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REVIEW PAPER

Paroxysmal non-epileptic events vs epilepsy – what we know and where we are in medicine?

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ABSTRACT

Introduction and aim. Paroxysmal non-epileptic events (PNEEs) are neurological conditions that include behavioral changes or disturbances of consciousness. The aim of the article is to compare individual paroxysmal non-epileptic events disorders, to indicate differences in their clinical picture and to discuss their differential diagnosis.

Material and methods. A review of the most common non-epileptic paroxysmal events is presented based on the available literature of PubMed and Google Scholar databases from 2000 to 2023.

Analysis of the literature. Depending on the age of the child, the nature and type of seizures are variable. Unfortunately, epilepsy is currently overdiagnosed, which results in the inclusion of antiepileptic drugs without the need to use them. This may be related to the immaturity of the central nervous system, malfunctioning of other organs or have a psychogenic background. In most cases, they do not require pharmacological treatment.

Conclusion. Paroxysmal non-epileptic events, due to the diverse and uncharacteristic clinical picture, pose a major diagnostic challenge. Because of the current overdiagnosis of epilepsy they should always bear in mind differential diagnosis. This is important because of the differences in the treatment of these disorders.

Keywords. epilepsy, non-epileptic seizure in childhood, paroxysmal non-epileptic events

Introduction

Paroxysmal nonepileptic events (PNEEs) are a diverse range of short-lived events characterized by sudden and brief alterations in motor or behavioral activity. These manifestations can closely mimic seizures, leading to clinical confusion.[1] Non-epileptic seizure disorders, due to the diverse and uncharacteristic clinical picture, pose a major diagnostic challenge. Unfortunately, epilepsy is currently overdiagnosed, which results in the inclusion of antiepileptic drugs without the need to use them. It is estimated that about 30% of patients who see a specialist with a diagnosis of epilepsy actually suffer from other non-epileptic seizure disorders.[2,3] In most cases, when epilepsy is suspected, patients are referred for a video electroencephalography (VEEG) examination. About 43% of them are diagnosed with PNEEs.[4] An important point to emphasise is that PNEEs with a lot of sundry symptoms such us vomiting, dizziness or irregular

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breathing can resemble all types of epileptic seizures.[5] Depending on the age of the child, the nature and type of seizures are variable. They may be related to the immaturity of the central nervous system or malfunctioning of other organs. In most cases, they are mild, subside spontaneously and do not require pharmacotherapy.[2,3] Recent studies report that the background of non-epileptic disorders is a combination of neurology and psychiatry representing nuerobehavioural conditions.[6]

Aim

The aim of the article is to compare individual paroxysmal non-epileptic events to indicate differences in their clinical picture, discuss their differential diagnosis, and compare their diagnostics to epilepsy.

Material and methods

A review of the most common non-epileptic paroxysmal events is presented based on the available literature of PubMed and Google Scholar databases from 2000 to 2023.

Analysis of the literature

Breath-holding spells

Breath-holding spells are among the most common non-epileptic seizure disorders in childhood. They affect about 5% of the population. They consist of a sudden cessation of breathing, preceded by crying or a strong emotional reaction, sometimes followed by loss of consciousness, hypotonia, and even seizures. Breath-holding spells, depending on the dominant clinical symptoms, are divided into cyanotic, pale and mixed. They are called affective because of the factors that trigger them – such as stress or strong emotions. Autonomic instability is suspected in the pathomechanism of seizures. Hereditary apnea is suspected in about a quarter of patients.[7] Attacks of breath-holding spells most often begin between 6–24 months of age. They disappear spontaneously between 5 and 6 years of age, sometimes a little later.[8]

Differentiation of breath-holding spells attacks from epileptic seizures remains a major clinical challenge. An epileptic seizure, unlike breath-holding spells, is not caused by an external factor. During the breath-holding spells, the EEG shows diffuse slowing of bioelectrical activity without convulsive activity. As with seizures, a child may or may not become excessively sleepy after breath-holding spells. Always include iron deficiency anemia in the differential diagnosis.

