Title: Treatment of Paroxysmal Dyskinesia

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Synopsis
Paroxysmal dyskinesia (PxD) are a heterogeneous group of syndromes characterized by the recurrence of attacks of abnormal movements, triggered by detectable factors, without loss of consciousness. The abnormal movements may be dystonic, choreic, ballistic, or a combination thereof. According to the precipitating factors they are classified in paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), and paroxysmal exercise-induced dystonia (PED). PxD can have a primary or secondary aetiology. The primary forms are mostly due to a genetic defect, with PRRT, PNKD (MR-1) and SLC2A1 being the most common gene causing PKD, PNKD and PED respectively. However, recent findings have led to a better understanding of the broad spectrum of genetic conditions underlying PxD, highlighting a clinical and genetic overlap among the syndromes and refusing the concept of one gene causing one phenotype.

The treatment of PxD is based on the combination of non-pharmacological and pharmacological approaches. The former consists especially in preventing the attacks, avoiding precipitating factors. This strategy can be sufficient in controlling the symptoms in many cases of PNKD and PED; whereas PKD is characterized by having an exquisite response to antiepileptic drugs. Pharmacological and non-pharmacological treatments effective for PNKD and PED are also available. In PxD refractory to conventional treatment, surgical approach might be an alternative therapeutic option. The course of PRRT2-PKD and MR-1-PNKD is benign, and treatment might not be needed with advancing age.
Key words (5-8) Paroxysmal dyskinesia, PKD, PNKD, PED, PRRT2, MR-1, SLC2A1, treatment

Key Points

- Paroxysmal dyskinesia are a heterogeneous group of disorders manifesting as recurrent attacks of abnormal moments (dystonic, choreic, ballistic, or a combination of these), without loss of consciousness
- According to the precipitating factors they can be classified in PKD, PNKD, and PED
- Causes can be primary and secondary. Each phenotype can be associated to different gene mutations, most commonly to PRRT2, PNKD (MR-1) and SLC2A1 gene mutations
- Preventing the attacks avoiding precipitating factors can be sufficient in controlling the symptoms (especially for PED), but pharmacological and other non-pharmacological treatment options are available
- PKD has an exquisite response to AED, particularly CBZ, whereas BDZ can be effective for PNKD. Refractory paroxysmal dyskinesia may respond to surgical treatment

Overview: Nature of the Problem

Definition

Paroxysmal dyskinesia (PxD) are a rare heterogeneous group of disorders manifesting as recurrent attacks of abnormal moments, without loss of consciousness (1). The abnormal movements may be dystonic, choreic, ballistic, or a combination of these. In medical literature, the terms “paroxysmal” and “dyskinesia” respectively refer to “sudden attack, recurrence or intensification of a disease” and “involuntary jerky or slow writhing movements, often of a fixed pattern, including tics, myoclonus, chorea and dystonia”. It is, therefore, clear that the definition is too broad and could erroneously include conditions that are not generally considered as PxD by movement disorders expert. The following paragraphs will help in clarifying this aspect.

Historical aspects

 PxD was first described in 1892 by Shuzo Kure in a 23-year-old Japanese man, who had frequent movement-induced paroxysmal attacks from the age of 10 (2). Later in 1901, Gowers reported a child with a similar picture, but he considered the attacks as an epileptic phenomenon (3). In 1940, Mount and Reback described a 23-year-old man with intermittent choreo-dystonic attacks of the trunk and extremities and labelled this condition “paroxysmal dystonic choreoathetosis” (4). In this case, the attacks were precipitated by alcohol, coffee or tea intake, fatigue and smoking, and could last several hours. Over the years, more families with a similar disorder were described, showing a clear autosomal dominant pattern of inheritance. In 1967, Kertesz (5) reported other families with
episodic attacks of involuntary movements; but, differently from the previous description, the attacks were very brief in duration and induced by sudden movements. Moreover, they responded well to anticonvulsants, particularly Carbamazepine (CBZ). Kerstesz called it “paroxysmal kinesigenic choreoathetosis”, to differentiate it from “paroxysmal dystonic choreoathetosis”. A third type of PxD was introduced in 1977 by Lance (6), who used the term paroxysmal exercise-induced dystonia (PED) to describe a family who had attacks lasting between 5 and 30 min, provoked by prolonged exercise. It was only in 1995 that Demirkiran and Jankovic merged the many terms adopted, organising PxD in three subtypes: paroxysmal kinesigenic (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), and PED (7). A fourth subtype of PxD, characterised by attacks occurring during sleep without detectible trigger, was also proposed (i.e., paroxysmal hypnogenic dyskinesias); however, it has been later discovered to be a form of autosomal dominant nocturnal frontal lobe epilepsy in most of the cases and therefore no longer regarded as a form of PxD.

