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Paroxysmal Dyskinesia.
Literature Review

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Content

Summary

Among rare genetical diseases, paroxysmal dyskinesia is one of them. It belongs to a heterogeneous group of neurological disorders with a complex pathophysiology, that is still not completely understood. Beyond that, there are multiple forms of the disease with a different pathophysiology, leading to the occurrence of a variety of symptoms. Among the leading symptoms are recurrent attacks of involuntary movement in a dystonic, choreatic or ballism-like manner without loss of consciousness. Paroxysmal dyskinesia can be classified into subgroups, including paroxysmal kinesigenic dyskinesia, paroxysmal non-kinesigenic dyskinesia and paroxysmal exercise-induced dyskinesia. The differential diagnoses incorporate, depending on the subtype, epileptic seizures, Sandifer syndrome, benign paroxysmal torticollis, transient dystonia of infancy, dopa-responsive dystonia, autoimmune disorders, focal seizures, Sydenham's chorea, anti-phospholipid antibody syndrome, GLUT-1 deficiency syndrome and paroxysmal-episodic ataxia. The diagnosis is composed of a detailed history taking and physical examination according to the clinical features. If the presenting clinical symptoms and the underlying etiology fit together and all other possible causes are ruled out, the diagnosis paroxysmal dyskinesia can be established. Treatment is depending on the subtype of the disease. Treatment options for affected patients consist of pharmacological choices and lifestyle changes. Among the pharmacological treatment options are low-dose antiepileptic drugs, like carbamazepine. Lifestyle changes are made up of the reduction of triggers and a ketogenic diet. In majority of cases, the disease shows a partial or complete remission of symptoms in adulthood.

Keywords: paroxysmal dyskinesia; paroxysmal kinesigenic dyskinesia; paroxysmal non-kinesigenic dyskinesia; paroxysmal exercise-induced dyskinesia; dystonia; PRRT2; PNKD; MR1; GLUT1; ECHS1; SLC2A1; GCH1

Introduction

In 1940, Mount and Reback described a 23-year-old male with involuntary, prolonged, writhing movements of the trunk and extremities caused by the consumption of coffee and alcohol. They named the condition paroxysmal dystonic choreoathetosis (4). A few years later, in 1967, Kertesz reported a family with episodic attacks of involuntary movements. He described attacks with short duration that were triggered by sudden movements. The patients improved clinically with the intake of anticonvulsants (carbamazepine). Kertesz named this disorder paroxysmal kinesigenic choreoathetosis (5). In 1977, Lance described the third form of the same disorder.

His patients were a family with attacks, that were triggered by prolonged physical activity lasting from 5 to 30 minutes. He named this syndrome as the intermediate type (6). Demirkiran and Jakovic linked these syndromes and formed the first classification under the name paroxysmal dyskinesia in 1995. They proposed a classification with four subgroups: paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), paroxysmal exercise-induced dyskinesia (PED) and paroxysmal hypnogenic dyskinesias (PHD) (7). Later PHD was removed from this classification and renamed as autosomal dominant nocturnal frontal lobe epilepsy (8).

Paroxysmal dyskinesia is a heterogeneous group of neurological disorders, which include recurrent attacks of involuntary movements without loss of consciousness. The involuntary movements can be classified as dystonia, chorea, ballism, or a combination of them and they vary largely in the duration of the attacks (1). The medical terms paroxysmal and dyskinesia implicate a broad description for this disorder. Paroxysmal arrives from the Greek word paroxusmós, which translates into attack, sudden increase, or recurrence of symptoms (2). The word dyskinesia has its origin in the Greek language as well and means impairment of performing voluntary movements resulting in fragmented or jerky motions (3).

The etiology of paroxysmal dyskinesia is very broad. This disorder could be primary, which means it develops because of a mutation in a gene, and secondary due to another disease. Secondary paroxysmal dyskinesia is caused by autoimmune, vascular, or metabolic disorders. This paper will focus on the primary paroxysmal dyskinesia due to the limited volume of the paper.

This work aims to convey a better understanding of paroxysmal dyskinesia by reviewing and summarizing the rather rare and relatively newly discovered neurological disease and its subtypes, including clinical picture, etiology, pathogenesis, diagnosis and treatment. The goal of this narrative review is to recognize and condense previously published material, providing a base for ongoing discussions, evaluating prior research, pinpointing areas in need of further investigation, and speculating on the most recent accessible interventions.

The search was conducted on PubMed, SpringerLink, National Library of medicine, and google scholar with the keywords: paroxysmal dyskinesia; paroxysmal kinesigenic dyskinesia; paroxysmal non-kinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia, dystonia, PRRT2, PNKD, MR1, GLUT1, ECHS1, SLC2A1, GCH.

56 out of 127 literature sources were used to give an overview on the topic. Following criteria let to the inclusion of the literature: articles, which focused on one or more of the above-mentioned subtopics, studies that were conducted on human or on mice and then later connected

to humans, studies that were not older than 10 years, unless they still had a clinical relevance on the topic and the study results were still up to date.
Following criteria let to the exclusion of the literature: studies older than 10 years, written in another language than English, meta-analyses, non-significant results of the study, and studies conducted for animals and not connected to humans.