Breath-holding spells usually do not require treatment. However, recently published studies have shown significant efficacy of piracetam. In double-blind studies, a reduction and, in some patients, cessation of attacks of breath-holding spells after treatment with piracetam was observed.[7]

Vasovagal syncope

Vasovagal syncope (VVS), also known as orthostatic syncope, accounts for approximately 60-80% of syncope in children.[9] They are characterized by a short and sudden loss of consciousness. The reason for this is a temporary decrease in blood flow to the brain.[10] The main causes of vasovagal syncope include: extreme stress, nervousness, prolonged standing in a fixed position, especially in a standing position, sudden changes in body position, the sight of blood or external factors such as high temperature, staying in crowded places.[11] Fainting can occur after very intense training or insufficient hydration. Children who develop vasogal syncope usually do not need any treatment.[12] Lifestyle modification is often recommended drinking more water and avoiding stressful situations. It is worth obtaining a thorough medical history, information from witnesses of the event, and information from the child's guardians in order to exclude cardiac causes.

Stereotypies

Stereotypies are involuntary repetitive movements that are performed in a coordinated, rhythmic manner. It is important to emphasise that every healthy person manifests stereotypical behaviour on a daily basis, e.g. when swaying to music. Anxiety should only arise when the activity is performed intensively and over a long period of time. It may also involve self-injury or interfere with daily functioning. Stereotypies are characterised by an unusually high degree of individual variability and a wide range of movement types, some of which disappear over the course of life and others persist and intensify. It is very difficult to clearly define and classify the condition, as it may be manifested by walking in circles in some people and licking the lips or picking at the skin in others. It is often confused with nervous behaviour, as it is often performed under a strong stress stimulus. Repetitive movements are often seen in infancy and in young children. They are also characteristic of people with developmental delay. It is important to emphasise that stereotypies occur in both children with normal development and those with any disorder. Initially, they may take the form of involuntary and aimless movements, only to become more conscious and deliberate as the child grows up. Usually, a properly performed differential diagnosis and a correctly made diagnosis are sufficient to provide the necessary information to parents without introducing a therapeutic process.[13]

Paroxysmal dyskinesias (PDs)

Paroxysmal dyskinesia is a condition in which there are characteristic sudden, violent, uncontrollable movements that can affect various parts of the body without impairment of consciousness. They may include involuntary movements of the face, arms, legs or other

muscles. This type of dyskinesia is considered a movement disorder and may resemble the symptoms of epilepsy. They can occur in children of all ages, but are more common in older children and teenagers, especially those aged 7 to 15 years. We distinguish primary and secondary characteristics.[14] Diagnosing paroxysmal dyskinesia in children can be difficult because the symptoms may be transient and mimic other movement disorders. The causes of paroxysmal dyskinesia in children are not fully understood. In some cases, they may be related to genetic factors, and may also be related to abnormal functioning of the nervous system. Sometimes paroxysmal dyskinesia can be caused by the use of certain drugs, chemicals. Factors causing paroxysmal dyskinesia may also be physical exertion or fatigue.[15]

The first descriptions of this condition appeared in 1977. The classification distinguishing these disorders was established 18 years later, and in 2004, the classification of paroxysmal dyskinesias, which is currently in use, was created. Currently, the following forms of the disease are distinguished: kinesigenic paroxysmal dyskinesia, paroxysmal non-kinesigenic dyskinesia, exercise-induced paroxysmal dyskinesia and paroxysmal hypnogenic dyskinesia. Typically, the diagnosis is based on patient or family reports, as these symptoms are rarely witnessed by a doctor.[16,17]

Paroxysmal kinesigenic dyskinesia (PKD)

Paroxysmal Kinesigenic Dyskinesia are among the most commonly encountered types of paroxysmal dyskinesias. They are triggered by sudden movements, changes in direction, or surprises. The most characteristic symptom is dystonia. The duration of an attack is very brief, ranging from a few seconds to a few minutes. Attacks can occur up to 100 times a day. This disorder is more commonly seen in men, occurring four times more frequently than in women. In most cases, the initial symptoms appear during childhood. Typically, the symptoms peak during adolescence, and remission is possible in adulthood.[18]