Classification

The clinical classification of PxD is mostly based on the criteria proposed by Demirkiran and Jankovic (1995)(7), subsequently refined by Bruno et al. (2007)(8). This classification relies on the precipitating event, which is considered the best predictor of clinical course as well as the most reliable predictor of the underlying genetic cause (7, 9). According to precipitating factors, PxD can be classified as PKD, PNKD and PED. Secondary categorization is based on duration of the attacks. Finally, a tertiary categorization involves presumed aetiology: primary (familial/sporadic) or secondary (Table 1). More recently, Erro et al. 2014 (9) proposed a new classification scheme of primary PxD, that includes all the above mentioned categorizations but takes also into account the more recent genetic discoveries. This new classification consists of two axes: clinical features (axis 1) and genetic determinants (axis 2), as shown in Table 2.
Table 1. Clinical features of paroxysmal dyskinesia

<table>
<thead>
<tr>
<th></th>
<th>PKD</th>
<th>PNKD</th>
<th>PED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset</td>
<td>Childhood/teens</td>
<td>Infancy/childhood</td>
<td>Variable</td>
</tr>
<tr>
<td>Clinical semiology</td>
<td>Chorea/dystonia</td>
<td>Chorea/dystonia</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Precipitating factors</td>
<td>Sudden movement</td>
<td>Coffee, tea, alcohol, stress, fatigue</td>
<td>Prolonged exertion</td>
</tr>
<tr>
<td>Duration of attacks</td>
<td>Seconds to minutes</td>
<td>Minutes to hours</td>
<td>Subside with rest (usually 15-40 minutes)</td>
</tr>
<tr>
<td>Frequency of attacks</td>
<td>From 1/month up to 100/day</td>
<td>From 1/year up to 2-3/day</td>
<td>Dependent on exercise</td>
</tr>
</tbody>
</table>

PKD: paroxysmal kinesigenic dyskinesia, PNKD: paroxysmal non-kinesigenic dyskinesia, PED: paroxysmal exercise-induced dystonia

Table 2. Classification of primary paroxysmal dyskinesias according to clinical (Axis I) and genetic (Axis II) characteristics

Axis I: Clinical characteristics
A) Inclusion criteria (1 plus one of 2a, b or c)
   1. Paroxysmal attacks of dystonia, chorea, ballism (or a mixture of those) with sudden onset and variable duration (seconds to hours).
   2. Paroxysmal dyskinesia are categorized according to the “trigger factor” into one of the following:
      a. Paroxysmal kinesigenic dyskinesia: attacks are triggered by sudden movements, acceleration, or intention to move
      b. Paroxysmal non-kinesigenic dyskinesia: attacks are triggered by coffee, alcohol, and other non-kinesigenic precipitants
      c. Paroxysmal exercise-induced dyskinesia: attacks are triggered by prolonged exercise
B) Exclusion criteria (both 1 and 2)
   1. Symptoms are due to another neurological condition
   2. Symptoms are psychogenic

Axis II: Genetic characteristics
1. Mutations confirmed in one of the known genes (i.e., PRRT2, MR-1, KCNMA1, SLC2A1)
2. No mutations in one of the known genes or genetic testing has not been performed (undetermined forms)
PKD