Classification

Paroxysmal dyskinesia (PxD) is a group of rare neurological disorders characterized by episodes of involuntary movements. The classification of paroxysmal dyskinesia has evolved based on the advances in the understanding of the underlying mechanisms and clinical features. As previously mentioned, the first classification of PxD was proposed by Demirkiran and Jankovic. This classification is mainly based on the preceding triggers. According to their classification, PxD can be divided into paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), and paroxysmal exercise-induced dyskinesia (PED). The second category focuses on the duration of the attack. The third category puts the focus on the etiology, which then divides PxD further into a family/sporadic type and a secondary type (7). Some authors claim, that the familial/sporadic PxD can be referred to as primary PxD (usually genetically), and the secondary PxD is related to another disorder (9). In this paper, I will refer to as primary PxD as the one, that has an underlying genetic cause or a sporadic etiology as primary PxD. With the increase in scientific research in the genetical field, Bruno et al redefined the classification of PxD and proposed a new definition with a genotype and phenotype correlation. This could suggested, that each subtype of PxD is related be assigned to a specific gene (10,11).
Nevertheless, with the progression in research, this suggestion was refuted in 2014 by Erro et al, who proposed a new classification for primary paroxysmal dyskinesia (PxD) based on a review of 500 genetically proven cases. This proposed classification of primary PxD is divided into two axes. Axis I will focus on the clinical characteristics, which are subdivided into inclusion criteria and exclusion criteria. The inclusion criteria deal with the type of attacks, attack duration, and triggers. The attack type includes episodes of dystonia, chorea, and ballism. The attack duration should be measured and can last from a few seconds to several hours. The trigger factor must be identified according to the type of PxD: PKD, which is triggered by sudden movements, acceleration, or intention to move; PNKD, which is provoked by coffee, alcohol, or other non-kinesigenic conditions; and PED, which is precipitated by prolonged

exercise. The exclusion criteria contain possible explanations for the symptoms due to another neurological condition or psychogenic factors.

Axis II concentrates on genetic characteristics, which include confirmation of a known mutation that induces PxD (i.e., PRRT2, MR1, KCNMA1, SLC1A1). If no mutation can be identified, this form is referred to as idiopathic (8).

In cases of secondary PxD, an underlying acquired condition must be identified, such as an autoimmune, vascular, or metabolic cause for the disorder (12).

1. Paroxysmal kinesigenic dyskinesia

PKD is the most common subtype of primary PxD and is inherited in an autosomal dominant manner. However, more than 25% of cases are sporadic. The prevalence is thought to be 1:150,000 (13), with the majority of cases being in China and Japan, followed by America and Europe (14). Males have a higher prevalence to develop the disease, with a male-to-female ratio of 4:1. In sporadic PKD, the male-to-female ratio is up to 1:8 (15). The onset of PKD can range from the first months of life up to 20 years. The trigger for the attacks is a sudden voluntary movement after rest, for example standing up from a chair or increasing the speed or amplitude of a certain movement (16). Additional possible triggers include emotional stress or stimulation by sound. The frequency of attacks can vary. Up to 100 attacks per day are possible, with the duration of the attack ranging from a few seconds to a few minutes, but in majority of patients it lasts less than one minute. The highest frequency of attacks is seen in puberty, and it decreases in adulthood (8). It is possible to have complete remission after 30 years of age. Having two attacks in a row is not possible, because excitable neurons have a refractory period during which it is unfeasible to trigger a new attack by voluntary movements. Many patients experience auras before an attack, which are described as numbness or muscle weakness. Some patients with PKD can slow down their movements and prevent an attack by recognizing the preceding aura. The most common identified types of attacks are a unilateral and bilateral dystonia. Beyond that, some patients show movements like chorea, ballism, or a combination of these three forms. Facial involvement might also occur (17).

1.1 Clinical features

PKD shows a heterogeneous clinical phenotype. To provide a sufficient overview of the clinical pictures, four different studies were analysed. The first study by Erro et al investigated 500 genetically proven cases of PxD, while the second and third study by Huang et al included 110

and 600 PKD patients, respectively. The last study by Bruno et al in 2004 evaluated 95 patients with idiopathic and familial PKD clinically.

PKD presents with a wide range in the age of onset in the different cohorts. Majority of patients experience their first attack in the first or second decade of life. The mean age of onset in different cohorts varies from 11 to 12 years (17,18).

Males are more often affected than females. In the cohort study of Huang et al, 110 patients with familial cases of PKD showed a male-to-female ratio of 2,7:1. However, in some studies, the ratio was 4:1. In sporadic cases of PKD, men are six times more often affected than women (18) (17).

PKD is typically triggered by sudden movements or physical activity, such as standing up, turning in bed, running, walking, or increasing the speed of movement. This kinesigenic trigger is present in 98% of cases. In some cases, the trigger may be a focal movement, such as movements of one arm. Non-kinesigenic triggers are less common, accounting for only 2% of cases. They can include emotional stress, fatigue, or alcohol consumption. Caffeine and physical fatigue are less frequent precipitants of PKD (11).

The phenomenology of PKD can vary widely among individuals, but typically involves abrupt, brief, and repetitive involuntary movements that are triggered by sudden movements or physical activities without loss of consciousness. These movements can be categorized into three main types: dystonia, chorea, and ballism (8).

Dystonia is the most frequent type of movement pathology seen in PKD, accounting for 57% to 62% of cases (11,18). It is characterized by sustained muscle contractions that can cause abnormal postures or twisting movements. Chorea, which is described by rapid, jerky, and unpredictable movements, is less common, occurring in only 4% to 15% of cases (8,18). Ballism, which involves sudden, flinging movements of the limbs, is very rare, accounting for less than 1% of cases (17).

In some samples, PKD can be associated with a combination of dystonia and chorea, or other movement types. This combination occurs in 33% to 67% of cases (8,11).

