Paroxysmal Movement Disorders

A Practical, Concise Guide

Kapil D. Sethi
Roberto Erro
Kailash P. Bhatia
Editors

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ISBN 978-3-030-53720-3 ISBN 978-3-030-53721-0 (eBook)
https://doi.org/10.1007/978-3-030-53721-0

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

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Chapter 1
Paroxysmal Dyskinesia: Definitions and Clinical Approach

Roberto Erro, Kapil D. Sethi, and Kailash P. Bhatia

Definitions

Paroxysmal dyskinesia (PxD) are a heterogeneous group of disorders characterized by recurrent episodes of abnormal movements, namely, dystonia, chorea, or a combination thereof, of variable duration and without loss of consciousness [1, 2]. Following earlier descriptions and inhomogeneous terminology used to describe different PxD subtypes (cfr. Chap. 2 on the early history of PxD), the classification proposed by Demirkiran and Jankovic in 1995 has been a significant turning point for several reasons [3]. First, they suggested adopting the term *dyskinesia* over previously adopted terminology (i.e., choreoathetosis, choreo-dystonia, etc.), since the specific phenomenology of the abnormal movements could only be presumed based on patients' description. Moreover, and more importantly, they discarded the duration of the attacks as the main anchor, which was the case in the earlier classification by Lance [4] (cfr. Chap. 2), and suggested a classification scheme based on attack triggers as both short and long attacks could be observed within each PxD subtype in their cohort of patients [3]. They therefore suggested four main PxD subtypes, only based on triggers, as follows: (1) paroxysmal kinesigenic dyskinesia (PKD) in which the attacks are characteristically triggered by sudden movements; (2) paroxysmal exercise-induced dyskinesia (PED), brought on by sustained and prolonged exercise; (3) paroxysmal non-kinesigenic dyskinesia (PNKD) in which neither

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_1

sudden movements nor exercise induces the attacks (triggers might be in this subtype quite heterogeneous or there are no identifiable triggers); and (4) paroxysmal hypnogenic dyskinesia (PHD) in which attacks occur only during sleep [3]. Each of these subtypes could be subsequently stratified into *primary* (either sporadic or familial) and *secondary* forms, based on the presence of detectable abnormalities on imaging or history of neurological disorders possibly associated with the attacks [3].

Although this trigger-based classification has dominated the clinical and research field, recent evidence stemming from the discovery of the main genes associated with PxD has challenged this classification scheme [5, 6].

Firstly, it has become clear that PxD occurring in well-defined genetic conditions (i.e., those formerly termed *primary* forms) can be delineated in most cases based on both the type of trigger and the duration of the attacks. For instance, PKD attacks due to *PRRT2* mutations (cfr. Chap. 3) are typically induced by sudden movements, hence kinesigenic, but are also very brief in duration in the large majority of patients, at variance with PNKD and PED (Table 1.1) [6]. Therefore, while we retained in this book the nomenclature of PxD based on triggers (cfr. Chaps. 3, 4, and 5), we would like to emphasize that the triggers but also the duration of the attacks should be explored in every PxD case, since both these features together are very useful when considering subsequent genetic analyses.

Secondly, the fourth subtype of PxD proposed by Demirkiran and Jankovic which was characterized by nocturnal attacks occurring in sleep (i.e., PHD) [3] was subsequently found to be a form of autosomal dominant frontal lobe epilepsy (ADFLE) in most cases [7]. Hence, this entity was dropped as a form of classic PxD, and later research has largely adopted a classification scheme with three main subtypes, which will be covered in this book, namely, PKD, PNKD, and PED (cfr. Chaps. 3, 4, and 5). It should be noted, however, that recently PHD have been reported with *PRRT2* mutations (cfr. Chap. 3) [8] as well as *ADCY5* gene mutation patients (cfr. Chap. 9) [9]. This has led to suggestions by some for a re-inclusion of

