotics may be used.[34]

Dystonia is usually associated with the use of medications, most often metoclopramide, bromopride, and neuroleptics. It should be emphasized that dystonia may occur as a side effect even when adequate doses of medications are used. Recovery is complete in minutes to hours. It is associated with muscular contractions, opisthotonos, torticollis, dysarthria, and eye movements. Biperiden or diphenhydramine can be used as antidotes in severe cases.

Gratification disorder (infantile masturbation) can be confused with involuntary movements or epileptic seizures due to their repetitive nature. This condition is characterized by pressure on the pubic and suprapubic region, rhythmic thigh movements accompanied by diaphoresis, facial flushing, and irregular breathing. It begins between 2 months and 6 years of age.[32] The movements cease with changes in environmental stimuli or distraction.[32] These behaviors rarely indicate obsessive–compulsive disorder, requiring behavioral therapy and medications such as serotonin reuptake inhibitors.

Spasmus nutans begins in childhood, typically between 4 and 18 months of age. This condition consists of nystagmus, head movements, and torticollis. It can be confused with myoclonic or tonic seizures. Consciousness is not compromised. Nystagmus is usually bilateral, horizontal, or pendular. It can be combined or uncombined. Unilateral or vertical nystagmus is less frequent. Neuroimaging and eye examinations should be ordered to rule out primary conditions such as brainstem lesions, glioma of the optic nerve or chiasm, retina problems, or severe deterioration of refraction. The prognosis is favorable, with symptoms disappearing 1 or 2 years after the condition begins.[32]

Opsoclonus consists of rapid, conjugated, chaotic, erratic, and involuntary eye movements in various directions and with variable amplitude (dancing eyes). It is often associated with myoclonus (trunk and head), ataxia, and irritability. It may be a manifestation of a paraneoplastic syndrome, especially in

neuroblastoma, or parainfectious syndrome. It usually occurs between 1 and 4 years of age, and the average age of onset is 18 months. Older children (over 9 years) are usually affected by infection, and these cases respond well to treatment with corticosteroids or have spontaneous regression. In paraneoplastic or idiopathic cases, treatment is more aggressive and involves a combination of corticosteroids, intravenous immunoglobulin, cyclophosphamide, plasmapheresis, mycophenolate, or rituximab. If a neoplasm is identified, it must be treated surgically.[35,36]

Tremors or chills usually begin in infancy and may occur several times per day. They involve axial muscles and may be associated with cervical and trunk flexion. The tremors are fast with low amplitude, and children refer to them as mild shocks. The episodes last only a few seconds. They happen during eating and during times of frustration, play, or happiness. They do not occur during sleep. Clinical examination and EEG results are normal. There may be a family history of epilepsy.[37] One recent study found no association with essential tremor and indicated that the median age of symptom onset is 13 months, with spontaneous remission between 3 and 7 years of age. Drug treatment is generally not necessary.[38]

Benign paroxysmal torticollis is a rare condition that begins in childhood at around 3 months with spontaneous remission by 5 years of age. It is characterized by episodes of cervical deviation, lasting minutes, hours, or sometimes days**.** It can be accompanied by pallor, agitation, and vomiting. Attacks can occur weekly or monthly and tend to resolve spontaneously. They are confused with tonic seizures, but consciousness is preserved and EEG result is normal during episodes. Between seizures, neurological examination, VEEG, and imaging results are normal. There is no need for treatment. Family history of migraine is common, and these children may develop migraine later in life.[39]

Essential tremor (ET) is typically of family origin; it involves postural or intentional active tremor in the hands and forearms. To a lesser extent, it may also affect the head, neck, voice, legs, and trunk. In 5%–30% of cases, onset occurs in childhood at around 6 years of age. Medical investigation usually occurs during adolescence. ET is a progressive condition, but may stabilize in adulthood. Depending on the severity and degree of incapacity, some cases should be treated with medications such as propranolol, primidone, gabapentin, topiramate, and clonazepam. In refractory cases, botulinum toxin and deep brain stimulation may be considered.[40,41]

Motor stereotypies usually begin before 3 years of age. The clinical condition is defined as involuntary, coordinated, and repetitive movements within a fixed pattern. The type of motion varies with each child; for example, it may involve flapping or undulations. There may also be head extension movements combined with eyes closing. Stereotypies occur during periods of joy, tiredness, monotony, excitement, or stress. These are suppressed by sensory stimuli or distraction and generally do not have a negative impact on the child's daily activities. They occur in healthy children, but worry parents and pediatricians due to similarities with stereotypies in patients with autism and intellectual disability.[32]