The side of action in PKD can also vary. Unilateral movements, affecting one side of the body, occurred in 17.6% to 41% of cases. Unilateral altering movements occurring on one side, and then switching to the other side, appeared in 4% to 12% of cases (8,11,18). Bilateral movements, affecting both sides of the body, existed in 25% to 55% of cases. Unilateral movements that turn into bilateral movements, affecting both sides of the body, were seen in 18% to 33% of cases (11,18). Different authors report a wide range of facial involvement in the different cohorts, varying from 22% (19) to 70%. The facial involvement is described as face

twitching, dysarthria, and rigidity of facial muscles. No pain was reported during the attacks and the patient remains neurologically unaffected between attacks (17).

Furthermore, complicated forms of PKD are also reported. These include additional syndromes like infantile convulsions, migraine, episodic ataxia and less often hemiplegic migraine (18).

The frequency of attacks in PKD can vary among individuals and can be influenced by various factors, such as stress or anxiety. The study by Erro et al with 374 PKD patients has shown, that attacks can occur on a weekly or monthly basis in some individuals (5,1%). In other cases, the attacks occurred more frequently, with less than 10 attacks per day reported in 13,1% of cases. Most identified cases (81.8%) have shown 10-100 attacks per day. An increased frequency of attacks has been seen during puberty (8).

The duration of attacks is generally described as very brief, lasting for less than one minute in most cases. More specifically, 93% of attacks lasted less than 30 seconds, while 100% of attacks lasted less than one minute, according to the study of Bruno et al 2004 (11). Other studies reported that 99%**Fehler! Textmarke nicht definiert.** of probands have attacks that lasted less than one minute. Only 1% of individuals with PKD may experience attacks lasting longer than one minute (17).

Aura, which is a subjective sensation that precedes the onset of an attack, is reported by a significant percentage of individuals with PKD. The reported frequency of aura varies among studies, starting from 48% (8) in some studies to 82% in other studies (11). It seems difficult for the patients to describe the aura. Aura might manifest as a focal numbness or tingling sensation in the extremities or an abnormal sensation in the affected limb preceding the involuntary movement (17). It is noteworthy, that some probands reported of being able to minimize the attack when experiencing aura by stopping their movements (8).

According to some studies, complete or partial remission occurred in approximal 50% of individuals with PKD (18). The age of occurrence of remission varied, but it is more likely to occur after puberty or in early adulthood (8).

It is important to note that these percentages may vary depending on the study and the population being studied.

1.2 Pathogenesis and Etiology

The most common genetical cause of PKD is the mutation of the proline-rich transmembrane protein 2 (PRRT2), but there have been other possible genetical causes identified, like SLC16A2, KCNA1, ADCY5, SLC2A1, SCN8A, SLC20A2, CLCN1, KCNMA1, DEPDC5 and even PNKD (20).

The gene for PRRT2 is located on chromosome 16q11.2 and consists of four exons, encoding a protein of 340 amino acids, the proline-rich transmembrane protein 2 (PRRT2). The protein is composed of a proline-rich, extracellular N-terminal domain and a membrane-bound C-terminal (21).

The pathophysiological mechanism behind PRRT2 related paroxysmal kinesigenic dyskinesia remains still largely unclear (22). About 95% of different PRRT2 mutations have been identified as a nonsense or frameshift mutation with autosomal dominant inheritance. The most common of these is the frameshift mutation (c.649dupC; p.Arg217Profs*8). It leads to a premature stop codon, generating an unstable mRNA or truncated protein, which is degraded. Majority of the PRRT2 mutations are predicted to be a loss-of-function mutation caused by Haploinsufficiency (23). The prevalence of PRRT2 mutation in PKD various from 34% to 80% (8,17).

PRRT2 is highly present in the human brain, particularly in the cerebral cortex, basal ganglia, and cerebellum. These locations match roughly with the symptoms associated with PKD (24).

The protein PRRT2 is mainly expressed in glutamatergic neurons and is located at the presynaptic level of the plasma membrane. It interacts with several other synaptic proteins, including SNAP25 (25kDa synaptosomal-associated protein), VAMP2 (vesicle associated membrane protein 2), and synaptotagmins (Syt) 1 and 2. These interactions implicate, that PRRT2 is involved in the calcium-sensing machinery, which is important for the final steps of neurotransmitter release (25).

Additionally, neurons with PRRT2 suppression display a significant impairment in the synchronized release of neurotransmitters at the site of excitatory synapses. However, there was no discernible effect seen on asynchronous release. Consequently, there was a notable increase in the ratio of asynchronous to synchronous release, suggesting that the fundamental process of vesicle fusion remains unchanged. The most likely cause of this dysfunction appears to be a specific defect in the coupling between calcium influx and exocytosis (24).

Furthermore, when examining short-time potentiation (STP) phenomena, which involves brief stimulations lasting two seconds and increasing frequencies ranging from 5 to 40 Hz, different effects were observed in excitatory (glutamatergic) and inhibitory (GABAergic) synapses. Excitatory transmission exhibits enhanced facilitation, whereas inhibitory transmission displayed enhanced depression (26).

Landolfi et al concluded from observing the imbalance of excitation and inhibitions in the short-term potentiation frequency domain, a state of hyperexcitability in neuronal network, where PRRT2 mutation is present. He suggested, that such a network dynamic could explain the

paroxysmal nature of dyskinesia, which manifest when the network is challenged with a kinesigenic trigger (24).