Table 1.1 Overview of the main primary forms of paroxysmal dyskinesia

	Paroxysmal kinesigenic dyskinesia (PKD)	Paroxysmal non-kinesigenic dyskinesia (PNKD)	Paroxysmal exercise-induced dyskinesia (PED)
Trigger(s)	Sudden movements, acceleration, or intention to move	Variable (often alcohol and/or caffeine)	Sustained exercise
Duration	Very brief (usually <1 min)	Long (usually >30 min)	Intermediate (usually about 10–20 min)
Age at onset	Usually <18 years of age	Usually <18 years of age	Variable (often in childhood)
Family history	AD/sporadic	AD	AD/sporadic
Additional features	Epilepsy, rarely episodic ataxia and/or hemiplegic migraine	None	Variable (depending on the severity of mutation)
Main gene	*PRRT2*	*PNKD* (formerly known as *MR-1*)	*SLC2A1* (GLUT1)

PHD as a PxD subtype [2]. Although sleep is not strictly the trigger in these cases, it may be considered equivalent to other triggers (such as sudden movement, exercise, etc.) as the answer when patients are asked the question of when the PxD attacks occur is during sleep.

Thirdly, one of the criteria for the clinical diagnosis of those PxD forms formerly classified as *primary* was a normal neurological examination between the attacks [1]. We discard this argument since there is evidence that PxD can be either isolated, hence with normal interictal neurological examination, or associated with other features [2]. The most notable example in this regard is represented by *SLC2A1* (GLUT1, glucose transporter type 1) mutations, which can produce isolated PED (previously assigned the DYT18 number), PED associated with interictal spasticity (previously assigned the DYT9 number), as well as several different phenotypes (cfr. Chap. 5).

Fourthly, there is an increasing discouragement in the use of the terms "primary" and "secondary," since the former implies there are no detectable abnormalities, whereas most *primary* PxD are in fact found to be *secondary* to a genetic defect. We support this concept and rehash for PxD the classification of dystonia in general [10], which consists of two axes: the first one recapitulating the clinical aspects of the PxD and the second one dealing with the etiological underpinnings of a given subtype. As such, any PxD subtype, for instance, PNKD (axis 1), can be idiopathic, genetically determined, or acquired (axis 2). However, we further felt that from a pragmatic standpoint it might be useful to clearly separate the genetically determined PxD, in which a good phenomenological-genetic correlation exists (Table 1.1; cfr. Chaps. 3, 4, and 5), from the acquired forms (i.e., those formerly ascribed to *secondary* PxD), in which the phenomenology is not usually indicative of the underlying disorder. As such, these acquired forms of PxD will be reviewed altogether in Chap. 6.

Recent evidence has also suggested that paroxysmal episodes of chorea or dystonia can occur in other disorders but have escaped the PxD classification as other features including, for instance, the distribution of attacks prevailed in the definition of the episodes. This is the case, for example, of recurrent episodes of arm dystonia in *ATP1A3* mutations (i.e., alternating hemiplegia of childhood) [11]. This and other similar conditions encompassing paroxysmal movement disorders, beyond the classical PKD, PNKD, and PED, will be covered in Chap. 9.

Finally, PxD and related disorders are firstly defined by the presence of involuntary movements, namely, chorea and/or dystonia, thus not encompassing other paroxysmal movement disorders including myoclonus and tremor. However, another rubric of conditions that are characterized by recurrent episodes of unsteadiness, namely, the episodic ataxia (EA), should be considered in the differential diagnosis in some cases, since they might additionally present with choreoathetosis [12]. Moreover, the discovery of mutations in genes encoding for ion channels and responsible for EA has also fostered the hypothesis that PxD could represent channelopathies, given some similarities between these two groups of disorders (cfr. Chap. 7) [13]. For these reasons, EA will be also covered in this book in Chap. 11.

Clinical Approach

When approaching to a patient with attacks of what might represent involuntary movements, the first step in the differential diagnosis is to understand whether the clinical abnormality is in fact a PxD subtype (and more in general a paroxysmal episode of chorea and/or dystonia) or not. By definition, the phenomenology of PxD is that of dystonia and/or chorea, with ballism being possible, so that other intermittent, fluctuating, or waxing and waning movement disorders, such as tics, action myoclonus, startle syndromes, and certain tremors, should be not intended as PxD. Moreover, there are a number of episodic neurological disorders including epilepsy, tetany, neuromyotonia, and periodic paralyses, some of which can produce intermittent disordered movements. These need to be excluded by appropriate history and ancillary investigations as prompted by specific clinical clues. For example, in a patient complaining of limb posturing upon exercise, the finding of delayed muscle relaxation after voluntary contraction might redirect the diagnostic suspicion from PED to myotonia.

