

REVIEW

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Recommendations for the diagnosis and treatment of paroxysmal kinesigenic dyskinesia: an expert consensus in China

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Abstract

Paroxysmal dyskinesias are a group of neurological diseases characterized by intermittent episodes of involuntary movements with different causes. Paroxysmal kinesigenic dyskinesia (PKD) is the most common type of paroxysmal dyskinesia and can be divided into primary and secondary types based on the etiology. Clinically, PKD is characterized by recurrent and transient attacks of involuntary movements precipitated by a sudden voluntary action. The major cause of primary PKD is genetic abnormalities, and the inheritance pattern of PKD is mainly autosomal-dominant with incomplete penetrance. The proline-rich transmembrane protein 2 (*PRRT2*) was the first identified causative gene of PKD, accounting for the majority of PKD cases worldwide. An increasing number of studies has revealed the clinical and genetic characteristics, as well as the underlying mechanisms of PKD. By seeking the views of domestic experts, we propose an expert consensus regarding the diagnosis and treatment of PKD to help establish standardized clinical evaluation and therapies for PKD. In this consensus, we review the clinical manifestations, etiology, clinical diagnostic criteria and therapeutic recommendations for PKD, and results of genetic analyses in PKD patients performed in domestic hospitals.

Keywords: Paroxysmal kinesigenic dyskinesia, Diagnosis and treatment, Expert consensus, China

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Introduction

Paroxysmal dyskinesias are a group of neurological diseases characterized by intermittent episodes of involuntary movements with different causes. The involuntary movements are manifested as dystonia, chorea, ballism, or a combination thereof. According to the triggers of the attack, paroxysmal dyskinesia can be divided into types of paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD), and paroxysmal exercise-induced dyskinesia (PED). PKD is the most common type of paroxysmal dyskinesia and was first described by Kertesz in 1976 [1]. Clinically, PKD is characterized by recurrent and transient episodes of involuntary movements precipitated by a sudden voluntary action [1]. PKD can be divided into primary and secondary types based on the etiology. The primary PKD is mainly an inherited condition, with most cases having an inheritance pattern of autosomal-dominant with incomplete penetrance [2, 3]. Proline-rich transmembrane protein 2 (*PRRT2*) was the first identified causative gene in 2011, accounting for the majority of PKD patients worldwide [4–6]. Subsequent studies have revealed clinical and genetic characteristics of PKD. To help standardize PKD clinical evaluation and therapies, we considered the views of domestic experts and propose an expert consensus regarding the diagnosis and treatment of PKD.

Clinical manifestations

Prevalence and age of onset

The prevalence of PKD has been estimated to be 1:150,000 individuals. The majority of PKD individuals are of Asian ethnicity and are from China and Japan, followed by North America and Europe [7, 8]. The age at onset of primary PKD generally ranges from several months to 20 years, with a particularly high incidence among 7- to 15-year-old children and adolescents [2, 8, 9]. Males are more susceptible to primary PKD than females, with a ratio of 2:1 to 4:1 [2]. A higher prevalence of sporadic PKD has been reported in males, with a ratio from 4:1 to 8:1 [10].

Triggers

Typical PKD attacks are induced by sudden voluntary actions, such as sudden standing, starting to run, getting on and off a car, and encountering traffic lights [2, 9, 10]. Changes in the speed or amplitude of movements, addition of another type of movement during an activity, or even the intent to move can also cause an attack. Episodes are more likely to be triggered when an individual is under emotional stress, stimulated by a sound or image, or hyperventilating [10].

Aura

The aura of PKD is defined as abnormal sensations prior to the appearance of involuntary movements induced by a sudden movement or movement intention [9]. The abnormal sensation is a feeling that is difficult to describe accurately and differs by individual. Approximately 78–82% of patients with PKD may experience aura [9]. The most common descriptions of aura are numbness, tingling, and muscle weakness [2, 9]. Some patients have been able to alleviate the dyskinesia attack by slowing their movements when experiencing aura [10]. In some cases, aura appears in isolation without subsequent dyskinesia attacks [9].