PKD is the most common PxD and it is characterized by brief, self-limiting attacks, precipitated by sudden movements, such as standing up quickly from a chair. A sudden increase in speed, amplitude, or strength or even the sudden additions of new actions during ongoing steady movements may induce an attack too (7, 10); while startle, sound/photo/vestibular stimulation, hyperventilation, or stress can also favour them (10). Usually the attacks last few seconds up to 1 minute but are multiple during the day (11). The frequency ranges from less than 1/month to up to 100/day. The clinical manifestation exhibited may be dystonia, chorea, ballismus, or a combination thereof; but among these, dystonia is the most common. The attacks may be focal, multifocal or generalized; they most often involve one or two limbs, but trunk and/or speech (through orofacial involvement) can also be affected (9, 10). Most patients experience “aura” abnormal sensation prior the involuntary movements, such as numbness or “pins and needles” in the affected limb or the epigastric region (11). The “aura” can be used as warning sign to prevent the attacks, for instance by slowing down or “holding tight” the affected limb (9). There is no pain or loss of consciousness during attacks, and no postictal confusion or drowsiness (11, 12). Onset age in PKD is usually between 7 and 15 years but has been described up to 40 years. There is a higher prevalence in males (4:1, even up to 8:1) in the sporadic form but not in familial cases (13).

Mutations in the PRRT2 gene are the cause of isolated PKD in about 40% to 90% of the cases (14-18), depending on case ascertainment (9, 19). In PKD, PRRT2 is inherited in an autosomal dominant manner but with variable penetrance ranging from 80–90% in familial cases to 30–35% in sporadic cases (20). In PRRT2 carriers, attack frequency peaks during puberty and decreases with age. PRRT2 mutations can cause also two related disorders, namely infantile convulsions and choreoathetosis (ICCA) and benign familial infantile epilepsy (BFIE), and it has been proposed that ICCA, BFIE, and PKD may represent a spectrum of related disorders (21). In addition, it is known that PRRT2 mutations can induce additional phenotypes including episodic ataxia and familial hemiplegic migraine (19, 22). When present in a single subject or in the family, these features make the occurrence of PRRT2 mutations more likely. Not all cases of PKD are due to mutations in the PRRT2 gene, and while some cases remain of unknown aetiology, others have been attributed to different genes. For instance, mutations in SCN8A can be a cause of the ICCA syndrome (23), as well as episodic dystonia (24). Possible PKD cases have also been attributed to mutations in SLC2A1, PNKD (MR-1), KCNMA1, and KCNA1 gene (25, 26). More complex phenotypes including developmental delays, intellectual disability and language abnormalities, minor dysmorphic facial features, and/ or autism spectrum disorder associated with PKD should raise the suspicion of 16p11.2 (micro)deletions (27).
The typical PNKD phenotype is characterized by dystonic and/or choreic attacks, lasting from minutes to hours. Precipitating factors include coffee, tea, alcohol and stress, whereas attacks may be alleviated by sleep. Less frequent triggers comprise change in external temperature, fever, menstruation, and tiredness. The frequency of the attacks is rarely more than 1 a day and most commonly 1 attack/week (9). The dyskinesias can be generalized or unilateral/focal. They often start in one limb and then spread over the body and become generalized. Speech impairment due to face involvement, with oral dyskesia or tongue dystonia, can be seen, and occasionally other additional features including oculogyric crises, blepharospasm, risus sardonicus, inability to move, and pain have been reported (9). Prodromal symptoms, when present, include weakness, shortness of breath, and migraine. Onset is usually in infancy or early childhood (9). Reliable data on PNKD gender prevalence are not available.

Mutations of the myofibrillogenesis regulator 1 (MR-1) gene were found to be causative of PNKD (28), and the MR-1 gene was consequently renamed as the PNKD gene. In patients carrying the gene, a general tendency to decreasing attack frequency with aging has been described.

While PNKD due to MR-1 mutations manifests as isolated PxD, in several gene mutations that have been recently linked to the PNKD spectrum, the involuntary movements are combined with other neurological features. For instance, in PNKD due to KCNMA1 gene mutations PxD are combined with a personal or familial history of epilepsy or neurodevelopmental delay (29). PNKD can also be associated with mutations in SLC2A1 (30, 31), ATP1A3 (32-34), ADCY5 (35), or in genes encoding the branched-chain a-ketoacid dehydrogenase complex (maple syrup urine disease) (36, 37). Of note, ADCY5 mutations can cause variable phenotypes and may manifest, even within the same patient, with PKD and PNKD (35, 38); while ATP1A3, in the context of alternating hemiplegia of childhood, can manifest with hemidystonic attacks resembling PNKD.