Once the clinical diagnosis is established, it is important to explore the presence of family history and to fully characterize the episodes in terms of age at onset, triggers, duration, and distribution. A clinical syndrome with onset in childhood, consistent triggers and duration of the attacks, will be more likely to be *primary* (i.e., associated with one of the main PxD genes). A large proportion of these cases will also have unrevealing neurological examination. If not, a syndromic approach should facilitate the differential diagnosis within each subtype (cfr. Chaps. 3, 4, and 5) [2]. The presence of additional (or atypical) features should raise the suspicion, especially with onset in adulthood and in the absence of family history for related disorders, of acquired forms (cfr. Chap. 6). Former proposals included functional (psychogenic) causes among these forms. However, it is our experience that these cases might be challenging to diagnose, also owing to the fact that no abnormalities on investigations are found, as in most genetically determined cases. We therefore felt that functional (psychogenic) forms of PxD deserve a dedicated chapter (cfr. Chap. 10).

Reaching a definitive diagnosis has crucial treatment implications. In fact, in most cases therapy choices heavily depend on the underlying etiology rather than on the specific phenomenology of the attacks. Although there is a good clinical-etiological correlation within the genetically determined forms of PxD (Table 1.1), clinical heterogeneity has been demonstrated within each subtype [2, 6, 14] and justifies additional efforts to reach a definitive diagnosis. Obviously, there will be cases where no definitive cause is found. These patients might be called idiopathic for now and treatment options considered on empirical basis, while awaiting future, genetic or otherwise, causes of PxD.

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Chapter 2
The Early History of Paroxysmal Dyskinesias

Stanley Fahn

Earliest Descriptions of Paroxysmal Dyskinesia Were Reported as Epilepsy

Gowers is usually credited with the initial description of movement-induced seizures [1, 2]. However, some of his cases were probably kinesigenic paroxysmal dyskinesia. One was a boy whose attacks lasted about 15 s. Another was an 11-year old girl, whose attacks occurred on suddenly arising after prolonged sitting. Subsequent to Gowers, a number of reports of "movement-induced seizures" appeared in the literature; some were called reflex epilepsy and some tonic seizures induced by movement. But unlike typical motor convulsions, there was no alteration in the state of consciousness. In addition, some of these reports described more than tonic contraction; there was sustained twisting, athetosis, and chorea. Today, they would be labeled as paroxysmal dystonia and paroxysmal choreoathetosis, rather than convulsive seizures. Even the presence of choreoathetosis did not lead to the conclusion that the attacks were a type of movement disorder. Instead, the earliest interpreters of these brief attacks considered them as a form of epilepsy, with the site of origin being in the basal ganglia or in the subcortical region.

Sterling used the term "extrapyramidal epilepsy" to describe a series of patients with encephalitis lethargica who had brief or prolonged (up to 6 h) painful sustained spasms that occurred intermittently [3]. Consciousness was unimpaired. He used the term tetanoid to describe the postures of the hands and feet. Years later, Lance questioned the use of the term extrapyramidal epilepsy because of the long duration of some of the attacks, as well as the origin of the attacks [4].

Stertz coined the term "striatal epilepsy" [5]. He described a postencephalitic patient who had developed seizures and then dystonia, with postmortem evidence of

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_2

lesions in the striatum. In the following year, Wimmer borrowed the same term to describe a boy who had attacks of torticollis and unilateral limb athetoid or torsion spasms, lasting a few seconds without loss of consciousness [6].

After the report of Gowers, the next report of movement-induced paroxysmal movements appears to be that of Spiller who described two patients with brief tonic spasms brought on by voluntary movement of the involved limbs and, in one of them, also by passive manipulation [7]. The contractions were painful and accompanied by sensations of heat or burning. Despite a lack of an autopsy, Spiller labeled the attacks as "subcortical epilepsy." He preferred this term rather than striatal epilepsy because of the pain associated with the attacks. Wilson described a 5-year-old boy who had brief attacks of unilateral torsion and tonic spasm that lasted up to 3 min and were precipitated by fright or excitement [8]. There was no loss of consciousness. The attacks could be preceded by pain. Wilson considered these to be reflex tonic epilepsy and thought it also to be subcortical in origin (Table 2.1).

