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Neuropathophysiology of paroxysmal, systemic, and other related movement disorders

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Abstract. – Movement disorders are neurological conditions affecting the ability to produce and control voluntary as well as involuntary movements, and may be categorized into akinetic/rigid and hyperkinetic disorders. The hyperkinetic disorders are generally perceived as being the most difficult to diagnose correctly. They are manifested by excessive, abnormal involuntary movements, and are referred to as dyskinesias. The conditions are further designated paroxysmal dyskinesias when the abnormal movements occur episodically, followed by a rapid return to normality without impaired consciousness between episodes. The events can be precipitated by sudden voluntary movements, or may occur spontaneously at rest, or precipitated by exertion or sleep. Most conditions are either inherited or sporadic, and some cases are associated with specific conditions. Although clinical scenarios can be confusing, considerable advances in the phenotype characterisation and genetic studies have provided important information that allowed simplifying the clinical definitions and diagnosis of the paroxysmal dyskinesias. These advances have helped understand the pathophysiology of these disorders and their variants.

Key Words:
Movement disorders, Paroxysmal, Dyskinesia, PKD, PNKD, PED, PHD, Systemic diseases.

Abbreviations

PKD = paroxysmal kinesigenic dyskinesia; PNKD = paroxysmal non-kinesigenic dyskinesia; PED = paroxysmal exertion-induced dyskinesia; PHD = paroxysmal hypnogenic dyskinesia.

Introduction

Movement disorders are a group of neurological conditions manifested by inability to produce and control voluntary as well as involuntary movements. They comprise a large group of diseases with a wide range of different aetiologies and very different clinical presentations. Conventionally, movement disorders are divided into two main categories. The first category, referred to as dyskinesias, is hyperkinetic movement disorder dominated by excessive, abnormal repetitive involuntary movements. The second category, referred to as akinetic/rigid disorder, is hypokinetic movement disorder manifested by paucity or slowness of movement[1]. Since hyperkinetic disorders are usually perceived as being more difficult to diagnose correctly, we will focus on these disorders, with emphasis on paroxysmal dyskinesias that is the core of hyperkinetic disorders. This subset represents a group of episodic abnormal involuntary movements manifested by recurrent attacks of dystonia, chorea, athetosis, ballism, or a combination of these disorders. Dystonia being defined as an involuntary sustained contraction of a group of muscles, producing twisting/repetitive movement or abnormal postures, and chorea representing an abrupt, unsustained contraction of different muscle groups, while athetosis represents a prolonged contraction of the trunk muscle, resulting in bending and writhing of the body, and finally ballism being an abrupt contraction of the limb muscles, resulting in flailing movement of the limbs.

Based upon precipitating factors that precede or trigger the episodes of abnormal involuntary movement, paroxysmal dyskinesias have been classified into paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), paroxysmal exertion-induced dyskinesia (PED), and paroxysmal hypnogenic dyskinesia (PHD)[2]. In patients with PKD, the episodes of hyperkinetic movements are provoked by sudden voluntary movement. In contrast, in those

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with PNKD, the attacks may occur spontaneously at rest, while episodes are precipitated by prolonged exertion or sleep in patients with PED or PHD, respectively.

Although the exact aetiology of paroxysmal dyskinesias remains unknown, most cases are inherited or sporadic. Substantial progress has been made in determining the genetic basis of these disorders. For some forms, specific genes have been identified and clear genotype-phenotype correlations have been demonstrated. In certain cases, paroxysmal dyskinesias are secondary to specific conditions[3]. This review summarizes the updates on classification, clinical presentation and aetiology of the four main forms of paroxysmal dyskinesia, and presents a short preview on other variants of paroxysmal dyskinesia.