The study of Fruscione et al showed, that PRRT2 plays an additional physiological role in explaining some clinical features observed in humans. He demonstrated, that PRRT2 can act as a negative modulator with the voltage-gated sodium channels Nav1.2 and Nav1.6 at the axon initial segment site. The lack of PRRT2 causes a hyperactivation of the voltage-dependent sodium channel in homozygous mutated PRRT2 humans and mouse neurons, which results in an abnormal neuronal firing, which in turn can be fully reverted by reintroducing PRRT2 (23). Calame et al reproduce the human phenotype of PKD in their mice study. The mice showed a phenotype, which resulted in dystonic posturing attacks, lasting less than two minutes. They demonstrated with the use of lacZ staining and quantitative reverse-transcriptase PCR, that the highest expression of PRRT2 was found in multiple brain areas during the postnatal development, most notably in the cerebellum. This implicated, that the cerebellar cortex is the causal agent in developing the motor phenotypes, which are seen in PKD (27).

1.3 Differential Diagnosis

Because PKD is a rare neurological disorder with characteristics like sudden and involuntary movements of the limbs and trunk that are triggered by sudden movements or physical activity, there might be diseases with some similarities. The differential diagnosis for PKD includes several other movement disorders like psychogenic movement disorder. This disease may present with symptoms similar to PKD, such as sudden and involuntary movements. However, psychogenic movement disorders often show features of distractibility and variability in the clinical presentation. In addition, other differences to PKD are observed, including an adult age of onset, an altered level of responsiveness during attacks, and an atypical response to medications (28).

Primary paroxysmal non-kinesigenic dyskinesia (PNKD) and paroxysmal exercise-induced dyskinesia (PED) need to be differentiated from PKD as well. These disorders also involve paroxysmal movements and share similar features to PKD, but they are triggered by different factors and include distinctive clinical features. Primary PNKD is triggered by non-kinesigenic factors such as coffee, alcohol, psychological stress, and fatigue, whereas PKD is typically triggered by sudden movements. The attacks can be like PKD attacks but have lower frequency. PED differs from PKD in trigger type and attack duration. The involuntary movements in PED are induced by long continuous exercise, and the attack duration ranges from 5 to 30 minutes (20).

Seizures in epilepsy can sometimes present with involuntary movements that are triggered by sudden manoeuvres or physical activity, making it difficult to distinguish them from PKD. However, there are differences that can help to distinguish PKD from epileptic seizures. PKD attacks are stereotypic and triggered by specific factors, such as sudden movements, and are not accompanied by loss of consciousness. In contrast, epileptic seizures have a more variable presentation, might not have a clear trigger, and can be accompanied by loss of consciousness. Frontal lobe epilepsy is a common type of focal epilepsy in childhood. It may present with similar phenomenology as PKD, but with a slight disturbance in consciousness. Additionally, seizures of frontal lobe epilepsy can occur during sleep. This is very helpful to distinguish between these two syndromes (14).

Tics are also included in the differential diagnosis for PKD. Tics are characterised by brief, sudden, and repetitive involuntary movements, or sounds. The attacks of tics are generally shorter than those of PKD, usually lasting from several seconds to a few minutes (9).

Sandifer syndrome is a rare disorder that is typically seen in infants and young children who suffer from gastroesophageal reflux disease (GERD). It presents with paroxysms of head tilt, arching of the back, and twisting of the neck and trunk, which can be mistaken for PKD. Sandifer syndrome occurs typically after eating and is thought to be caused by the child´s attempt to relieve the discomfort of GERD (14).

Another differential diagnosis for PKD is hyperekplexia. This syndrome is characterized by abnormal movements like in PKD, which can be triggered by sudden noise or touch. Howsoever, the core feature of hyperekplexia is an excessive startle response, which is typically characterized by a blink reflex and flexor spasm of the trunk or limbs. The most striking feature of hyperekplexia is, that it presents from birth or is noted in the last trimester of the pregnancy, while PKD typically only manifest in later childhood (29,30).

Benign paroxysmal torticollis is also part of the differential diagnosis for PKD. It is indicated by recurrent episodes of head tilt, often associated with malaise, pallor, irritability, ataxia, and nausea or vomiting. In some cases, it may present with migraine and a form of aura. The episodes can last several hours and commonly resolve spontaneously. The condition typically presents in infants and young children and may resolve with the age of 5 or 6 years (30).

Transient dystonia of infancy is a condition that affects only infants, as the name suggests, and involves a sudden and abnormal posture of the infant’s upper limbs. The abnormal posture usually determines with voluntary movements. It typically appears between 5 to 10 months of age, lasts up to 5 years, and does not result in any remaining developmental or neurological

deficits. The cause and underlying mechanisms of this condition stay unclear, but medical professionals are actively researching this topic (30).

Since PKD presents with a large amount of differential diagnosis, it is important to take precise medical history and neurological examination, including an assessment of triggers, timing, duration, and characteristics of the attacks. Additional testing, such as imaging or neurophysiological testing, may also be required to distinguish between these disorders (14).

1.4 Diagnosis

It remains a challenge to distinguish PKD from other paroxysmal dyskinesias, including PNKD and PED, as well as from other differential diagnoses, particularly in very young children when the trigger may not be so obvious.

A detailed medical history and neurological examination and identification of any associated symptoms can help to diagnose PKD. Video documentation of the episodes play an important role, particularly in cases in which the attacks are not witnessed during clinical evaluation. Videos taken at home by family members or friends, demonstrate a useful tool to monitor the attacks and provide additional information, because the majority of patients with primary PKD show a normal neurological status between the attacks (28).

In 2021, Cao et al proposed new clinical diagnostic criteria based on the results of a large-scale study, in which 600 patients were analysed according to the phenotype and the genetic spectrum of PKD. In his diagnostic work up, he included three subgroups: core symptoms, supportive evidence, and possible disorders that may cause secondary PKD (14).

The presence of kinesigenic triggers, attacks presenting with dystonia, chorea, ballism, or a combination of them, and no impairment of consciousness during the attacks, are considered core symptoms.