However, the label of movement-induced seizures continued into the early 1970s. For example, Lishman and colleagues described seven patients with tonic and athetoid spasms induced by movement while remaining conscious [10]. Abnormal sensations of numbness, vibration, and tightness, but not pain, were noted in the affected limbs before the attacks. Like Gower, these authors considered that the movement-induced attacks were a form of reflex epilepsy and discussed other idiopathic cases in the literature (e.g., Pitha [9] and Michaux and Granier [11]). Two years after Lishman's 1962 paper, he and his colleagues reported five additional cases of movement-induced seizures [12]. Burger et al. described two patients with this label [13]. Japanese neurologists [14] and others [15] have also referred to these as some form of epilepsy.

Table 2.1 Some of the earliest reports of paroxysmal dyskinesia reported as seizures

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	[a]Type of movement	Treatment
Gowers (1885) [2]	1	M	Boy	Probably idiopathic	?	Movement	–	?	
	2	F	1	Probably idiopathic	?	Movement	–	?	
Sterling (1924) [3]	1		10	Epidemic encephalitis					
Wimmer (1925) [6]	1	M	Boy	Probably idiopathic				Athetoid	
Spiller (1927) [7]	1	F	62	Probably secondary	0	Movement	+		
	2	F	46	Probably vascular	0	Passive and active movement	+		
Wilson (1930) [8]	1	M	5	Probably idiopathic		Excitement	+	Torsion	
Pitha (1938) [9]	1	M	6	Idiopathic	0	Movement	+		Anti-convulsants

Abbreviations used: + present or yes, – absent or no, ? no information given

[a]Movements consisted of sustained postures (dystonia) plus any other type listed

James Lance, who was instrumental in eventually providing a classification of the paroxysmal dyskinesias, had, like his predecessors, also initially labeled these attacks as seizures, calling them tonic seizures. A major introduction to the field at that time was his observation that not all attacks of tonic spasms are induced by movement [4]. His initial report described eight patients with attacks of tonic (dystonic) spasms, some with choreoathetosis, usually affecting only one side of the body and often preceded by pain or tingling. Two patients had secondary attacks (static encephalopathy and multiple sclerosis). One was idiopathic and sporadic, and the remaining five were members of the same family. The attacks lasted less than 1 min in two patients, 2–5 min in the patient with multiple sclerosis, and 5–60 min in the five familial cases. These attacks were not precipitated by movement. The familial cases were aggravated by excitement and fatigue. No EEG abnormality was recorded between attacks. A decade and a half later, Lance recognized them as *paroxysmal dystonic choreoathetosis* (PDC) and coined this new term [16]. Since then, these attacks of tonic, often twisting, contractions without loss of consciousness have been considered paroxysmal dyskinesias rather than seizures. Partially responsible for this switch may be the development of the subspecialty of movement disorders in the 1980s.

Actually, papers bearing the title of "paroxysmal choreoathetosis" began to appear in the late 1960s [17–19]. Particularly for those cases induced by movements, this new terminology was a departure from *reflex epilepsy*. Even in the late 1960s, there were still occasional papers referring the condition to a seizure disorder [20], and some authors linked paroxysmal dyskinesia and seizures [21].

Differentiation between cortical seizures and paroxysmal dyskinesia can sometimes be difficult. Clouding of consciousness, if it occurs, would point to a seizure disorder. This is exemplified by the case reported by Falconer and colleagues [22] of a man who had focal seizures induced by movement and lasting for 10–20 s. There was clouding of consciousness with severe attacks, but not with mild attacks. The patient underwent a craniotomy and had a cicatrix removed from the involved hemisphere which resulted in a cessation of further attacks. Lishman and colleagues [10] refer to the report by Strauss [23] of an individual with a movement-induced Jacksonian march as another example of movement-induced epilepsy. However, this case does not justify the other reports of cases without a Jacksonian march as being examples of epilepsy, because the presence of the march is so distinctive and specific that it would clearly be an example of a cortical-induced seizure.