Attack forms

The forms of a PKD attack include unilateral or bilateral dystonia, chorea, ballism or a mixture of them [2, 10]. Dystonia is the most common, followed by chorea and ballism, which is the rarest form of PKD [9, 11]. Face involvement has been reported by approximately 70% of patients, mainly manifesting as face twitching, rigidity of facial muscles and dysarthria, which may be related to the dystonia of facial or laryngeal muscles [9, 12].

Duration and frequency of attacks

The duration of PKD attacks is < 1 min in over 98% of patients [2, 9]. For patients with prolonged duration, the secondary factors of PKD should be excluded [9]. The frequency of PKD attacks varies significantly among individuals and in patients with different disease stages, ranging from several times a year to more than 100 times per day [9, 12, 13]. The frequency of PKD attacks usually peaks during puberty and decreases after the age of 20 years. Some patients rarely experience attacks or even experience spontaneous remission of the disease after the age of 30 years [9].

Clinical classification

Clinically, PKD is classified into the pure and complicated types according to the absence or presence of other symptoms or diseases.

Patients of the pure form present only with kinesigenic involuntary movements.

Patients with complicated type of PKD present with neurological symptoms in addition to the kinesigenic dyskinesia. These combined manifestations include benign familial infantile epilepsy (BFIE), febrile convulsion, migraine, hemiplegic migraine, episodic ataxia, epilepsy and other episodic diseases [2, 14–16]. A few patients exhibit developmental delay, intellectual deficit, language dysfunction or autism [17–19].

Etiology and pathogenesis

PKD can be classified into the primary and secondary PKD due to different causes [20]. The primary PKD is further categorized into familial and sporadic PKD. Currently, the primary familial PKD is considered to be primarily caused by genetic factors with autosomal dominant inheritance, accompanied by incomplete penetrance that is estimated to be 60–90% [21]. Genetic studies have identified multiple genes related to the pathogenesis of PKD, including *PRRT2*, *PNKD*, *SLC2A1*, *SCN8A*, *KCNMA1*, *KCNA19* and *DEPDC5* [4, 5, 15, 22–28].

PRRT2 is the major causative gene for PKD [8, 9, 15]. It is located on chromosome 16p11.2 and contains 4 exons, encoding 340 amino acids. To date, more than 80 mutations of *PRRT2* have been reported worldwide [9], with nonsense and frameshift mutations being the main types, followed by missense mutations. Among the documented mutations, c.649dupC is a hotspot [9, 12, 29]. However, the function and pathogenic mechanism of *PRRT2* remain unclear. *PRRT2* is an integral component of the SNARE complex, interacting with SNAP-25, synaptic binding protein-1, synaptic binding protein 2 and synaptic vesicle protein 2, which endows the SNARE complex with calcium sensitivity [30, 31]. Furthermore, *PRRT2* is a key negative modulator of Nav1.2 and Nav1.6 channels [32]. The abnormal basal ganglia–thalamic–cortical circuit is currently considered to be the pathophysiological basis of PKD [33–36]. Functional magnetic resonance imaging (MRI) studies have revealed an abnormal connectivity between the thalamus and the motor cortex in patients with PKD, and the functional abnormality is associated with the duration of the disease [37]. In patients with *PRRT2* mutations, the thalamo–prefrontal hypoconnectivity has been observed, indicating that the *PRRT2* mutations result in inefficient thalamo–prefrontal integration and dysfunction of motor inhibition [38]. Mechanistic studies have also revealed that the core pathogenesis of PKD is the disturbed cell excitability caused by *PRRT2* mutation, which is associated with presynaptic dysfunction, abnormal neurotransmitter release and the lack of negative regulation of Na⁺ channels [31, 32].

Still, approximately one-half of patients with primary PKD do not harbor mutations in the aforementioned genes, suggesting the existence of other disease-causing genes.