Supportive evidence includes the presence of aura, attack duration under one minute, positive high knee exercise test, and good response to low-dose voltage-gated sodium channel blockers such as carbamazepine.

Furthermore, with positive core symptoms and one or more supportive evidence, is it possible to clinically diagnose PKD. To confirm primary PKD, secondary causes must be excluded. This requires plenteous testing for a detailed assessment, including testing of thyroid function (T3, T4, FT3, FT4, TSH, thyroid ultrasonography, and thyroid iodine uptake rate), calcium and phosphorus metabolism (serum phosphate and serum calcium), parathyroid hormone and calcitonin testing and cerebral CT scan to assess intracranial calcification, measuring of blood sugar, serum bilirubin, serum ceruloplasmin, performing a head MRI, EEG, and

neuropsychological assessment. If the tests show normal results, the diagnosis of primary PKD is confirmed. However, if abnormalities that suggest a secondary cause of PKD or comorbidity are found, further evaluation and appropriate management is needed.

Additionally, Cao et al indicated red flags in the diagnostic workup. They include an attack duration over one minute, the age of onset over 20 years, abnormalities in brain CT/MRI scanning or presence of other neurological symptoms. The red flags are not an exclusion criterion. They are meant to question the diagnosis, for example, PKD presents in most cases with an attack duration less than one minute, but it is possible to have a longer attack.

It is important to note, that genetic testing can support the diagnosis of PKD, but it is not mandatory, due to the natural remission and the good response to low-dose anticonvulsants. PKD is often attributed to hereditary factors, PRRT2 mutations are the most common genetic cause of primary PKD, and other genes such as PNKD, SLC2A1, SCN8A, KCNMA1, KCNA1, and DEPDC5 have also been linked to the disorder (14).

1.5 Treatment

The treatment of PKD relies on expert consensus, observational studies and anecdotal evidence. The existence of successful treatments before the identification of underlying genotypes suggests, that a therapeutic trial based on the phenotypes could be effective (16).

Low doses of antiepileptic drugs (AEDs), particularly carbamazepine, are effective in treating PKD. Carbamazepine is the first-line treatment of PKD. The reviewed literature reports, that a complete or partial remission can be achieved with a low dose of this drugs. The dosage usually ranges between 200 and 400 mg/day for adults or 1.5 to 2 mg/kg for children (31,32). A recent study proved, that oxcarbazepine and carbamazepine are equally effective, and oxcarbazepine is a good option when carbamazepine is not well tolerated by patients. The recommended dosage varies from 50 to 300 mg daily. It is important to remember, with introduction of the treatment, the initial dose should start from the lowest possible dosage and should slowly increase until the patient receives a satisfying relief of the symptoms (33).

Furthermore, several other AED, including phenobarbital (34), levetiracetam (35), gabapentin (36), valproic acid (37), lamotrigine (38) and topiramate (39), have demonstrated significant benefit as well. Alongside pharmacological options, there are other nonpharmacological approaches to manage the condition, such as avoiding known triggers like sudden movements. Managing stress, ensuring adequate sleep, and controlling anxiety can also help to reduce the frequency of PKD episodes (40).

2. Paroxysmal non-kinesigenic dyskinesia

2.1 Clinical features

Paroxysmal non-kinesigenic dyskinesia (PNKD) is a rare genetic disorder that is characterized by episodic and involuntary movements. Three different studies are included in this paper to analyse the reported clinical features of PNKD.

The study by Jarmen et al describes a large British family with dominate inheritance of PNKD, with 20 affected family members showing clinical features. The attacks in PNKD are precipitated by caffeine, alcohol, or emotions. The disorder was formerly described as paroxysmal choreoathetosis (41).

Bruno et al calculated in another study the penetrance of the myofibrillogenesis regulator 1 (MR1) gene in PNKD, with a penetrance of 98% (10). The study of Erro et al analysed 73 individuals with positive symptomatic PNKD and reported the clinical features of 71 patients (49 MR1 positive and 22 MR1 negative) (8).

The three studies showed, that the onset of PNKD occurred during early childhood. The sex distribution within the probands revealed, as in PKD, that men are more often affected than women. The male-to-female ratio ranges from 1,7 to 1,2:1. This indicates that males are slightly more affected than women (8,10).

PNKD can be triggered by a variety of factors, including caffeine or alcohol consumption. This was reported by 94.5% of patients. Stress or anxiety as triggers were reported by 82.2% of patients, excitement or laughing was reported by 15,1% of patients, prolonged exercise was reported by 19.1% and other factors as fever or tiredness were reported by 19,1% of probands (8). Other less common precipitants reported by Bruno et al included menstruation (in 6% of probands), heat (in 22% of probands), and hunger (in 6% of probands) (10). Patients may also experience prodromal sensations such as tingling in the skin and tightness of muscles, along with a feeling of inner tension and restlessness. In the study of Jarmen et al, 41% of patients experienced prodromal syndromes, 80% of them described focal limb sensations such as stiffness or numbness, and 20% of probands described an internal feeling of anxiety (41).

The majority of patients experienced a combination of dystonia and chorea (65,1% and 88% of the probands, respectively) (8,10). A smaller percentage of probands experienced only dystonia (about 20 to 30%), and 2% of the probands experienced only chorea. The attacks started in all cases in the limbs and progressed to hemidystonia (8). Speech involvement in severe cases is possible (41). Less common features of the phenomenology of PKND are blepharospasm, risus sardonicus, and diplopia at the peak of the attack (10).