**PED**

The third group of PxD was recognized by Lance (1977)(6), as, differently from PKD, the attacks were not brought on by sudden movements but by physical exhaustion after continuous exertion. Indeed, by definition, PED are precipitated by prolonged or sustained exercise. In some cases, fasting, stress and anxiety could trigger the episodes as well (9). Most commonly the attacks last from 15 to 40 minutes, and rarely less than 5 minutes (9). Frequency of attacks ranges from several per day to 1/month, with the majority of the patients reporting several attacks per week. The most common
presentation is dystonia, but isolated chorea has been also described. It usually has focal/unilateral involvement affecting the lower limbs, and generalization of attacks is rather unusual (22). Additional features reported during the attacks include oculogyric crises, gait disturbances, clumsiness, weakness, and migraine (9).

Mutations in SLC2A1 gene are the main cause of PED, which can be isolated or part of a more complex phenotype (31, 39-44). SLC2A1 encodes the glucose transporter type 1 (GLUT1), a membrane-bound protein that facilitates glucose transfer across the blood-brain barrier. Heterozygous mutations in SLC2A1 result in the GLUT1 deficiency syndrome, which is a complex disorder characterized by intellectual impairment, epilepsy, microcephaly, movement disorders including paroxysmal forms. PED is considered as a non-classical variant of the GLUT 1 deficiency syndrome (43), inherited in an autosomal dominant manner, although most cases are de novo (45).

Pyruvate dehydrogenase complex-E2 (PDC-E2) deficiency and mitochondrial short-chain enoyl-CoA hydratase deficiency (ECHS1) are two potentially treatable neurological disorders rarely reported to have an initial presentation with only isolated PED (46, 47). Other possible causes of PED are young-onset Parkinson’s disease due to Parkin mutation (48) and GCH1 mutations (9, 49).

Summary

PxD are characterized by recurrent attacks of abnormal movements, typically dystonia, chorea or a combination of them, without loss of consciousness. According to the precipitating factor, PxD can be classified in three main subtypes: PKD, PNKD and PED. Each subtype is associated with a causative gene, respectively PRRT2, PNKD (MR-1) and SLC2A1; however, recent genetic findings have extended the spectrum of genes associated to these syndromes, suggesting certain degree of clinical and genetic overlap and refusing the concept that one phenotype is attributable to one single aetiology (Table 3). Of note, PxD can also be secondary to a variety of acquired, immunological and neurodegenerative causes (50) (Table 4). In this case, the clinical picture might different from the classical presentation, as they occur later in life compared with the main genetic forms, and manifest with additional signs or symptoms that guide the diagnostic workup.
Table 3. Most common genetic causes of paroxysmal dyskinesia

<table>
<thead>
<tr>
<th>Gene</th>
<th>Subtype</th>
<th>Inheritance</th>
<th>Other paroxysmal disorders</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRRT2</td>
<td>PKD</td>
<td>AD</td>
<td>Epilepsy, migraine, FHM, ataxia</td>
<td>-</td>
</tr>
<tr>
<td>MR-1</td>
<td>PNKD (PKD)</td>
<td>AD</td>
<td>Migraine (rare)</td>
<td>-</td>
</tr>
<tr>
<td>SLC2A1</td>
<td>PED (PKD, PNKD)</td>
<td>AD</td>
<td>Ataxia, epilepsy</td>
<td>Anaemia, hypotonia, spasticity</td>
</tr>
<tr>
<td>KNCMA1</td>
<td>PNKD</td>
<td>AD</td>
<td>Epilepsy</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>SCN8A</td>
<td>PKD</td>
<td>AD</td>
<td>Epilepsy</td>
<td>Mental retardation</td>
</tr>
<tr>
<td>ECHS1</td>
<td>PED</td>
<td>AR</td>
<td>-</td>
<td>Leigh Syndrome</td>
</tr>
<tr>
<td>PDC-E2</td>
<td>PED</td>
<td>AR</td>
<td>-</td>
<td>Leigh Syndrome</td>
</tr>
<tr>
<td>ADCY5</td>
<td>PNKD (PKD, nocturnal)</td>
<td>AD</td>
<td>-</td>
<td>Axial hypotonia, non-paroxysmal dystonia and chorea</td>
</tr>
<tr>
<td>ATP1A3</td>
<td>PNKD (hemidystonic)</td>
<td></td>
<td>Hemiplegia, ataxia</td>
<td>-</td>
</tr>
<tr>
<td>GCH1</td>
<td>PED</td>
<td>AD</td>
<td>-</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Parkin</td>
<td>PED</td>
<td>AR</td>
<td>-</td>
<td>Parkinsonism</td>
</tr>
</tbody>
</table>