Classification of Paroxysmal Dyskinesias

The first classification of paroxysmal dyskinesias proposed by Lance[4] in 1977 was based on the duration of attacks, precipitating factors, and phenomenology of abnormal movements. This classification resulted into three forms, including paroxysmal kinesigenic choreoathetosis with movement-induced short attacks, paroxysmal dystonic choreoathetosis with long attacks not induced by movement, and paroxysmal exercise-induced dyskinesia with intermediate duration of the attacks[4]. Later in 1995, Demirkiran and Jankovic[2] proposed a new classification that was based exclusively on the precipitating factors, arguing that the precipitant was the best predictor of clinical course of paroxysmal dyskinesias and that the attacks in these disorders were not necessary choreic or dystonic, but could also be any form of dyskinesia[2]. Therefore, they broadly classified patients as having paroxysmal kinesigenic dyskinesia (PKD) if the disorder was induced by sudden movement or paroxysmal nonkinesigenic dyskinesia (PNKD) if it was not. Cases in which exercise was the precipitating cause were described as paroxysmal exertion-induced dyskinesia (PED), and those in which dyskinetic episodes occurred only at night during sleep were classified as having paroxysmal hypnogenic dyskinesia (PHD). Depending on the aetiology, cases under each form were also classified as primary or secondary (Figure 1).

Clinical Feature of Paroxysmal Dyskinesias

Figure 2 presents the most important clinical data related to primary paroxysmal dyskinesias.

PKD: The attacks in PKD are usually triggered by sudden movements like stand up, walking, running or startle, sudden acceleration or change in direction of movement. Before the attacks, most patients describe sensory aura such as limb paresthesia or vague premonitory sensation in the head or abdomen[5,6]. Dystonia is the most common attack with unilateral, bilateral, or alternating occurrence. Speech can be affected owing to dystonic spasms of the face or jaw. However, consciousness is preserved, and the attacks are not painful. Most attacks are very brief, lasting a few seconds to a few minutes, but recurring up to 100 times per day. The frequency of attacks is variable, usually peaking in puberty, with improvement or even remission in adulthood[5]. Age at onset is usually during childhood or early adulthood. The condition[5] more commonly affects males with a male to female sex ratio of 4:1.

PNKD: The attacks in PNKD are precipitated by caffeine, alcohol, fatigue, or emotional stress. As in PKD, many patients report an aura-like sensation just prior to the onset of the attack. This may take the form of paresthesias, tension in the limbs or an undefined feeling that patients recognize as the onset of another attack. Most commonly, the attacks manifest as episodes of dystonia, chorea, or athetosis involving one limb and gradually spreading to other limbs and face. Speed may be affected during the attack, but consciousness is always preserved like in PKD. However, patients with PNKD have longer and less frequent attacks compared with those with PKD. The attacks in PNKD, usually last four minutes to hours, sometimes up to a day, and occur a few times per week or just a few times in a lifetime. In general, the frequency varies from 1-3 per day to two per year, and the patients may have months of attack-free intervals. Most cases[5] have no detectable abnormalities between attacks, and the attacks occur more often in males than in females in the sex ratio of 4:1. Majority of the cases had their onset in childhood or early teens, and the attacks tend to diminish with age.

PED: The attacks in PED are typically precipitated by prolonged or sustained exercise[4]. However, in some cases, muscle vibration, exposure to cold, passive movement, electric nerve stimulation can trigger attacks[7]. Although the attacks can be variable, the most common presentation is dystonia and the legs are usually more affected. The usual duration is between 5 and 30