When patients with PNKD grow older, usually there is a decrease in the frequency of attacks. In children and adolescents, the attacks can occur once per day up to once per week. However, in adulthood, the frequency of attacks decreases to once per month or even once per year (41). The duration of the attacks varies from 10 minutes to 12 hours, but in most cases, it ranges between 30 minutes to 2 hours (8). Patients also reported a different response while sleeping. In many cases it was possible to abort the attack with deep sleep. When sleeping was not possible, even relaxing could improve the outcome of the symptoms (10).

2.2 Pathophysiology and etiology

The most common cause of paroxysmal non-kinesigenic dyskinesia is the mutation of the PNKD gene (paroxysmal non-kinesigenic dyskinesia gene), formerly known as the MR1 gene. The gene is linked to the chromosome 2q35 and encodes three different PNKD proteins (paroxysmal non-kinesigenic dyskinesia protein): PNKD-Long, PNKD-Medium, and PNKD-Short. These proteins consist of 385 amino acids (PNKD-L), 365 amino acids (PNKD-M), and 142 amino acids (PNKD-S), respectively. The long isoform (PNKD-L) is expressed in the central nervous system, while the medium and short isoforms are ubiquitously expressed (42). The most common mutations are two missense mutations, p.Ala7Val followed by p.Ala9Val. The exact function of the PNKD protein is still not fully understood. It was initially thought that the PNKD protein is homologous with the hydroxyacylglutathione hydrolase (HAGH), which is expressed by the HAGH gene, because this subtype of PxD is triggered by alcohol, caffeine, and stress. HAGH plays a role in the catalysation of methylglyoxal to lactic acid and reduces glutathione, which can be found in alcoholic beverages and coffee. However, this theory was dismissed because of an in vivo study, which showed that PNKD-L could not improve HAGH activity (43).

A new study by Shen et al (44) proposed a novel concept for the function of the PNKD protein. Shen and colleagues localized PNKD-L in vitro in the cell membrane and defined the protein as a novel synaptic protein with an interaction between PNKD-L and the synaptic active zone proteins RAB-3-interacting molecule 1 and 2 (RIM1 & RIM2). RIM1 and RIM2 play an essential role in neurotransmitter release. The researchers showed, that in a mouse model with the wild type (without any mutations), the PNKD protein inhibits the RIM-dependent increase of neurotransmitter release. Shen et al observed in PNKD deficient mice a decrease of RIM levels, impaired synaptic transmission, and abnormal motor behaviour. They proposed a model, in which the function of the PNKD protein is to stabilize and inhibit the RIM-dependent pathway to suppress the presynaptic neurotransmitter release of calcium. With these results,

they concluded a new possible pathophysiological pathway of PNKD. At the presynaptic terminal, caffeine acts as an agonist at the ryanodine receptor and stimulates calcium efflux from the endoplasmic reticulum. Shen et al speculated, that in the case of a mutation of the PNKD gene, the neurons are more vulnerable to elevated calcium levels, which results in hyperexcitability when challenged with coffee, alcohol, and stress (44).

2.3 Diagnosis

PNKD is more difficult to distinguish from other episodic movement disorders than PKD due to the absence of a clear triggering event. Nevertheless, it is necessary to distinguish PNKD from other paroxysmal dyskinesias, seizures, tics, dopa-responsive dystonia, and functional movement disorders. Dopa-responsive dystonia is classically observed in childhood and can exhibit significant daily variations, with patients improving with rest and worsening with physical activity (9). Other potential differential diagnoses of PNKD are discussed in the PKD differential diagnosis part.

To diagnose PNKD, a detailed evaluation is necessary, which involves obtaining a thorough personal and family history and identifying the clinical characteristics of PNKD. These characteristics include episodes of dystonia, chorea, and/or ballism, with onset during infancy. Attacks may be provoked by alcohol or caffeine but are not typically triggered by sudden movement or sustained exercise. Episodes can last several minutes to hours and rarely occur more than once per day. During an attack, there is no loss of consciousness, and there is generally poor response to pharmacologic treatment, although clonazepam or diazepam can be effective (45).

A brain MRI is used to rule out secondary causes (9,45) of basal ganglia lesions caused by multiple sclerosis, including tumours, vascular lesions, penetrating brain injuries, and central pontine myelinolysis. In addition, the differential diagnosis should consider other conditions that may present with paroxysms of dystonia, such as autoimmune disorders, focal seizures, Sydenham's chorea, antiphospholipid antibody syndrome, and chorea gravidarum. Paroxysmal chorea can also be seen with systemic lupus erythematosus, diabetes mellitus, hypoparathyroidism, pseudohypoparathyroidism, and thyrotoxicosis. If these etiologies are taken into consideration, appropriate relevant laboratory testing should be conducted. EEG is an essential part of the investigations of focal seizures (45).

The diagnosis of PNKD can be established with the above-mentioned characteristics. To confirm the diagnosis, the identification of the heterozygous pathogenic variant in PNKD by a molecular gene testing is needed. A multigene panel testing is possible. It includes the PNKD

gene and other possible genes from the differential diagnosis like PKD (PPRT2 gene), glucose transporter type I deficiency syndrome (SLC2A1 gene), ADCY5 related dyskinesia, altering hemiplegia of childhood (ATP1A3 gene) and benign hereditary chorea (NKx2-1). Important to note is, that the confirmation of another gene does not ensure the exclusion of the previously diagnosed phenotype of PNKD (45). The mutation of SLC2A1 is most likely identified with PED, but there are cases in which this mutation results in the phenotype of PNKD (46).