AD: autosomal dominant, AR: autosomal recessive, FHM, familial hemiplegic migraine, PDC: pyruvate dehydrogenase complex, PED: paroxysmal exercise-induced dyskinesia, PKD: paroxysmal kinesigenic dyskinesia, PNKD: paroxysmal non-kinesigenic dyskinesias

In parenthesis, less common subtype.
<table>
<thead>
<tr>
<th>Immune mediated disorders</th>
<th>Vascular</th>
<th>Metabolic causes</th>
<th>Trauma</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis and other demyelinating diseases</td>
<td>Stroke</td>
<td>Hypo/hyperglycaemia</td>
<td>Central and peripheral</td>
<td>Basal ganglia calcifications</td>
</tr>
<tr>
<td>Autoimmune encephalopathy (anti-VGKC, Anti-Caspr2, Hashimoto)</td>
<td>Moyamoya</td>
<td>Hypocalcaemia/hypoparathyroidism/pseudohypoparathyroidism</td>
<td></td>
<td>Central pontine myelinolysis</td>
</tr>
<tr>
<td>Systemic autoimmune disorders (SLE-APS-Behcet’s disease)</td>
<td>Cerebral palsy</td>
<td>Thyrotoxicosis/hypothyroidism</td>
<td></td>
<td>Kernicterus</td>
</tr>
<tr>
<td>Parry-Romberg syndrome</td>
<td></td>
<td>Wilson’s disease</td>
<td></td>
<td>Encephalitis/postinfectious</td>
</tr>
<tr>
<td>Paraneoplastic limbic encephalitis</td>
<td></td>
<td>Maple syrup urine disease</td>
<td></td>
<td>Brain neoplasm</td>
</tr>
<tr>
<td>Celiac disease</td>
<td></td>
<td>Lesch-Nyhan disease</td>
<td></td>
<td>Early-onset Parkinson’s disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Functional disorders</td>
</tr>
</tbody>
</table>

APS: antiphospholipid syndrome, SLE: systemic lupus erythematosus, VGKC: voltage gated potassium channel-complex
Patient Evaluation Overview

It is generally assumed that clinical examination of PxD is normal between the attacks; however, while this might be the case for PRRT2-PKD and for MR-1-PNKD, it is not necessarily true for the other forms as in many cases they present with additional features. Therefore, the criterion of normal interictal examination should be avoided.

The first relevant step of the diagnostic process is to obtain a detailed personal clinical history. Important features that should be considered comprise attack’s phenomenology, triggers, and duration as well as family history and comorbidities. If possible, the neurological examination should be performed both during and between the attacks, to identify interictal examination findings that may allow for diagnostic possibilities to be narrowed. When attacks do not occur in the clinical settings, videotapes should be encouraged.

While the disorder is intermittent in nature, it does not wax-and-wane over a period of time such as tics. Moreover, considering the phenomenology, it ranges from dystonia to chorea, and rarely involves ballism, but does not encompass tremor or myoclonus. In case of unusual features, such as the lack of specific and consistent triggers, variable durations and adulthood onset, secondary causes need to be excluded, including functional disorders.

Paroxysmal attacks comprise also epilepsy, tonic spasms, tetany, neuromyotonia, periodic paralyses and episodic ataxias, which need to be excluded clinically or by additional investigations whenever appropriate.

PED diagnosis can be supported by a low cerebrospinal fluid/serum glucose ratio (< 0.60), but as for the other syndrome it is confirmed by genetic analysis. Some cases could remain unsolved, but treatment is to be pursued empirically.