Paroxysmal dyskinesias (PDs) are a group of movement disorders characterized by sudden episodes of involuntary unilateral or bilateral movements; these movements may be choreic, ballistic, dystonic, or combination of these. PDs are categorized into three types. The kinesigenic type is triggered by sudden movements such as running or lifting and lasts <1 min; it is treated with anticonvulsants, with carbamazepine as the first choice. The non-kinesigenic type is triggered by drinking coffee or alcohol as well as fatigue or stress; it lasts from minutes to hours. Treatment involves avoiding triggering factors; clonazepam can be used. Finally, paroxysmal exertion--induced dyskinesia generally occurs after prolonged physical exercise and lasts for 2–5 min; treatment is a ketogenic diet. Some patients respond to gabapentin, levodopa, trihexyphenidyl, and acetazolamide; in resistant cases, stereotactic surgery can be used.[42]

Gastro-esophageal reflux disease (GERD) in children may manifest as non-epileptic paroxysmal events, mimicking an epileptic seizure. It may involve extension of the head and neck, irritability, deviation of head and eyes, contractions of the arms, sleep disorders, lip-licking or swallowing, weakness, flexor spasm, or myoclonus.[43] Sandifer syndrome is a rare complication of GERD and is characterized by sudden-onset transient spasmodic torsion dystonia, with posture in intermittent opisthotonos and torticollis. Chronic anemia may be present.[44] Paroxysmal changes from GERD may occur several times daily and are usually related to eating. The age of onset varies from the first weeks of life until adolescence.[32] The mechanism is not fully understood, but abnormal movements are understood to result from a mechanism to protect the airways from reflux material and relieve the discomfort of acid reflux.[43] The presence of other characteristics of GERD may strengthen the suspected diagnosis; these may include regurgitation and vomiting, refusal to eat, heartburn, nausea, epigastralgia, coughing, and wheezing.[45] Diagnosis is based on clinical history and physical examination. Complementary examinations and actions may be necessary, according to the patient's age (barium contrast study, esophageal manometry, PH-metry, impedance audiometry, upper digestive endoscopy, and empirical acid suppression testing).[45] Complementary testing for neurological deficit is negative. Treatment is based on specific measures for reflux and controls the seizures.[44,45]

Migraine-Associated Disorders[2]

Benign paroxysmal vertigo occurs in preschool-aged patients and is characterized by vertigo and recurrent episodes of imbalance. The child usually appears afraid, looking for a place or an adult to hold on to. The episodes are associated with nystagmus, loss of posture, pallor, sweating, and vomiting. They last for minutes without loss of consciousness. Episodes can occur daily, weekly, monthly, or even more rarely. Re-

mission is spontaneous after school age (average of 5 years). This condition is often confused with atonic seizures. Detailed anamnesis, clinical examination, and normal EEG clarify the diagnosis. Many patients develop migraine, with a positive family history in many cases. There is no need for treatment.

Migraine may induce syncope by affecting the basilar artery. Alternating hemiplegic migraine is characterized by flaccid hemiplegia on one or both sides, usually associated with autonomic phenomena. Seizures may be associated with strabismus, nystagmus, and tonic and dystonic phenomena. Onset occurs in the first 18 months of life and can be triggered by bathing and bright stimuli. Children can develop ataxia, developmental delay, and choreoathetotic movements. There is a familiar hemiplegic form, which starts later between 5 and 7 years of age. This form may be associated with nystagmus. Trauma, physical exercise, and stress can trigger episodes. Four genes have already been identified, which indicate involvement of sodium and calcium channels.

Mental confusion associated with migraine (confusional migraine) occurs in school-aged children and is characterized by episodes of agitation, disorientation, and little contact with the environment. It can last from 3 to 5 h and is often diagnosed as encephalitis or complex partial crisis, although automatisms are rare. These episodes progress to typical migraine conditions within weeks or months. During or after the events, the EEG results may show slowing in the tracing.