PKD diagnostic criteria:[19]

- triggered by movement
- onset between 1 and 20 years of age
- attack duration less than 1 minute
- no loss of consciousness during the attack
- good response to antiepileptic treatment
- absence of pain during the attack
- symptoms of attacks include dystonia and/or chorea

Mutations in the PRRT2 gene are the main factor causing the isolated form of paroxysmal dyskinesia. Such a mutation is present in 27% to 65% of cases.[20] It is also worth emphasizing that paroxysmal dyskinesia induced by movement may also be caused by secondary factors, such as strokes, multiple sclerosis or metabolic disorders.[16,21]

Paroxysmal non-kinesigenic dyskinesia (PKND)

Non-kinesigenic paroxysmal dyskinesiasare characterized by episodes of dystonia and/or chorea that occur without a clearly defined, immediate trigger. These episodes last longer than PKD, ranging from several minutes to even several hours.[20] Episodes of this form can be exacerbated by caffeine, alcohol, feelings of fatigue, or intense emotional stress. The frequency of episodes varies - attacks may occur several times a week but can also be sporadic, happening only a few times throughout one's lifetime. Most commonly, patients experience attacks from 1 to 3 times a day or twice a year. Similar to PKD, these attacks are more frequent in men.[18]

Diagnostic criteria for PNKD:[22]

- symptoms of attacks include dystonia and/or chorea
- no loss of consciousness during the attack
- onset of the disease typically occurs in childhood
- lack of a clear triggering factor, although precipitating factors may be present
- duration of attacks: from 10 minutes to 4 hours
- antiepileptic treatment, except for benzodiazepines, usually does not provide significant improvement.

Paroxysmal exercise-induced dyskinesia (PED)

Paroxysmal exercise-induced dyskinesiasare seizures characterized by the occurrence of dystonia and/or chorea triggered by physical exertion. The attack typically initiates in the muscles that were most heavily stressed during the physical activity.[16] The variety of attacks is wide, but most often these dystonias affect the legs. The condition usually first appears in childhood. The occurrence of seizures is observed in a male-to-female ratio of 2:3.[18]

PED diagnostic criteria:[23]

- trigger factor: exercise
- duration of attacks: from 5 minutes to 30 minutes
- dystonia and/or chorea attacks
- no loss of consciousness during the attack
- no significant response to antiepileptic treatment
- the onset of the disease typically occurs in childhood.

Paroxysmal hypnogenic dyskinesia (PHD)

Paroxysmal hypnogenic dyskinesia involves sudden episodes of dystonic and tonic movements that occur during sleep.[20] The duration of an attack ranges from 30 seconds to 50 minutes. The frequency of occurrence varies widely, from several episodes per night to several episodes per year. These attacks are more common in men than in women.[18] Currently, PHD is mostly considered a form of frontal lobe epilepsy, known as autosomal dominant nocturnal frontal lobe epilepsy.[16]

Tourette syndrome (TS)

Tourette syndrome is a neuropsychiatric disorder characterized by chronic motor, vocal or phonic tics and often accompanied by obsessive compulsive disorder and

attention deficit hyperactivity disorder. It has an incidence of 7.7 per 1,000 children, with a 4-fold prevalence in boys. The maximum severity of tics occurs between the ages of 10 and 12. Genetic, environmental and immunological factors are responsible for the development of TS. Typical motor tics include eye blinking, arm jerking, head jerking, facial grimacing, nose rubbing. Vocal tics include grunting, sniffing, clucking, squeaking. Coprolalia is characteristic of TS. Motor tics usually precede vocal tics. As many as 85% of children with TS have one or more comorbid neurodevelopmental or psychiatric conditions, such as attention deficit hyperactivity disorder and obsessive compulsive disorder. Therapy of patients with TS should be tailored to individual needs and focused on the most troublesome tics. Patient, family and school education is a key element of successful treatment. Some patients do not necessarily require specific therapy. Sometimes education about the disease is enough. If the tics are severe and cause functional impairment, pharmacological intervention may be indicated. Sometimes education about the disease is enough. If the tics are severe and cause functional impairment, pharmacological intervention may be indicated. Sometimes education about the disease is enough. If the tics are severe and cause functional impairment, pharmacological intervention may be indicated.[24-26]