Summary

The evaluation of patients with PxD is based on ictal and interictal clinical examination, as well as a thorough medical history. The latter should be focused on attacks features (such as precipitating triggers, duration, and phenomenology), possible additional symptoms and detailed family history. The clinical diagnosis can be confirmed by means of appropriate genetic test, however a definitive cause is not always found. In that event, treatment should be started on empirical base. When medical history points towards secondary causes, additional investigations might be pursue as appropriate.
**Management Goals**

The management of PxD is focused on the reduction of attacks frequency and the prevention of secondary complications such as falls or interference with activities (for instance driving). This goal can be achieved by avoiding precipitating triggers, and/or preventing the attacks by pharmacological and non-pharmacological treatments.

If comorbidities, like epilepsy, are present, appropriate treatment should be considered. Importantly, possible side effects of the drugs used, should be monitored.

There are no guidelines for the treatment of PxD, which is based on clinical experience and known pathological mechanisms.

In secondary forms of PxD, treatment is mainly focused on the underlying cause, especially when it is reversible.

**Pharmacologic Treatment Options**

**PKD**

PKD is characterized by their exquisitely response to antiepileptic drugs (AEDs). The first-line of treatment is CBZ, at low dose, but phenytoin is often used too (9, 51) (Table 5). A dramatic response to them is seen especially in PRRT2-PKD compared to other forms (52, 53), although treatment failure to AEDs has been reported in homozygous or compound heterozygous PRRT2 mutation carriers (54, 55).

CBZ and oxcarbazepine appear to be equally effective (56), but other AEDs, such as phenobarbital (57), levetiracetam (58), gabapentin (59), valproic acid (9), lamotrigine (60), and topiramate (61), have been proven to be beneficial to same extent too.

The use of these drugs is based on class IV level of evidence, e.g. observational studies without controls.

The biological mechanisms underlying PKD are not entirely clear, therefore the reason why CBZ is the most effective drug is still not known. It has been proposed that the mutant PRRT2 interacts with the SNAP-25, a presynaptic Q-SNARE protein involved in the fusion of neurotransmitter vesicles to the cellular membrane, which modulates the kinetics of voltage-gated Ca2+ channels leading to neuronal hyperexcitability (62). On this basis, it has been suggested that any voltage-gated sodium channel blockers (such as CBZ, phenytoin, lacosamide etc.) could be potentially therapeutic.
The effect of conventional AEDs is limited in PNKD, but symptoms may respond to benzodiazepines (BDZ), which represents the first-line treatment option. Among them, the most commonly used are clonazepam and diazepam (class IV level of evidence) (Table 5), as either prophylactic or rescue drugs. It has been shown that they are able to reduce both frequency and severity of the attacks in up to 97% of the patients (8). Other BDZ, including lorazepam, can be effective too. Oxcarbazepine has been recently reported to be beneficial in one case (63), whereas CBZ is ineffective in the majority of patients (64). The effect of other drugs on PNKD have been tried with partial success (haloperidol, anticholinergics, gabapentin, levetiracetam, nitric oxide synthetase inhibitors, adenosine agonists/antagonists, acetazolamide, piracetam and levodopa (65-67)).