PSYCHOGENIC NON-EPILEPTIC EVENTS

Conversion Disorder

Psychogenic PNEs are understood, in the context of DSM-5, as manifestations of conversion disorder (CD), also called functional neurological symptom disorder.[33] In CD, there are one or more symptoms of motor function or sensory changes that are not well explained by other mental disorders or medical conditions.[33]

The psychogenic events resemble an EE, with changes in behavior, motor activity, consciousness, or sensation, but no epileptiform activity in the EEG.[8] These events are not uncommon in childhood and adolescence. Studies show a prevalence of 1%–9% in children with suspected epilepsy[46] and an occurrence of 3.5%–20% in VEEG studies.[47] Psychogenic events have been reported in children from 5 years of age; the frequency of this type of event increases with age, with psychogenic events being the most common non-epileptic events in adolescence.[48]

Identification of psychogenic PNE can be quite difficult, with a delay of up to 5 months to 7 years for a correct diagnosis.[49] Approximately 10% of patients with psychogenic PNE or PNE also have epilepsy.[4,50] Patients with associated conditions tend to use a greater number of antiepileptic drugs and fewer psychiatric medications in comparison to those with pure psychogenic events.[51]

Differential diagnosis should rule out **factitious disorder** and **simulation disorder**.[33] Factitious disorder is characterized by falsification of signs and symptoms or inducing injury or disease; fraud is identified, but obvious external gains are not. An example would be falsely reporting a seizure to the physician, without this generating some identified reward. Simulation, in turn, involves intentional and conscious production of signs and symptoms for personal gain (for example, simulating a seizure to miss class).

Psychogenic PNE in childhood can be classified as a motor event (body part or whole body), affective or emotional behavior (such as crying, screaming, and tantrums), dialeptic (absence of response to external stimuli, falling, and flaccidity), with "aura" (a subjective sensation during the event without external manifestations), or mixed (previously described phenomena associated).[47] In children aged <12 years, symptoms of falling (akinetic) are the most common, and boys and girls are equally affected. Between 12 and 18 years of age, motor symptoms predominate and prevalence is higher in females.[48]

The following characteristics of the event favors a diagnosis of psychogenic PNEs rather than EEs: longer duration, fluctuating course, uncoordinated and asynchronous motor phenomena, pelvic movements, opisthotonos, rotation of the body, side-to-side head movements, closed eyes, irritability during the episode, memory of the episode when the patient was apparently unconscious, lack of unresponsiveness or post-ictal confusion, and post-ictal flaccidity.[52,53] Recently, an instrument based on six of these characteristics was proposed as a practical aid for the correct bedside identification of psychogenic events. Eyes, head and limb movements, body line (opisthotonos), rotational movement, and symptom evolution are analyzed by this instrument.[53]

The features of EEs and psychogenic PNEs overlap, and diagnosis should consequently be based not just on presentation of one sign or symptom.[52] The description of the event by visual witnesses provides data that favor diagnosis.[7] The use of suggestion techniques to trigger the episode can be helpful.[52]

Specifically, with regard to the duration of the event, a study on adults has shown that the average ictal duration in psychogenic PNE is significantly longer than that in EE. An event lasting ≥5 min is 24 times more likely to be a psychogenic PNE.[54] Distinction between types of long events is especially important to avoid unnecessary invasive and iatrogenic treatment such as use of high doses of intravenous drugs, admission to the intensive care unit, and endotracheal intubation.[7]

Three main forms of EEG can be used in the investigation: VEEG, ambulatory EEG (AEEG), and conventional EEG. The gold standard for evaluation is VEEG,[47,52] which is traditionally performed at a specialized center, following standardized safety measures.[55] In cases of psychogenic PNE, absence of ictal changes and presence of the normal waking rhythm are expected before, during, and after the event recorded on video; the examination results should be carefully interpreted.[52] AEEG is carried out in an extended manner in the patient's normal environment, similar to the cardiac Holter monitoring.

It can be associated with video recording of events by the patient or by a family member/witness. Recent studies with the associated technique, called video-AEEG, have shown good results, with indices of diagnostic accuracy between 67% and 73%.[56,57] Conventional interictal EEG can assist in the level of suspicion of psychogenic PNEs when unchanged.