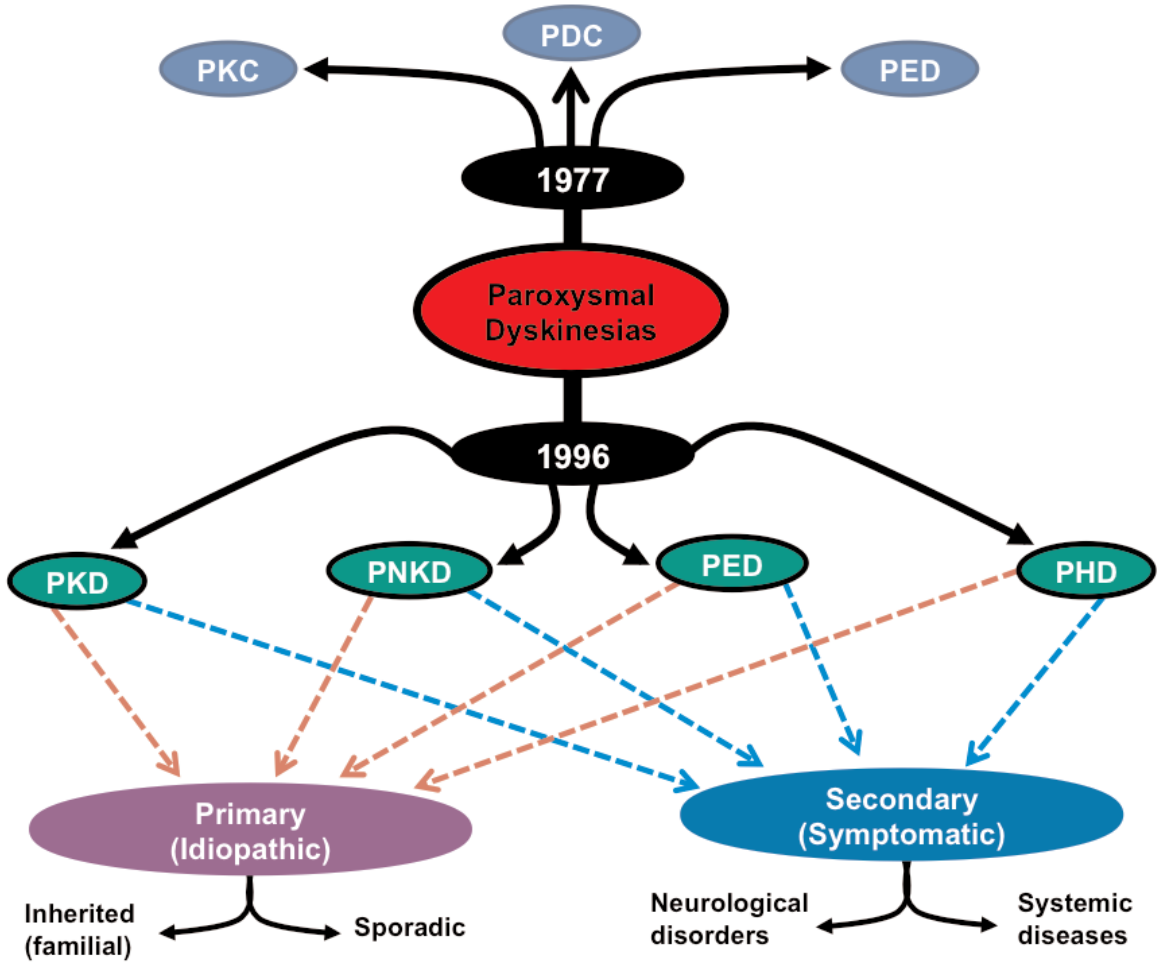

Figure 1. Classification of paroxysmal dyskinesias. PKC, paroxysmal kinesigenic choreoathetosis; PDC, paroxysmal dystonic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal non-kinesigenic dyskinesia; PED, paroxysmal exertion-induced dyskinesia; PHD, paroxysmal hypnogenic dyskinesia;

minutes and the frequency varies from one per day to two per month. The neurological examination is always normal between attacks. The attacks may be accompanied by migraine without aura[8] or a combination of alternating hemiplegia, epilepsy, and ataxia[9]. In some patients, PED may be the presenting sign of young-onset idiopathic Parkinson's disease[10]. The mean onset age is in childhood[11], ranging from 2 to 30 years, and the attacks occur with a male-female ratio of 2:3.

PHD: Typically, PHD manifests as attacks of dystonia chorea, ballism during non-rapid eye movement sleep associated with sudden awakening, whistling, uttering guttural sound, and appearing frightened[2,12]. The attacks may last from 30 seconds to 50 minutes, and occur from a few per night to a few per year[13]. The onset is commonly in childhood or early adulthood[11], and the attacks occur with a male-female ratio of 7:3.

Causes of Primary Paroxysmal Dyskinesias

Although the cause of paroxysmal dyskinesias remains unknown, most cases are primary, categorized as either familial or sporadic. Substantial progress has been made in determining the genetic basis of these disorders. For some forms of paroxysmal dyskinesias, specific genes have been identified (Figure 3).