Hyperekplexia

Hyperekplexia is a rare neurological disorder characterized by an exaggerated startle response, which can manifest as sudden eye blinking or body spasms in response to tactile or auditory stimuli.[27] During seizures, individuals with hyperekplexia may experience severe rigidity in their trunk, limbs, and, in some cases, even their respiratory system, which can lead to life-threatening laryngospasms. Additional symptoms may include muscle twitches and clenched fists. While the onset of hyperekplexia can occur during fetal life, it more commonly presents after birth or during childhood.

The inheritance pattern of hyperekplexia typically follows an autosomal dominant trait, although autosomal recessive or, rarely, X-linked inheritance has also been reported. Typically, hyperekplexia is caused by mutations in the alpha 1 subunit of the glycine receptor gene, known as GLRA1.[28] The exaggerated startle response observed in hyperekplexia can manifest as rapid jerks or a series of jerks, which can sometimes mimic myoclonic, tonic, or tonic-clonic seizures. VEEG plays a valuable role in aiding the diagnosis of this condition. In the full range of typical epileptic seizures in the case of hyperflexia, no changes are visible in the VEEG recording.[29]

Episodic ataxia

Episodix ataxiasare autosomally inherited disorders. A mutation in the potassium gated release KCNA1 gene is responsible for the development of coba.[30] It occurs with a frequency lower than 1/100,000, but this data may be inaccurate due to unknown genes that could be responsible for the condition.[31] Episodic ataxia causes difficulties with activities such as maintaining balance, walking, and movement. These symptoms can also be accompanied by pain, dizziness, double vision and dysarthria. This condition can occur daily or sporadically.

Muscle tremors

Muscle tremors are involuntary, rhythmic, oscillating movements of equal amplitude around a specific axis. They are divided into fine waves of high frequency (>6 Hz) and low amplitude (<3 cm) and coarse waves of low frequency and high amplitude. They can be recurrent, and then they are called tremors.[32] They occur in up to two-thirds of newborns during the first three days of life. Their intensity increases during crying. The pathogenesis of their formation is not precisely explained. One theory is that tremors are related to the immaturity of spinal inhibitory interneurons. There are also reports of the possibility of tremors occurring as a result of elevated concentrations of catecholamines in the blood. Tremors may also be a symptom of other conditions, i.e.: hypoglycemia, hypocalcaemia, sepsis, hypoxic encephalopathy, intracerebral bleeding or drug discontinuation.[33] Muscle tremors must be distinguished from epileptic seizures. Unlike seizures in epilepsy, muscle tremors can be triggered by various stimuli. They are not accompanied by forced opening of the eyes, hypertension or apnea. Muscle tremors can be stopped by gentle, passive flexion and immobilization of the trembling limb. If muscle tremors are not associated with perinatal complications, where the risk of long-term neurological complications reaches 30%, their prognosis is good. Most resolve spontaneously by 6-10 weeks of age. When diagnosing recurrent seizures in children, blood glucose and calcium levels should be checked first. Imaging tests and a thorough interview with the child's guardian are also important in order to exclude recent drug withdrawal.[33,34]

Migraine and Alice in Wonderland syndrome

According to the latest data, migraine may affect 10% of school-aged children.[35] Symptoms of the disease in the pediatric population are often less severe and diagnosis is more difficult than in adults. Migraine is most often manifested by a severeheadache, which may be accompanied by sensitivity to light, sounds and nausea. Migraines occur with the same frequency in girls and boys until late puberty. Later, the disease is more common in girls.[36] The disease can cause problems with concentration and memory, which is associated with poorer educational results at school and problems with peers. Basilar migraine also known by the name migraine

Table 1. Comparison of the characteristics of paroxysmal non-epileptic events and epileptic seizure*