Based on investigation with a combination of positive clinical history, witnessed event, and EEG or VEEG, the paroxysmal event can be classified as possible, probable, or documented psychogenic PNE.[52] Additional tests such as serum prolactin level during the ictal period, variation in heart rate, pulse oximetry, psychological and cognitive evaluation, polysomnography, and cranial magnetic resonance imaging can add more data for understanding the case. However, there are no diagnostic tests for psychogenic PNE.[8]

One strategy that has been studied to assist in differentiation between EEs and psychogenic events, especially when VEEG is not available, is conversation analysis, i.e., analysis of the patient's description of the event. Patients with psychogenic PNE tend to be less collaborative, report almost complete amnesia of the event, reconstruct the event from the perspective of others, and describe the event as an internal entity.[58] Moreover, these patients have more complaints on a symptom review questionnaire and more anxious, panic-type symptoms than people with EEs.[59,60]

The etiology of psychogenic PNE is still not well understood. Specifically, for children and adolescents, the literature indicates association with medical comorbidities (including epilepsy) and psychiatric disorders, anxiety symptoms, stressful life events, family conflicts, parental tendency toward somatization (in themselves and in their children), and family psychopathology.[8] History of childhood physical or sexual abuse is a risk factor that has been identified in studies with adults.[61]

Recently, an explanatory model for psychogenic PNE has been proposed, which is intended to integrate previous conceptions, known as the integrative cognitive model. This suggests that the observable and subjective elements of psychogenic events result from the automatic execution of a learned mental representation of epileptic seizures, typically in a context of inhibitory dysfunction related to chronic stress, hyperactivation, and other factors affecting the individual's level of function. This representation comprises a sequence of perceptions and motor activities initially formed from experiences, acquired knowledge, and modeling. Activation of this sequence can be triggered by internal and external stimuli, such as a conditioned reflex.[62]

Treatment of psychogenic PNE should involve a multidisciplinary team to care for the child and family, with neurological, psychiatric, and psychological assistance. One important aspect is communication of the diagnosis. Initially, the parents and patient should be separately approached, so that questions can be effectively answered and to evaluate possible negative reactions from family members. It is recommended to conduct the conversation as a team, providing a review of the interdisciplinary diagnostic process and a discussion and interpretation of the objective findings. The team should clearly state that the condition is not epilepsy and explain that there is no simulation or intention on the part of the patient.[8] In cases with concomitant EE, it is important to address the differences between the types of events.[61]

Intervention strategies include psychoeducation and psychotherapy.[61] Comorbid disorders, learning problems, and issues related to school and peer relationships should be addressed.[8] Psychopharmacological treatment may be employed for comorbidities.[61] Early diagnosis and intervention, soon after the onset of symptoms, favor a good prognosis.[8]

One Brazilian study showed that specialized epilepsy centers have no specific intervention protocol for psychogenic PNE, although most centers act in a uniform manner. Furthermore, few services have a structured educational program for team training, and an important difficulty involves patient access to psychotherapy.[63] There is consequently a need to improve the interventions offered.

Panic Disorder

Anxiety disorders should also be considered in the differential diagnosis of non-epileptic paroxysmal events, particularly panic disorder. This consists of recurrent and unexpected episodes of sweating, palpitations, tremor, dyspnea, breathlessness, chest pain, abdominal pain, dizziness, nausea, paresthesia, chills, heat waves, derealization or depersonalization, and fear of dying. Signs and symptoms are intense and peak in minutes. There may be association with other anxiety disorders, depressive disorder, and suicidal ideation.[33]

According to a review study, the prevalence of this disorder in children and adolescents varies from 0.5% to 5%, but may reach 10% in child psychiatry services. Occurrence is most common in adolescence, with a peak between 15 and 19 years of age.[64]

Since the disorder involves intense somatic manifestations, it may be misdiagnosed as neurological (seizures, syncope, night terrors, and vestibular alteration), cardiovascular (arrhythmias, angina, and myocardial infarction), pulmonary (asthma), or gastrointestinal (irritable bowel syndrome) conditions. Psychoeducation, psychotherapy, and antidepressant medication (tricyclics and selective serotonin reuptake inhibitors) may be indicated for treatment.[64]

FINAL CONSIDERATIONS

This article reviewed the main non-epileptic events (physiological and psychogenic) that may be confused with seizures. The physician should know the clinical presentation and general lines of treatment for PNEs for early identification and appropriate intervention. Children and adolescents mistakenly diagnosed with seizures may undergo unnecessary testing, inappropriate treatment with antiepileptic medications, and negative psychosocial consequences.

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