In a few cases, PKD may be secondary to other factors [39], such as demyelinating diseases of the central nervous system, cerebrovascular diseases, traumatic brain injury, or metabolic abnormalities [39–41]. Multiple sclerosis (MS), particularly the relapsing–remitting MS, is the most common cause of secondary PKD [42–46]. The lesions of MS related to PKD involve the thalamus, the lenticular nucleus, the globus pallidus and the

internal capsule [43], and these demyelinating lesions may result in increased axon sensitivity that causes symptoms [43]. Calcification of the basal ganglia, including the idiopathic basal ganglial calcification and the basal ganglial calcification secondary to hypoparathyroidism or pseudo-parathyroidism, may also cause the secondary PKD [47–51].

Diagnosis and differential diagnosis

Differential diagnosis

a. Epilepsy

Although PKD attacks are stereotypic, precipitated by certain factors and not accompanied by loss of consciousness, it is difficult to distinguish them from seizure disorders, particularly the frontal lobe epilepsy. Patients with seizure disorders present with an abnormal ictal or interictal electroencephalogram (EEG) or no EEG change. The frontal lobe epilepsy is a common type of focal epilepsy of the childhood. Some patients with frontal lobe epilepsy also present with recurrent and stereotypic chorea and dystonia, with slight disturbance of consciousness during the attack and sometimes normal interictal electrograms. Unlike the frontal lobe epilepsy, however, the PKD attacks have a clear kinesigenic trigger and the individuals remain conscious during the attack, which can be used to distinguish between the two disorders. In addition, seizures of the frontal lobe can occur both during wakefulness and more commonly in sleep, while PKD is only evident when patients are awake.

b. Primary PNKD

The onset of PNKD usually occurs in childhood, with clinical features of involuntary movements triggered by nonkinesigenic factors such as tea, coffee, alcohol, psychological stress and fatigue. The attack presents with unilateral or bilateral dystonia and chorea. PNKD attacks usually last longer than PKD attacks, ranging from 10 min to 1 h [2, 52]. A few patients may experience even longer attacks. The frequency of PNKD attacks is lower than that of PKD attacks. Approximately one-half of the patients may experience aura prior to a PNKD attack, similar to that in PKD.

c. PED

The age at onset of primary PED is between 2 and 30 years. PED attack is induced by long or continuous exercise (5–30 min), but not by nonkinesigenic factors such as cold, alcohol, or coffee [53]. The duration of the attack ranges from 5 min to 45 min, typically not exceeding 2 h.

d. Psychological movement disorders and pseudoepilepsies

Both psychological disorders and PKD can manifest as paroxysms with normal interictal neurological examinations. Because of the clinical characteristics of PKD, attacks are usually not witnessed by physicians. Moreover, most patients with PKD are also diagnosed with anxiety or depression [54]. Therefore, in some cases, it is difficult to distinguish psychogenic movement disorders and pseudoepilepsies from PKD. Psychogenic disorders have features of distractibility, variability of clinical presentations of different paroxysms, and suggestibility [55]. Other red flags for suspecting psychogenic disorder include adult age of onset, altered level of responsiveness during attacks, additional psychogenic physical signs, medically unexplained somatic symptoms, and an atypical response to medications [55, 56]. Administering a high-knee exercise test may also help physicians make differential diagnoses.

e. Tics

Tics are very brief jerks or dystonic postures that are typically shorter in duration than PKD attacks.

f. Hyperekplexia

Hyperekplexia manifests as a group of diverse, complex, abnormal movements triggered by sudden noise or touch that can mimic PKD [55, 57]. An excessive startle response (typically including eye blinking and a flexor spasm of the trunk) to unexpected and innocuous (particularly auditory) stimuli is the most striking feature of hyperekplexia, which is present from birth or evident prenatally in the last trimester [58]. In contrast to the physiological startle response, the excessive startle leads to prolonged stiffening in neonates and young infants [59, 60].

g. Sandifer syndrome

Sandifer syndrome is secondary to gastroesophageal reflux, and the diagnosis of Sandifer syndrome should be suspected in young children with paroxysms of head tilt after eating [55, 61].

h. Benign paroxysmal torticollis (BPT) [62]

BPT is present as recurrent episodes of abnormal, painless head postures, alternating from side to side. Attacks may last from a few minutes to several days. Onset usually occurs before 3 months of age, and migraines that appear later have been widely reported, suggesting that BPT should be considered as an age-dependent migraine disorder to include periodic syndromes of childhood [63]. Treatment is not usually needed unless the symptoms of irritability, discomfort, or vomiting necessitate symptomatic management.