2.4 Treatment

PNKD treatment primarily involves avoiding triggers such as caffeine and alcohol. Pharmacologic treatment response is limited, nonetheless benzodiazepines like clonazepam or diazepam were found to be effective in at least 50% of individuals with PNKD (31). Other medications such as gabapentin, levetiracetam, and acetazolamide have also been reported to hold some benefit (47). However, the response to antiepileptic treatment is limited, and carbamazepine is generally ineffective. Benzodiazepines remain the first-line treatment option, with clonazepam and diazepam being the most used. Other benzodiazepines like lorazepam and oxazepam show some effect as well. More drugs have been tried out with partial success, including haloperidol, anticholinergics, gabapentin, levetiracetam, nitric oxide synthetase inhibitors, adenosine agonists/antagonists, acetazolamide, piracetam, and levodopa. For ATP1A3, flunarizine is used to treat hemidystonic attacks, but other medications like topiramate, aripiprazole, steroids, amantadine, as well as oral ATP and a ketogenic diet have also been reported to have some benefit (9,45).

3. Paroxysmal exercise-induced dyskinesia

3.1 Clinical features

Paroxysmal exercise-induced dyskinesia (PED) is less common than PKD and PNKD. There are fewer systematic studies of this PxD phenotype. In the reviewed case report, the age of onset varies, but in majority of cases, the disease started in childhood or adolescence (48). Erro et al reported a mean age of onset of 15,8 +/- 12,4 years and a disease duration up to the age of 19 +/- 15,6 years (49). Because of the insufficient amount of diagnostic cases of PED, it is difficult to draw a conclusion about the gender distribution. Some resources report a 2:3 male-to-female ratio (15). The duration of attacks is very variable. Some literatures reveal a mean duration of up to 30 minutes and others documented a mean duration of 2 minutes to 2 hours (15,48). The frequency of attacks varies depending on the routine exercise level. The reported frequency

fluctuates from ones per day to 2 times per month (15). Different triggers were identified. In comparison to PKD, the trigger in PED is extensive exercise like prolonged walking, cycling or playing (49). Moreover, some sources reported prolonged writing as a trigger for upper limb dystonia. Furthermore, additional trigger were determined by Danti et al. They described besides exercise, fasting and fever as trigger for PED as well due to the increased energy metabolism (50). The phenomenology of PED was reported with dystonia and chorea predominantly in lower limbs, but also dystonia of the upper limb is possible in some cases (49).

3.2 Pathophysiology of PED

3.2.1 Pathophysiology SLC2A1

The main causative defect of PED is a mutation in the SLC2A1 gene, which encodes for the glucose transporter 1 (GLUT1). This mutation is inherited in an autosomal dominant manner and can lead to an isolated or complex phenotype of PED (Glut1 deficiency syndrome), which could be accompanied by epilepsy, ataxia, spasticity, dystonia, intellectual disability, migraine, hemiplegic attacks or episodic ataxia (50). The prevalence of SLC2A1 mutation in PED cases is less than 20% (15).

The variation in physical characteristics resulting from a mutation in SLC2A1 can be attributed to the type of genetic mutation. Loss of function mutations such as splice site, nonsense, insertions, and deletions are associated with a severe clinical phenotype of GLUT1 deficiency syndrome, which includes epilepsy, hypotonia, spasticity, ataxia, and developmental delay. In contrast, missense mutations are more frequently associated with PED, whether isolated or not (13).

Suls et al proposed in their study a hypothesis about the pathogenesis of SLC1A2 related PED. According to the researchers, the mutation leads to a reduction of glucose uptake at the blood brain barrier. The mutation does not affect the general function of GLUT1 to transport glucose across the membrane. On the contrary, it affects the general velocity of transport, which gives a possible explanation of the appearance of symptoms after a prolonged exercise. In case of prolonged exercise, the energy demand of the brain is higher than the supply (51).

3.2.2 Pathophysiology of GCH1

GCH1 related paroxysmal dyskinesia is a rare genetic disorder caused by mutations in the GTP-cyclohydrolase 1 (GCH1) gene, with autosomal dominant inheritance. GCH1 is the rate-

limiting enzyme in the metabolism of tetrahydrobiopterin (BH4), which is required for the synthesis of several neurotransmitters, including dopamine, serotonin, and nitric oxide (52).
The most common phenotype of GCH1 gene mutation is dopa-responsive dystonia (13). Dale et al reported a case about a family with paroxysmal dyskinesia, caused by a nonsense mutation, leading to a premature stop codon in the GCH1 gene. This mutation impairs the function of the enzyme, leading to a deficiency of BH4, which in turn impairs the synthesis of dopamine in the brain. Dale et al investigated a family with the clinical features of PED and the GCH1 mutations as causative cause. They explained, that the GCH1 mutation commonly causes dopa-responsive dystonia, and this mutation has heterogenous phenotypes between families and within families. In contrast, the investigated family member shared a homogenous phenotype of PED. This phenotype includes a childhood onset, dystonia that was triggered by exercise and attacks lasting several minutes. The researchers' possible explanation included a specific effect of this GCH-1 mutation (p.E84X) on the special phenotype or an unidentified gene, which modifies the dystonia phenotype (53).

3.2.3 Pathophysiology of ECHS1

The mutation of enoyl CoA hydratase 1 (ECHS1) follows an autosomal recessive inheritance. This mutation has a variable phenotype, which includes leigh syndrome or leigh-like syndrome, with different combinations of psychomotor retardation, epilepsy, spasticity, optic atrophy, sensorineural deafness or paroxysmal dyskinesia. PED can occur alone or in combination with other disorders (15). Olgiati et al showed in their study the phenotype of two siblings with the mutation of ECHS1. The older sibling presented with a phenotype of generalized dystonia with mild neurological and cognitive deficits and the two-years younger sibling showed a less severe phenotype of PED (54).
Missense mutations, such as p.Ala173Val and p.Lys273Glu, have been identified in patients with PED. These mutations affect the function of crotonase, which is involved in the catabolism of fatty acids and amino acids, such as valine. The mutations have been linked to a diminished pyruvate oxidation, ATP production, and activity of complexes I and IV of the respiratory mitochondrial chain. This results in the accumulation of toxic metabolites, such as methacrylyl-CoA, which can cause lesions in the basal ganglia (15).