ADCY5 patients may have mild functional gain with clonazepam or clobazam, but whether these drugs improve also the paroxysmal episodes it is not specifically reported (68). In ATP1A3, the hemidystonic attacks can be treated by flunarizine, a calcium channel blocker, with dose ranging from 5 to 20 mg/day; however, there are reports of response of hemiplegias/dystonias episodes also to topiramate, ketogenic diet, aripiprazole, steroids, amantadine, oral ATP (69).
### Table 5. Most common pharmacological treatment for paroxysmal dyskinesia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dosage</th>
<th>Side-effects</th>
<th>Effective for</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBZ</strong></td>
<td>50-200 mg</td>
<td>Skin rash (particularly in people of Asian descent), aplastic anaemia, agranulocytosis, dizziness, drowsiness, nausea, vomiting, dry mouth, oedema, loss of balance or coordination</td>
<td>PKD</td>
</tr>
<tr>
<td><strong>Oxcarbazepine</strong></td>
<td>75– 300 mg</td>
<td>As CBZ</td>
<td>PKD</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td>100– 200 mg</td>
<td>Headache, nausea and vomiting, constipation, dizziness, drowsiness, slurred speech, loss of balance or coordination, insomnia, cardiac arrhythmias, skin reactions</td>
<td>PKD</td>
</tr>
<tr>
<td><strong>Lacosamide</strong></td>
<td>50-100 mg</td>
<td>Dizziness, spinning sensation, loss of balance or coordination, blurred vision, nausea and vomiting, drowsiness, tiredness, headache, skin reactions</td>
<td>PKD</td>
</tr>
<tr>
<td><strong>Clonazepam</strong></td>
<td>Low dose</td>
<td>Alertness decreased; drowsiness; dysarthria; fatigue; headache; hypotension; mood altered; muscle weakness; nausea; withdrawal syndrome (at low dose)</td>
<td>PNKD</td>
</tr>
<tr>
<td><strong>Diazepam</strong></td>
<td>Low dose</td>
<td>As clonazepam</td>
<td>PNKD</td>
</tr>
</tbody>
</table>

CBZ: carbamazepine, PKD: paroxysmal kinesigenic dyskinesia, PNKD: paroxysmal non-kinesigenic dyskinesia
Compared to other forms of PxD, PED due to GLUT1 mutations respond less to pharmacological treatment (64), while lifestyle and diet modifications are very important in preventing the attacks. Nevertheless, partial benefit has been reported with levodopa, trihexyphenidyl and BDZ (7, 13).

If associated to Parkinson’s disease or GCH1 mutations, PED improves with levodopa; whereas in ECHS1, the paroxysmal attacks can respectively respond to a mitochondrial cocktail including thiamine, riboflavin, carnitine, coenzyme Q, vitamin B6 and vitamin C (70).

**Non-pharmacologic Treatment Options**

**PKD**

Lifestyle: avoidance of established trigger, i.e. sudden movements. Stress, sleep deprivation, anxiety, and other triggers can increase the likelihood for PKD episodes, therefore their control can help in preventing attacks.

**PNKD**

Lifestyle and diet: avoidance of methylglyoxal-containing food and beverages such as alcohol, coffee, tea and chocolate may benefit these patients, as well as the avoidance of other predisposing factors, such as fatigue. Lifestyle modifications and diet can reduce or almost abolish attacks in up to one-third of patients with MR-1 mutations (71).

**PED**

Lifestyle and diet: prolonged continuous exertion in PED may prevent the occurrence of attacks. In case of GLUT1 deficiency, PED can respond to ketogenic diet (72), but compliance to it can be rather poor and the modified Atkins diet, with less strict fat-to-non-fat ratio and no restriction of food or fluid intake, has been proposed as an alternative, with good results (73). More recently, triheptanoin, an odd-chain triglyceride which acts by replenishing metabolic intermediates in the Krebs cycle, has been shown to dramatically reduce the attacks in PED, with the advantage to be better tolerated than Atkins diet (74).

Ketogenic diet is successful also for the treatment of PDC-E2 deficiency (75).
Combination Therapies

There are not reports on the use of combination therapies for the treatment of primary PxD, unless the goal is to address both the paroxysmal attacks and comorbidities (such as epilepsy, non-paroxysmal dystonia etc.).

Acetazolamide it might be a useful adjunct to CBZ in the treatment of PKD, especially when due to demyelinating lesions (13).

Surgical Treatment Options (if applicable)

PKD

A surgical approach for the treatment of PKD was tried in four members of the same family, positive for PRRT2 mutations, with benefit. In two members, unilateral stereotactic surgery was performed in 1967, which resulted in complete resolution of the episodes. Based on this result, other two components of the family similarly affected, despite the good response to CBZ which however reduced but not completely stopped the attacks, decided to undergo the same surgery, consisting of right ventro-oral thalamotomy. Following surgery, the number of attacks reduced significantly in one patient and completely disappeared in the other one (76).