i. Transient dystonia of infancy [62]

Transient dystonia of infancy consists of paroxysmal episodes of abnormal upper limb posture, with occasional concomitant involvement of the trunk and a single lower limb [64]. The interictal examination and neuroimages are normal. The age of onset is typically between 5 and 10 months, and the condition gradually resolves between 3 months and 5 years without developmental or neurological abnormalities. The etiology and pathophysiology of transient dystonia of infancy are unclear.

j. Benign myoclonus of early infancy (BMEI) [62]

BMEI was originally described as a nonepileptic paroxysmal motor disorder characterized by the occurrence of myoclonic jerks of the head and/or of the upper limbs, usually occurring in clusters and mimicking infantile spasms. Consciousness is preserved during attacks, which usually occur during wakefulness and more rarely during sleep or drowsiness. Ictal EEG, neurological status and development must be normal to confirm a BMEI diagnosis. The attacks usually have abrupt onset and frequently appear in clusters. Each attack usually lasts a few seconds, but multiple episodes per day often occur and are frequently triggered by excitement, frustration, postural changes, or sensory stimuli [63]. The onset occurs in the first year of life (mainly between 4 and 7 months), and attacks usually cease by the age of 2 years,

Table 1 Revised clinical diagnostic criteria for primary PKD

Core symptoms:

1. Kinesigenic triggers and attacks presenting as dystonia, chorea, ballism, or a combination of them;
2. No impairment of awareness during attacks.

Supportive evidence:

1. Presence of aura;
2. Attack duration < 1 min;
3. Positive result of high-knee exercise test;
4. Good response to low-dose voltage-gated sodium channel blockers, especially carbamazepine/ oxcarbazepine.

Diseases listed in the following should be excluded:

1. Cerebrovascular disease;
2. Demyelinating disease, especially multiple sclerosis;
3. Metabolism disorders:
 - a. Hyperthyroidism;
 - b. Calcium-phosphate metabolism disorders (hypoparathyroidism, pseudoparathyroidism, parathyroid hyperthyroidism, pseudoparathyroid hyperplasia), primary familial brain calcification;
 - c. Glucose metabolism disorder;
 - d. Kernicterus
4. Brain trauma;
5. Psychological disorder.

The following red flags may indicate secondary causes or an alternative diagnosis:

1. Duration of attacks > 1 min;
2. Age of onset over 20 years;
3. Abnormalities in brain CT/MRI scanning or the presence of other neurologic/systemic problems;
4. No response to anticonvulsants;
5. Abnormal results of interictal examinations.

although sometimes persisting into the childhood. The pathophysiology is unknown, and no treatment is needed, but parents may need reassurance.

Clinical diagnostic criteria

Based on the results of a large-scale clinical study of patients with PKD in China [9], we propose the modified clinical diagnostic criteria for PKD (Table 1), detailed as below:

- 1) Patients suspected of having PKD must present with all core symptoms.
- 2) Supportive evidence endorses the diagnosis of PKD.
- 3) Secondary factors such as vascular, demyelinating, and metabolic causes must be excluded. In the case of appearance of any red flags, a comprehensive evaluation should be conducted to exclude secondary PKD.

Specific assessments include:

- a. Thyroid function evaluation: measurement of serum T3/FT3, T4/FT4, and thyroid stimulating hormone (TSH) levels; thyroid ultrasound; and examination of the iodine uptake rate if necessary;
 - b. Assessment of calcium and phosphorus metabolism: measurements of serum calcium, phosphorus, parathyroid hormone and calcitonin levels, and a cerebral CT scan is recommended for assessing intracranial calcification;
 - c. Blood glucose test;
 - d. Test of bilirubin levels;
 - e. Test of serum ceruloplasmin levels;
 - f. Head MRI;
 - g. EEG;
 - h. Neuropsychological assessment.
- 4) High-knee exercise test [9]: Similar to other epileptic disorders, PKD attacks are seldom witnessed by physicians, and the clinical diagnosis is made mainly based on patients' statements. An imprecise description of clinical features may lead to a misdiagnosis, and witnessing the attack may significantly improve the accuracy of diagnosis. Therefore, it is recommended that PKD attacks be induced through a high-knee exercise test. The operation of the high-knee exercise test [9] requires patients to perform high-knee exercise in place, under observations by neurologists. When performing the high-knee exercise, the patient should immediately stop the exercise upon experiencing an aura, and physicians then record the