Features	Onset	Ending	Duration	Trigger factors	Clinical picture	Treatment
Breath-holding spells	6–24 months of age	5–6 years of age	less than one minute	anger, frustration, fear or injury	crying with cessation of breathing, cyanosis, loss of consciousness and muscle tone, opisthotonus, jerks	not require treatment or piracetam
VVS	variable	variable	10–30 second	prolonged standing, dehydration, abnormal posture, emotional stress	visual and/or auditory progressive fading, pallor, diaphoresis, after that flaccidity, with or without brief myoclonus, opisthotonus (rare)	Avoiding triggers, discontinuing medicines that lower blood pressure, drinking plenty of fluids
Stereotypies	between 2 and 5 years	may occur in adulthood, especially in patients with intellectual disabilities	from a few seconds to a few hours	excitement	repetitive movements or sounds	cognitive behavioural therapy (CBT), self-help
PKD	6 months	33 years old, possible remission in adulthood	from a few seconds to a few minutes	sudden movements, changes in direction, or surprises	mutual dystonic movements or involuntary unilateral movements or dysarthria.	low doses of antiepileptic drugs
PNKD	childhood, about 8 years old	the severity of attacks decreases with age	from 10 min to 4 hours	alcohol, smoking, stress, coffee, tea, fatigue	attacks of dystonia and/or chorea	benzodiazepines, deep brain stimulation, antiepileptic drugs, except for benzodiazepines, typically do not produce the desired results
PED	2 years	30 years old	from 5 min to 30 min	exercise	dystonia, most often affects the legs	symptomatic treatment with antiepileptic drugs can sometimes be effective, while at other times, treatment of the underlying disease may yield results
PHD	childhood or early adulthood	around adolescence or early adulthood	about 45 seconds	occur only during sleep	attacks of dystonic and tonic movements	antiepileptic drugs
TS	childhood, especially from 4-6 years, symptoms must have occurred before the age of 18	lasts a lifetime	tics may occur individually or in series	anxiety, excitement, stressful events, fatigue, allergies, systemic diseases	chronic motor, vocal or phonic tics	cognitive behavioral therapy
Hypereklpexia	fetal life, more commonly presents after birth, childhood.	variable	loud of sudden noises, stress, anxiety	astonishment	sudden eye blinking or body spasms in response to tactile or auditory stimuli, rigidity in their trunk, limbs, and, in some cases, even their respiratory system	speach and language therapy, play-based applied behavioral analysis
EAs	childhood or adolescence	variable	from a few seconds to several days	stress, sudden movements, alcohol, caffeine, heat, fever	attacks of cerebellar ataxia, dysarthria, tremor, vertigo, nausea, diplopia, dystonia	acetazolamide
Muscle tremors	first three days of life	6–10 week of age	variable	crying	involuntary, rhythmic, oscillating movements of equal amplitude around a specific axis	can be stopped by gentle, passive flexion and immobilization of the trembling limb
Migraine	childchood or adolescence	lasts a lifetime	from 5 to 60 minutes	stress, fatigue, alcohol, drugs, smoking, weather changes, unpleasant odors	severe headache, which may be accompanied by sensitivity to light, sounds, nausea	analgesics, triptans, ergotamines, calcitonin gene-related peptideInhibitors, beta-blockers, antidepressants, antiepileptic drugs, calcium channel blockers
Epileptic seizure	variable	variable	1–2 minutes	stress, fatigue, missed medications, alcohol, drugs, lack of sleep, menstruation, nutrient deficiencies, systemic diseases	uncontrollable jerking movements of the arms and legs, loss of consciousness or awareness, fluttering eyes, staring blankly into space, stiffness, strange sensations, unusual smells or tastes, and a tingling feeling in your arms or legs	anti-epileptic drug: sodium valproate carbamazepine lamotrigine levetiracetam topiramate; epilepsy surgery, vagus nerve stimulation, deep brain stimulation, responsive neurostimulation, ketogenic diet