PNKD

There are two reports on the effective treatment of PNKD with deep brain stimulation (DBS). The first (77) is about a 26-year-old man, with a very long history of mental retardation, chorea and episodes of flexion and jerky movements of the legs, arm, neck and face. These episodes were classified as PNKD, although his condition remained undiagnosed. He underwent implantation of bilateral DBS in the globus pallidus internus (GPI), with a significant and sustained improvement of the attacks, as well as balance, gross motor function and walking. In the second report, two patients clinically diagnosed with PNKD, refractory to conventional treatment, had a good response to GPI DBS with completely suppression of the PxD (78).

Bilateral GPI DBS can improve the episodic choreoathetoid and dystonic movements in ADCY5 (68, 79).

PED

In a case of PED, of unknown aetiology, the dystonic attacks of the right foot ceased completely after left posteroverentral medial pallidotomy (80).
Treatment Resistance/Complications/Disease Recurrence

In most of the patients affected by PKD and PNKD, the symptoms can be easily controlled by the combination of non-pharmacological and pharmacological therapies, with low chance of disease recurrence. The response to the pharmacological treatment seems to be related to the underlying cause, with PRRT2-PKD and MR-1-PNKD being the most successful responders to conventional treatment. In small numbers of refractory cases, surgical approaches have been successful. Treatment of PED largely relies on the avoidance of attack triggers, and a good compliance and response to non-pharmacological treatment has been reported.

The possible side-effects are related to the drug used, as detailed in the tables. Worth mentioning, the risk of hypersensitivity reactions to CBZ is increased by the presence of specific human leukocyte antigen (HLA) alleles. The HLA-B*15:02 allele is strongly associated with CBZ-induced Stevens–Johnson syndrome/toxic epidermal necrolysis in populations where this allele is most common, such as Asian populations. In these populations, the use of CBZ should be avoided and an alternative selected.

Evaluation of Outcome, Adjustment of Treatment, and Long-Term Recommendations

Treatment outcome is based on the recurrence of the attacks, and therefore mostly on patients’ report. In this regard, it might be useful to ask patients to keep a diary of the episodes, specifying the duration and precipitating factors. In case of poor response to the first-line treatment, after adjusting the dose of the recommended drug (keeping in mind that PKD and PNKD usually respond to low dose of AEDs/BDZ), the other options should be pursued and chosen according to their side-effect profile and patient comorbidities. Differently from PED due to GLUT1 deficiency, the frequency of the episodes in PKD and PNKD decreases with advancing age, and treatment might be unnecessary by that time.

Conclusion / Summary

PxD defines clinical heterogeneous syndromes distinguished by the recurrence of attacks of abnormal movements, triggered by detectable factors, without loss of consciousness. According to the precipitating factors, PxD are classified in PKD, PNKD, and PED; however, other features, such as duration of the attacks, response to treatment, and aetiology might differentiate them. PxD can be further stratified into primary and secondary disorders. The primary are mostly due to a genetic
defect, with PRRT, PNKD (MR-1) and SLC2A1 being the most common gene involved and causing respectively PKD, PNKD and PED. Nevertheless, the spectrum of genes associated to these syndromes have been broaden by recent findings, highlighting a clinical and genetic overlap among these syndromes and declining the one-gene-one-phenotype notion.

The clinical diagnosis of PxD is based on ictal and interictal neurological examination, a detailed personal and family medical history, and presence of comorbidities. The clinical diagnosis can be confirmed by means of appropriate genetic test or next generation sequencing approaches. If the clinical evaluation suggest secondary causes, additional investigations should be pursued as appropriate.

The treatment of PxD is based on the combination of non-pharmacological and pharmacological approaches. PKD has an excellent response to AEDs (especially CBZ), whereas in many PNKD and PED cases the symptoms can be controlled by avoiding the precipitating factors. In case this is not sufficient, the use of drugs, such as BDZ for PNKD, and diet changes, such as ketogenic or Atkins diet for PED due to GLUT1 deficiency, can be effective. Moreover, PKD and PNKD have a benign course, and the recurrence of involuntary movements’ episodes tends to decrease over the years. Patients with a known genetic cause, such as PRRT2 or PNKD (MR-1), have a better response to conventional treatment compared to the undiagnosed ones; however, in the latter it is recommended to start the appropriate treatment on empirical base. Of note, in PxD refractory to conventional treatments, surgical approach should be keep in mind as an alternative option.
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