details of the attack, including the form and the duration of the attack and the presence or absence of facial involvement. If a dyskinesia attack or an aura is induced, the test result is presumed to be positive. If no attack is induced after 30 s of high-knee exercise, the test is terminated and the result is presumed to be negative.

Notably, if the patient is taking anticonvulsants or his/her symptoms are naturally in remission, attacks may not be induced. Considering the refractory period between two attacks, the results of the high-knee exercise test may also be negative when the exercise is conducted shortly after a previous attack.

Genetic diagnosis

The primary PKD is mainly attributed to hereditary factors, and the most commonly mutated gene is *PRRT2*. About one-third of patients with primary PKD carry *PRRT2* mutations [9, 12], among which the c.649dupC has received much attention [9, 12, 29] and accounts for 76% of PKD patients with *PRRT2* mutations [9]. Other genes related to episodic diseases can also contribute to PKD, including *PNKD*, *SLC2A1*, *SCN8A*, *KCNMA1*, *KCNA1*, and *DEPDC5* [4, 5, 15, 22–28].

Since PKD is a benign disease with natural remission and anticonvulsants are effective in controlling attacks, genetic screening is not mandatory and is recommended depending on the patients' willingness. Second, the diagnosis of PKD is mainly based on clinical features rather than laboratory examinations; thus, negative genetic findings cannot exclude a diagnosis of PKD. Last, genetic screening is not recommended in asymptomatic populations, infants, or unborn babies.

The recommended flowchart for the diagnosis of PKD is shown in Fig. 1.