Primary PKD: Most cases have a familial history of autosomal dominant inheritance with incomplete penetrance, but there are also many apparently sporadic cases. Several studies preformed independently using whole sequencing

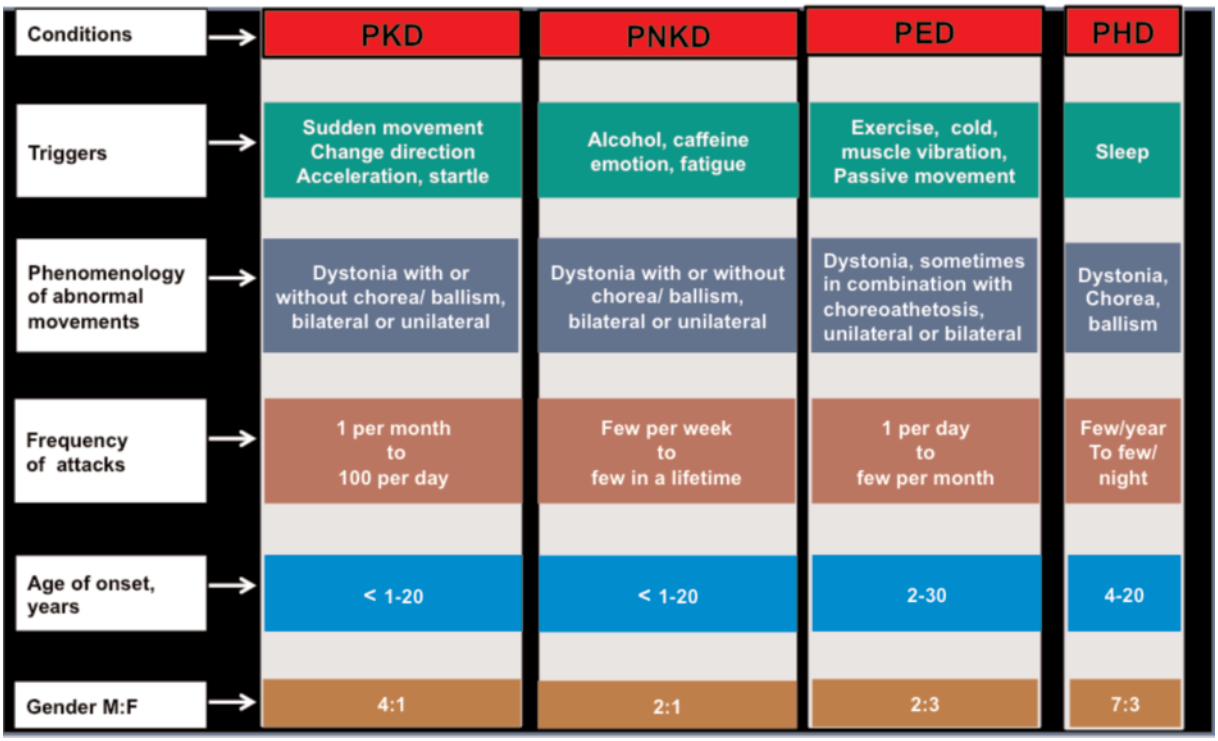

Figure 2. Clinical data of the primary paroxysmal dyskinesias. PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal non-kinesigenic dyskinesia; PED, paroxysmal exertion-induced dyskinesia; PHD, paroxysmal hypnogenic dyskinesia.