Earliest Reports That These Types of Conditions Are a Paroxysmal Disorder of Involuntary Movements

In 1940, a new concept was introduced by Mount and Reback [24]; they labeled attacks of tonic spasms plus choreic and athetotic movements as a paroxysmal type of movement disorder. They described a 23-year-old man who had "spells" since infancy, both "large" and "small." Both types were preceded by a sensory aura of tightness in parts of the body or by a feeling of tiredness. The movements involved

the arms and legs and were usually a combination of sustained twisted posturing and chorea and athetosis. The small attacks lasted from 5 to 10 min. Longer attacks were considered large and also involved the neck (retrocollis), eyes (upward gaze), face, limbs, (ipsilateral, if the limb involvement was unilateral), and speech. These large attacks lasted for as long as 2 h, and the movements were considered to resemble those seen in Huntington disease. There was never a loss of consciousness or clonic convulsive movements, biting of the tongue, or loss of sphincter control. Drinking alcohol, coffee, tea, or cola would often bring on an attack. Fatigue, smoking, and concentrating were other precipitating factors. The attacks would clear more rapidly if the patient lay down and would be aborted by sleep. The patient had an average of one large and two small attacks a day. Between attacks, the neurologic examination was normal. Phenytoin and phenobarbital were without effect, and scopolamine was the only drug found to reduce the frequency, severity, and duration of the attacks. The family history revealed 27 other members who had similar attacks, with the pedigree showing autosomal dominant inheritance with what appears to be complete penetrance. Mount and Reback called this disorder "familial paroxysmal choreoathetosis."

The paper by Mount and Reback has become the seminal paper in the field of paroxysmal dyskinesias. Following its publication, most of the reports in the literature referenced it over the next five decades. However, the chronologically next report of a large family with similar attacks of muscle spasms did not refer to it. In 1961 Forssman [25] described a family with autosomal dominant inheritance in which there were attacks lasting from 4 min to 3 h. The attacks were induced by cold, mental tension, irritation, fatigue, lack of sleep, alcohol, and caffeine. The attacks consisted of sustained muscle contractions, usually of a twisting nature. The onset of the attacks was in early childhood in most of the affected members. An attack might begin with tonic spasm in one hand, spread up the arm, to the other arm, both legs, and then cranial muscles, including tongue, so that the individual could not speak in a severe attack. Clonic spasms could appear at the height of the attack. The onset would often be preceded by a "tugging" sensation in the affected body part. Forssman considered the disorder to be a new entity, possibly related somehow to myotonia and paramyotonia. He ruled out these conditions because they are not triggered by alcohol. He did not consider it a form of epilepsy since there was no alteration of consciousness, although the patient had been considered an epileptic by other neurologists.

The next large family described was in 1963 by Lance [4] (mentioned above). Like Forssman [25], Lance also did not relate this to nor reference Mount and Reback's report nor did he mention the report by Forssman. In fact, Lance considered his patients to have a form of epilepsy, similar to the concept of Spiller [7], Wilson [8], and Lishman et al. [10]. Later, in 1977, Lance [16] was to write one of the definitive papers in this field, containing a useful classification scheme, in which he relates this family to those of Mount and Reback [24], Forssman [25], and Richards and Barnett [26].

In 1941, the year following Mount and Reback's paper, Smith and Heersema [27] reported three similar cases (two of them familial) seen at the Mayo Clinic

which they labeled as "periodic dystonia." The ages at onset were 7, 8, and 14. These authors thought that their cases were similar to the family of Mount and Reback. Their first patient was described as being able to induce the involuntary movements by shaking a leg. Two and a half decades later, Hudgins and Corbin [21] provided a follow-up report of the three individuals reported by Smith and Heersema [27] while reporting a new family seen at the Mayo Clinic with three members affected by brief attacks of torsion movements of the torso and choreoathetosis of the limbs precipitated by initiation of sudden movement. From their review of the Mayo Clinic records, Hudgins and Corbin recognized that the initiation of movement was the principal factor in the provocation of the daily dystonic attacks in the three cases reported by Smith and Heersema. Thus, it appears that the first report of paroxysmal kinesigenic choreoathetosis/dystonia labeled as a paroxysmal dyskinesia (periodic dystonia) was that by Smith and Heersema, although these authors did not particularly recognize the phenomenon of sudden movement as a critical factor.