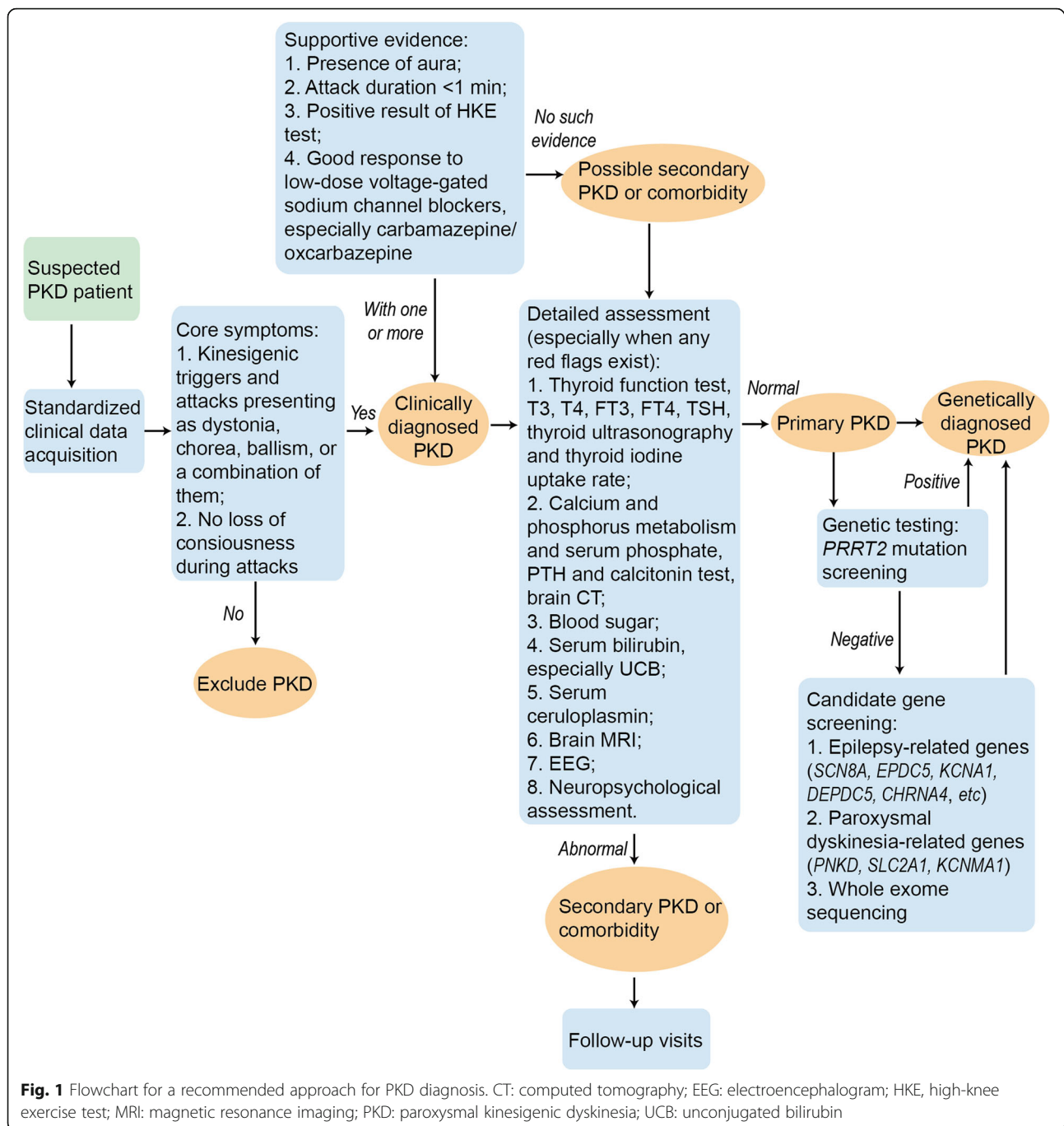
Treatment

The treatment of PKD includes medication and psychotherapy. For patients with secondary PKD, etiological treatment is crucial.

Since the primary PKD is a benign disease with natural remission, the application of medication should be considered on the basis of the patient's age, the frequency and degree of attacks, the psychological impact of the attack on the patient's life, and the patient's willingness.

Medication

Drugs can be prescribed to patients with frequent and severe attacks (causing instability or even falls), severe psychological impacts, and individuals who are willing to control the attacks. Primary PKD has a dramatic response to anticonvulsants, particularly the sodium channel blockers, of which carbamazepine/oxcarbazepine are preferred [9, 12, 65, 66]. Approximately 97% of patients



receiving carbamazepine/oxcarbazepine treatment have reported a complete or partial relief of attacks [9]. More than 85% of patients can achieve complete remission with low-dose carbamazepine (50–200 mg/day) or oxcarbazepine (75–300 mg/day), and approximately 10% of patients can achieve partial control (frequency reduced by at least 75%) [9]. Importantly, the dosage should be flexible, as the extent of satisfaction with the treatment is subjective and individualized. Some patients may tolerate auras without attacks, while others may strictly

require complete relief of symptoms. Thus, individualized treatment is recommended, and adequate communication regarding the prognosis of the disease, the adverse effects of the medication and the expected outcome of the treatment is warranted before the use of medication. The initial dosage of carbamazepine for PKD treatment is recommended to be 50 mg and can be adjusted according to the practical effect [9, 66]. Regarding oxcarbazepine, 75 mg is recommended initially [9]. As the weight varies in children, the initial dosage of

carbamazepine for pediatric patients with PKD can be set to 1 mg/kg and gradually titrated to the appropriate dosage. Furthermore, although most patients can well tolerate carbamazepine, the dizziness caused by carbamazepine may disturb the patients' daily activities. Thus the medication should be taken at bedtime to minimize this adverse effect. In addition, as carbamazepine may result in Steven-Johnson syndrome/toxic epidermal necrolysis particularly in the Han Chinese population, HLA-B*15:02 screening should be implemented before initiating treatment to reduce the risk of adverse cutaneous reactions [9, 12]. For patients who harbor HLA-B*15:02 or cannot tolerate the dizziness or drowsiness of carbamazepine, other voltage-gated sodium channel blockers, including lamotrigine, topiramate, and phenytoin sodium, are recommended as the second-line treatment [9].