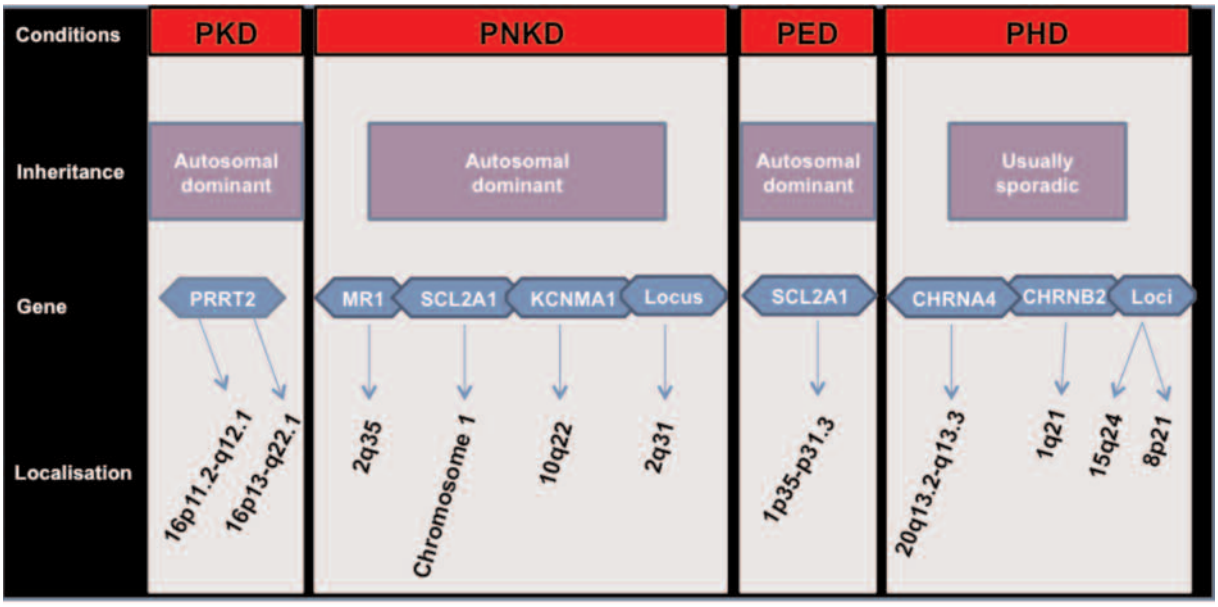

Figure 3. Genetic data of the primary paroxysmal dyskinesias. PKD, paroxysmal kinesigenic dyskinesia; PNKD, paroxysmal non-kinesigenic dyskinesia; PED, paroxysmal exertion-induced dyskinesia; PHD, paroxysmal hypnogenic dyskinesia

have identified heterozygous mutations in PRRT2 gene as the cause of PKD[14-17]. Subsequent to this discovery, an increasing number of reports confirmed that PRRT2 mutations are the major cause of PKD[18-23]. Most of these mutations are truncating and are predicted to result in haploinsufficiency. The PRRT2 gene is located within locus 16p11.2-q12.1, and PKD

associated with mutations in this gene is usually an autosomal dominant disorder. However, variable penetrance and *de novo* mutations in the PRRT2 have been reported[22-25]. Moreover, other PRRT2-negative families with PKD were found to have a gene mutation linked to chromosome 16q13-q22.1, or no mutation on chromosome 16[26-28]. Remarkably, patients with PRRT2 mutations were found to have younger age of onset and higher frequency of attacks than PRRT2-negative patients[6,29]. Moreover, mutation analysis has revealed an association of PRRT2 mutations with migraine, hemiplegic migraine, episodic ataxia, febrile seizure, sporadic infantile convulsion and paroxysmal torticollis, alone or in various combinations[30]. Furthermore, homozygosity of PRRT2 mutations was reported in 2 families with more severe clinical features including intellectual disability, episodic ataxia, and infantile seizures[31].

Primary PNKD: Most cases of PNKD are familial with an autosomal dominant inheritance and a high but incomplete penetrance[32]. All the typical familial cases of PNKD were found to link to chromosome 2q35[33]. Subsequently, the causative gene was identified and a missense mutation in the myofibrillogenesis regulator (MR1) was detected[34]. Mutation analysis of this gene has revealed that patients with MR1 mutations had onset of attacks in infancy or early childhood, precipitation of attacks by caffeine, and alcohol. In contrast, patients with PNKD who did not carry a MR1 mutation were more variable in their age of onset, provoking factors, and paroxysmal feature[35]. In a family with many members having developed PNKD with spastic paraparesis, mutation was detected in SLC2A1 gene on chromosome-1 encoding glucose transporter (GLUT1)[36], while mutation in the calcium-sensitive potassium channel (KCNMA1) gene on chromosome 10q22 was found in a family with PNKD with epilepsy[37]. Another gene candidate was mapped on chromosome 2q31 in a family with PNKD affecting the hands and feet symmetrically[38].

Primary PED: Although sporadic cases have been described[7,11], PED is usually inherited in an autosomal dominant fashion. Mutations in the SLC2A1 gene on chromosome 1p35-p31.3, encoding for GLUT1 were detected in several families and sporadic patients with PED[39-41]. The classical phenotype associated with these mutations includes epilepsy, hemiplegic migraine, developmental delay, infantile seizures, altering hemiplegia, and hypoglycorrhachia[40,42]. Moreover, heterogeneity of SLC2A1 mutation was causatively associated with progressive spastic paraplegia in patients with PED, but not in patients with hereditary spastic paraplegia without paroxysmal dyskinesia[36].