* VVS – vasovagal syncope; PKD – paroxysmal kinesigenic dyskinesia; PNKD –paroxysmal non-kinesigenic dyskinesia; PED – paroxysmal exercise-inducded dyskinesia; PHD – paroxysmal hypnogenic dyskinesia; TS – Tourette syndrome; EAs – episodic ataxia

with brainstem aura is a disorder that can last from 5 to 60 minutes. This form is characterized by the onset of symptoms associated with brainstem dysfunction. Dizziness, tinnitus, diplopia, visual disturbances and dysarthria may be present. Disturbances of consciousness have also been reported in children, but these symptoms were very rare. Then, after the onset of such symptoms, headache appears, which is located in the occipital region, which distinguishes this type of migraine from other types where the pain is in the frontal or temporal region.[37] The Alice in Wonderland Syndrome can be a part of the migraine aura or, more commonly, herald the onset of migraine in the future. It is a condition that was discovered in 1955. The name refers to the main character in Lewis Carroll's book 'Alice in Wonderland', who often perceived her body as smaller or larger than

it was. The syndrome is characterised by an inadequate, distorted perception of one's own body schema and that of other objects. A person affected by the syndrome may experience changes in the perception of object size, distance, shapes and proportions.[38] The pathogenesis of the syndrome is not yet fully understood. Cases have been reported in the literature where onset has been linked to infections of viral and bacterial origin.[39] It can be associated with viral infection caused by viruses such as: Epstein-Barr, varicella and Cytomegalovirus. Among the most common bacterial infections, Mycoplasma pneumoniae, Borrelia burgdorferi and Streptococcus pyogenes were distinguished. It is very important that each person with the syndrome undergoes a thorough neurological examination, performs magnetic resonance imaging, EEG and collects cerebrospinal fluid.[38]

Summary

PNEEs are neurological conditions that involve changes in behaviour or disturbances of consciousness. They represent a difficult diagnostic and therapeutic medical problem. They are often confused with epileptic seizures, which give a very similar clinical picture to the symptoms presented. Comparison of the characteristics of paroxysmal non-epileptic events and epileptic seizure presented in Table 1.[7,8,10-13,16,18-20,22-27,30-33,40-43] The list includes features, duration, time of onset and end of features, trigger factors, clinical picture and treatment.

However, they are not caused by abnormal electrical discharges in the brain. It is extremely important to take a thorough history from the parent, as a misdiagnosis may result in overly unnecessary diagnostic tests and cause damage to the child's social functioning. PNEEs encompasses conditions spanning all age groups from newborns to adults. Unlike adults, children do not experience the psychogenic nature of the disorder. Video recordings of seizures at home and provocations with a placebo test can be helpful in differentiating epileptic seizures from other disorders.[44,45] An important point to emphasise is that PNEEs often mimic non-epileptic seizures due to the similarity of clinical symptoms such as syncope, loss of consciousness, headache, vomiting, dizziness, irregular breathing or emotional and psychological problems.[1] There is no single specialised medication or treatment method specific to PNEEs that can help young patients. So far, mainly psychological and psychiatric care has been used, as well as treatment of any comorbidities (e.g. cardiac problems with vasogastric syncope).[46] It is extremely important in the treatment process to orient the patient to the reported problem. Therapy with a psychologist to help the young patient cope with daily functioning plays an important role.[47]

Conclusion

PNEEs represent a diagnostically and therapeutically difficult group of conditions specific to early childhood. Careful attention should be paid to the symptoms presented by patients, as a misdiagnosis can have a huge impact on their future. Pre-diagnosis of epilepsies is a huge problem in today's society, so special attention should be paid to the initial diagnosis.

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Author contributions

Conceptualization, B.S., A.Z. and K.S.; Validation, B.S., A.Z. and W.S.; Resources, A.Z., W.S. and M.Ż.; Data Curation, B.S., A.Z. and N.W.; Writing – Original Draft Preparation, B.S., A.Z., W.S., M.Ż. and N.W.; Writing – Review & Editing, B.S., A.Z., W.S. and N.W.; Supervision, K.S. and M.C.K.; Project Administration, B.S., K.S. and M.C.K.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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