Psychotherapy

Mental stress can increase the frequency and severity of PKD attacks. In addition, research on the psychological status of PKD patients revealed that PKD attacks can cause a certain degree of negative effect on patients, particularly adolescent patients. About one third of PKD patients have varying degrees of anxiety and depression [54]. Therefore, it is important to avoid stress, sleep deprivation, anxiety, and other psychological triggers that may increase the likelihood of PKD episodes, in order to prevent attacks and/or reduce the attack frequency. The psychological stress of patients is mainly attributed to the lack of knowledge about the etiology, development and prognosis of the disease. Thus, education among patients is particularly necessary to help them understand that PKD is a benign disease with a tendency toward natural remission to eliminate the psychological effects on patients' lives and work.

Special populations

a. Patients with BFIE

BFIE is an infantile cluster epilepsy that generally has a complete recovery [67]. Most BFIE cases are caused by *PRRT2* mutations, while mutations in other genes, including *SCN2A*, *SCN8A*, and *KCNQ2*, can also contribute. Therefore, genetic screening can assist in subsequent management. However, no specific interventions have been known to decrease the risk of subsequent development of PKD in BFIE patients, even in those with *PRRT2* mutations [7]. For BFIE patients carrying *PRRT2* mutations, carbamazepine or oxcarbazepine tends to be the preferred anti-epileptic drug (AED) because of the known favorable response in patients with PKD, although the responses to these drugs have not been well studied in patients with BFIE [7]. Benzodiazepines, including lorazepam, diazepam and midazolam, can be used to treat seizures lasting longer than 5 min or seizure clusters [7].

However, the response of *PRRT2*-associated seizures to benzodiazepines is less robust [7].

b. Pregnancy management

Some female patients have reported alleviation of attack frequency during pregnancy, but the underlying mechanism is unclear. However, prenatal exposure to AEDs may increase the risk of adverse fetal outcomes (depending on the type and dose of the drug and the stage of pregnancy at which medication is taken). Ideally, a comprehensive evaluation of the risks and benefits of AED medication during pregnancy should be conducted prior to conception [7]. For female patients with mild manifestations of PKD, discontinuing AED therapy prior to or during pregnancy should be considered due to the fetal risk related to AED therapy [7].

Conclusions

PKD is a type of paroxysmal dyskinesia with high clinical and genetic heterogeneity. Although PKD is the most common type of paroxysmal dyskinesia, its low prevalence makes it a rare condition. This expert consensus on PKD diagnosis and treatment was proposed based on several large-scale clinical and genetic analyses of patients with PKD in domestic cohorts, in order to help establish standardized clinical evaluations and therapies for PKD. The diagnosis of PKD is based mainly on clinical features, and necessary evaluations are needed to exclude secondary etiologies. Personalized medical therapy and psychotherapy are recommended.

Abbreviations

PKD: paroxysmal kinesigenic dyskinesia; *PRRT2*: proline-rich transmembrane protein 2; PNKD: paroxysmal nonkinesigenic dyskinesia; PED: paroxysmal exercise-induced dyskinesia; BFIE: benign familial infantile epilepsy; AED: anti-epileptic drug

Acknowledgments

We express our gratitude to all the neurologists who contributed to this paper.

Authors' contributions

LC, BST and SDC presided over the discussion of the diagnostic and therapeutic recommendations for PKD in China. LC and XJH drafted and revised the manuscript and prepared the illustration. NW, ZYW, CZ, WHG, SYC, JHM, LW, YCD, QF, QN, JW, ZXW, YY, JYT, SFT, HYB, HJ, XRL, YL, MZS, JJW, EHX, TC, TC, XC, WL, SJL, QHL, XNS, YT, PY, YY, MZ, XZ, YHZ, RXZ, YOY, JTY, QZH, QK, YRY, ZZ, XHZ, GHZ, FRL, NC, JHH, and RP participated in discussions of the diagnostic and therapeutic recommendations for PKD in China and made comments on the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors have no competing interests to declare.

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Received: 23 August 2020 Accepted: 16 January 2021

Published online: 16 February 2021

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