Primary PHD: Most cases are sporadic, and some cases are familial with an autosomal dominant inheritance and mutations in gene coding for nicotinic acetylcholine receptor. These mutations are associated with nocturnal frontal lobe epileptic, and the mutated genes include CHRNA4 gene on chromosome 20q13.2-q13.3, CHRNB2 gene on chromosome 1q21, and loci on chromosomes 15q24 and 8p21[43,44].

Causes of Secondary Paroxysmal Dyskinesias

A variety of neurologic and a wide spectrum of systemic diseases as well as certain drugs can produce symptoms resembling paroxysmal dyskinesias (Figure 4).

Secondary PKD: The most common cause of secondary PKD is multiple sclerosis[45]. The attacks may be kinesigenic but are most consistently precipitated by hyperventilation and can be extremely painful. Attacks typically are unilateral with or without the face. Each attack lasts from a few seconds to a few minutes, and multiple attacks can occur during the day. The attacks tend to subside spontaneously over many weeks. The lesions reported in multiple sclerosis-related PKD cases included the contralateral thalamus, lentiform nuclei, globus pallidus, internal capsule, mesencephalic peduncle and cervical cord[46-48]. Other causal associations are cerebral palsy, metabolic disorders, head injury, cerebrovascular disease, strock, hypoparathyroidism, hypoglycaemia, perinatal hypoxic encephalopathy, and diabetes mellitus.

Secondary PNKD: Similar to PKD, the most frequent cause of secondary PNKD is multiple sclerosis. However, the attacks are very brief and often painful being, thus, typical of tonic spasms of multiple sclerosis and not the long-duration attacks of classical PNKD. These attacks consist of dystonic posturing of the arm and/or the leg on side of the body, and sometimes the face. They can be precipitated by