3.3 Diagnosis

PED is a clinical syndrome with various underlying causes. Early recognition of the underlying condition is crucial as many of them are treatable, and a misdiagnosis could result in

inappropriate treatment. A syndromic approach, in which the age at onset, the inheritance pattern, and the presence of associated features are considered, may help clinicians in finding the right diagnosis. However, reliable clinical features, that aid in the differential diagnosis, especially in isolated cases of PED, are lacking. Thus, a systematic diagnostic workup is advisable when confronted with patients with suspected PED (13).

In 2021, Danti et al proposed a diagnostic approach for patients with PED and stated, that PED could be a part of a more complex phenotype (50).

The first step in forming a diagnosis correctly is to recognize the clinical phenomenology. Danti et al divided the phenomenology into three main groups including paroxysmal moment disorder, exercise intolerance and paroxysmal exercise-induced movement disorder and proposed for each group a diagnostic flowchart. PED is grouped together with episodic ataxia (EA) in the group of paroxysmal exercise-induced movement disorders. EA is subdivided into EA1 and EA1. To differentiate it from PED, the clinical features are used. EA1 is commonly reported with brief episodic attacks triggered by exercise with postural imbalance and dizziness, in contrast to PED, which presents usually with an attack duration of 5 to 30 minutes. EA2 presents with longer attacks, which could last up to several days. The episodes present with general weakness and vertigo (50).

Danti et al propound, that in cases in which clinical symptoms of PED present only in adolescence, it is recommended to perform a DAT scan to monitor the activity of the dopamine transporter. If the test is positive, it is recommended to test for a mutation of PARK2. One of the phenotypes of the mutation is juvenile parkinsonism, which is presenting with a mean onset of 30 years. Furthermore, there are cases in which PED presents as the first symptom of this disorder.

However, in case of childhood onset, a brain MRI is recommended. When the MRI presents in an abnormal manner, the diagnosis of symptomatic PED is suggested. Nevertheless, further metabolic testing such as lactate/pyruvate, plasma amino acids, and urine organic acid are recommended.

Danti et al suggested, in the absence of brain MRI abnormalities, biochemical investigation of the cerebrospinal fluid (CSF) is recommended to test for the levels of glucose, pterins, and dopamine metabolites. In the presence of low glucose levels in the CSF compared to the serum glucose, it is justified to do genetic testing of SLC2A1 mutation. SLC2A1 related PED could appear as an isolated form or as a more complex phenotype (GLUT1 deficiency syndrome).

Furthermore, CSF testing of pterins and dopamine metabolites such as tetrahydrobiopterin (BH4), homovanalinaic acid (HVA), and 5-hydroxyindolacetic acid (HIAA) is prudent. When

these laboratory markers present with low levels in the CSF, genetic testing for GCH1 mutation is appropriate. As in juvenile parkinsonism, PED may also be the first symptom to develop in dopa-responsive dystonia.

Danti et al recommended in case of a normal range of glucose, pterins and dopamine metabolites in the CSF to consider the previously mentioned metabolic investigations followed by genetic testing for ECHS1, HIBCH, DLAT, PDHA1, PDHX1, TBC1D24, ADCy5, PRRT2, and PNKD(MR1) (50).

3.4 Treatment

PED behaves differently in comparison to other subtypes of PxD. PED responds less effectively to pharmacological treatment. The treatment of PED depends on the different etiology, that is why the diagnostic workup of this subtypes is very important (50).

In case of SLC1A2 mutation with a GLUT1 deficiency syndrome, a ketogenic diet remains the golden standard and is proven to be effective in many cases. After starting this specific diet, patients experienced a partial or complete remission of the attacks (34)(55).

GCH1 related PED responses well to levodopa. L-dopa supplementations might be useful in patients with a parkin mutation, but anticholinergic drugs or botulinum toxin injections might be needed as well (13).

When PED is connected to a pyruvate dehydrogenase deficiency (mutation of ECHS1, PDHA1, DLAT, PDHX1), it responds well to thiamine and is therefore a partially treatable condition. Some cases show an improvement of the symptoms with a ketogenic diet. One case report described a beneficial outcome in a patient with ECHS1 related PED with treatment of a mitochondrial cocktail which includes thiamine, riboflavin, carnitine, coenzyme q, vitamin B6 and vitamin C (56).

Conclusion

This literature review suggests that paroxysmal dyskinesia is a rare genetic disease with a variety of subtypes, classified according to different triggers. In recent years there were plenty of new research projects to identify etiological causes for paroxysmal dyskinesia, with the help of the introduction of genetical screening.

There have been trials to investigate specific proteins in order to understand the underlying pathophysiology of the disease. Nevertheless, the need for more research to fully understand the pathophysiological mechanisms behind the disease remains.

The difficulty in conducting studies about paroxysmal dyskinesia underlies in the fact, that it is challenging to find appropriate probands due to the rarity of the disease.

Fortunately, there is a high chance for the disease to regress on its own or at least response well enough to symptomatic treatment, which ensures a good quality of life for the patients.

Once there is more research in the future about the exact pathophysiological mechanism, clinicians could provide the patients with more individualised treatment according to the underlying mechanism of the disease.

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