Although there were reports of patients whose paroxysmal dyskinesias were induced by sudden movement, they were not particularly denoted by any special terminology until 1967, when Kertesz [19] introduced the label "paroxysmal kinesigenic choreoathetosis" (PKC). This label has developed into a most useful and widely accepted designation since the kinesigenic feature has proven to be so characteristic. Kinesigenicity has an important place in the classification of the paroxysmal dyskinesias, although as will be pointed out below, the PKC designation can be applied to some select patients who do not have the dyskinesia triggered by sudden movement (or startle).

Kertesz [19] reported ten new cases of paroxysmal dyskinesia and reviewed the literature. Among the important features of his paper, Kertesz differentiated the kinesigenic variety (induced by sudden movement) from that described by Mount and Reback, by Forssman, and by Lance, which were not aggravated by movement but by alcohol, caffeine, and fatigue. It should be noted that Kertesz differentiated the kinesigenic type from that reported by Mount and Reback [24] and by Lance [4], but he did not mention the paper by Forssman [25].

Williams and Stevens [28], Stevens [17], and Rosen [29] all described kinesigenic cases, but did not label their cases as kinesigenic but adopted the term paroxysmal choreoathetosis as proposed by Mount and Reback. There have been a large number of additional kinesigenic cases reported after the introduction of the kinesigenic terminology by Kertesz [19].

After the 1963 paper by Lance, Weber [30] reported a family of four affected members with non-kinesigenic paroxysmal dystonia and used the term "familial paroxysmal dystonia." Richards and Barnett [26] reported another big family with the same type of paroxysmal dyskinesia as Mount and Reback's case and thought that Lance's family [4] represented a variant since there was only tonic spasms and no movements in that family. The family of Richards and Barnett consisted of nine affected members with the trait inherited in an autosomal dominant pattern. They emphasized the non-kinesigenic nature of the attacks and felt that a wide array of terms could describe the attacks, depending on the severity of each one. They considered that the terms rigidity, tremor, dystonia, torsions spasm, athetosis, chorea,

and hemiballism could all be used for such movements, often blending into each other. To emphasize the postural change and increased tone, they added "dystonic" to the label. They recommended avoiding the term "epilepsy" until the pathophysiology is better known. Richards and Barnett coined the term "paroxysmal dystonic choreoathetosis" (PDC), which was later adopted by Lance in 1977 [16]. The terms "paroxysmal non-kinesigenic choreoathetosis" and "paroxysmal dystonia" were sometimes used instead of PDC [31].

Although phenytoin was recognized earlier as a very useful agent for paroxysmal kinesigenic choreoathetosis/dystonia, carbamazepine was later found to be as useful and was introduced as a treatment by Kato and Araki [32]. This drug still appears to be the one most commonly used for this disorder.

The original cases reported as paroxysmal dyskinesia were idiopathic (Tables 2.2 and 2.3) and usually familial. It was not long before symptomatic cases began to be reported in which the attacks of movements were reported as a paroxysmal dyskinesia: perinatal encephalopathy [29], encephalitis [18], and head injury [12, 33]. However, earlier reports of symptomatic paroxysmal non-kinesigenic dyskinesia had been described as a manifestation of multiple sclerosis but considered as a form of epilepsy [34–36] and of idiopathic hypoparathyroidism (Tables 2.4 and 2.5).

Perhaps the earliest enlightening paper in this field in terms of classification is that by Lance [16]. Lance (1) discovered Forssman's paper [25]; (2) placed together as one syndrome the families reported by Mount and Reback [24], Forssman [25], Richards and Barnett [26], and himself [4], bringing them all in under the term familial paroxysmal dystonic choreoathetosis (PDC) which has a duration of attacks from 5 min to 4 h; (3) expanded the description of his own previously reported family [4] that he now classified as having this disorder instead of a seizure disorder as he originally had reported it; (4) added another family of paroxysmal dyskinesia that had attacks induced by continuous exercise and not sudden movement that affected the legs and with a duration between 5 and 30 min; (5) classified the paroxysmal dyskinesias into three groups separated primarily by duration of action (prolonged, intermediate, and brief attacks) and secondarily by precipitating factors; (6) reported the therapeutic response to clonazepam in some patients with the prolonged attacks; (7) mentioned normal autopsy findings in two individuals with the prolonged attacks; (8) summarized the literature to that date; (9) mentioned that the Forssman and Lance families with the prolonged attacks had dystonic postures without choreoathetosis while the Mount and Reback and the Richards and Barnett families had choreoathetosis; (10) described that over time those with sustained spasms can eventually develop writhing movements, thereby linking these phenotypes together; and (11) commented that in all types of paroxysmal dyskinesia, males are more affected than females.