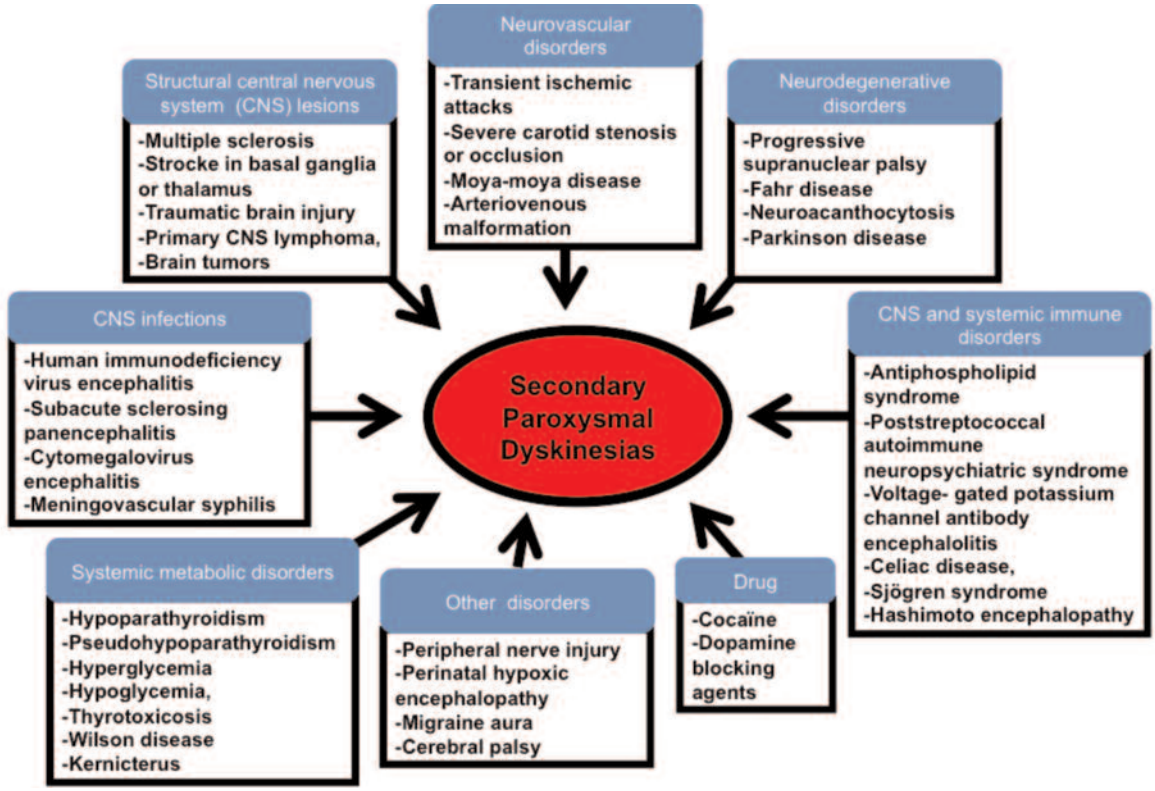

Figure 4. Cause of secondary paroxysmal dyskinesias.

voluntary movement, tactile stimulation or hyperventilation, and preceded by a sensory aura in either the affected or the contralateral limbs. In addition of multiple sclerosis, there have been numerous other reported causes including encephalitis, head trauma, hypoparathyroidism, thyrotoxicosis, basal calcification, and a case with AIDS. Overall, most disorders causing PKD have also been associated with PNKD, and in some reports it is unclear whether the patient had PKD, PNKD, or both.

Secondary PED: Causes of secondary PED have been reported only occasionally and in those cases they appear to be secondary to trauma[2,49].

Secondary PHD: Since the first description of PHD, no secondary case has been documented. All reported cases of PHD are primary.

Other Variants of Paroxysmal Dyskinesia

In addition of the four main subtypes already described, there are other variants of paroxysmal disorders that do not fit into any of the descriptions.

Paroxysmal torticollis in infancy: This variant is a self-limiting disorder in infants characterized by attacks of head tilt or turn to alternating side, lasting for minutes to 2 weeks. The attacks remit by the age of 2 years.

Transient paroxysmal dystonia in infancy: This variant is another self-limiting disease of children younger than 2 years, manifesting as attacks of dystonia in the neck and limbs, and opisthotonus of a few minutes duration. The attacks are triggered by certain movements or position and thus may present an infantile variant of PKD.

Benign paroxysmal tonic upgaze: This variant manifests as sudden sustained upward deviation of the eyes in early childhood with onset around 9 months. This may be associated with mild ataxia with down-beating nystagmus on attempted down gaze and apparently preserved horizontal eye movement.

Paroxysmal ataxias: These variants are rare genetic disorders caused by the mutations in the genes encoding membrane ion-channel proteins inherited in autosomal dominant fashion. They manifest as brief recurrent attacks of ataxia, sometimes associated with other ictal symptoms, and typically normal interictal neurologic examination except for myokymia, nystagmus, or mild ataxia in some type of

ataxias. The onset in most ataxia types is childhood or early adulthood.

Familial paroxysmal dyskinesia with facial myokymia (FDFM): This variant is a rare autosomal dominant disease characterized by childhood onset of choreiform movements in the limbs associated with periorbital and myokymia. The attacks are precipitated by anxiety. A high prevalence of heart disease in adult patients with FDFM has been reported. Mutations in the gene of adenylyl cyclase 5 were identified in familial and sporadic cases[50].

Paroxysmal tongue: This variant is characterized by a delay onset of episodic, rhythmic, involuntary movement of the tongue following head or neck trauma. Focal tongue contractions are usually slow, about 3 per second, and episodes last approximately 10 seconds, persisting for 2-4 months. In some other cases, episodic lingual dystonia has also been sometimes related to brain stem ischemia or anoxic encephalopathy as well as a primary disorder.

Conclusions

Movement disorders with predominant paroxysmal dyskinetic feature occur in a wide variety of genetic and acquired conditions. Although the resulting clinical scenarios can be confusing and difficult to interpret by physicians, there have been major advances in the understanding of the genetics of these disorders, leading to better clinical definitions based on genotype-phenotype correlation in the familial idiopathic forms. However, secondary cases are notable for their variability in age of onset as well as the presence of both kinesigenic and nonkinesigenic symptoms in some patients. Therefore, awareness of the variable phenomenology and the spectrum of causes associated with secondary paroxysmal dyskinesias will allow for more timely diagnosis and early intervention.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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