The next historical advances were the recognition that (1) idiopathic PDC can occur sporadically and not just in families [31] and (2) that sporadic PDC is often psychogenic in origin [31, 106].

Before closing this section, it should be noted that an argument had been raised by Martinelli and Gabellini [107] that a description of PKC was made in 1884, but their description of the original communication is not convincing.

Table 2.2 Early reports of idiopathic paroxysmal kinesigenic dyskinesia (PKD) (formerly called PKC)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Smith and Heersema (1941) [27]	1	M	8	Idiopathic	+	Sudden mvt	–	
	2	M	14	Idiopathic	–	?	+	
	3	M	7	Idiopathic	+	Movement	+	
Michaux and Granier (1945) [11]	1	F	6	Idiopathic	–	Sudden mvt	+	Anticonvulsant
Pryles et al. (1952) [37]	1	M	8	Idiopathic	+	?	+	PHY, AMPH
	2	M	13	Idiopathic	+	?	+	Anticonvulsant
Kishimoto (1957) [38]	1	M	8	Idiopathic	+	Sudden mvt	–	
	2	M	12	Idiopathic	+	Sudden mvt	–	
	3	M	9	Idiopathic	+	Sudden mvt	?	Barbiturate
	4	M	9	Idiopathic	+	Sudden mvt	–	
Lishman et al. (1962) [10]	1	M	3	Idiopathic	–	Sudden mvt	+	Anticonvulsant
	2	M	5	Idiopathic	–	Sudden mvt	?	Anticonvulsant
	3	M	14	Idiopathic	–	Sudden mvt	+	Anticonvulsant
	4	M	20	Idiopathic	–	Exercise	–	
	5	M	7	Idiopathic	–	Sudden mvt	–	Anticonvulsant
	6	M	15	Idiopathic	–	Sudden mvt	+	PHY
	7	M	11	Idiopathic	–	Sudden mvt	+	PHY
Williams and Stevens (1963) [28]	1	F	1	Idiopathic	?	Sudden mvt	+	PHY
Whitty et al. (1964) [12]	1	M	13	Idiopathic	–	Sudden mvt	+	Anticonvulsant
	2	M	12	Idiopathic	–	Sudden mvt	–	Anticonvulsant
	3	M	13	Idiopathic	–	Sudden mvt	–	Anticonvulsant
	4	M	<18	Idiopathic	+	Sudden mvt	–	Anticonvulsant
	5	M	8	Idiopathic	+	Sudden mvt	–	Phenobarb

(continued)

Table 2.2 (continued)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Hudgins and Corbin (1966) [21]	1	M	5	Idiopathic	+	Sudden mvt	–	Anticonvulsant
	2	F	11	Idiopathic	+	Mvt, stress	+	Anticonvulsant
	3	F	13	Idiopathic	+	Movement	?	Remission
Stevens (1966) [17]	1	Same case as reported by Williams and Stevens, 1963						
	2	M	14	Idiopathic	–	Sudden mvt	?	Anticonvulsant
	3	M	33	Idiopathic	–	Sudden mvt	?	PHY
	4	M	Child	Idiopathic	+	Sudden mvt	+	
Dowzenko and Zielinski (1966) [20]	1	F	18	Idiopathic	–	Sudden mvt	+	PHY
Kertesz (1967) [19]	1	F	9	Idiopathic	+	Sudden mvt	+	PHY
	2	M	14	Idiopathic	+	Sudden mvt	+	
	3	F	13	Idiopathic	–	Sudden mvt	+	Remission
	4	M	10	Idiopathic	–	Movement	+	
	5	M	12	Idiopathic	+	Sudden mvt	+	Anticonvulsant
	6	M	10	Idiopathic	+	Sudden mvt	+	Remission
	7	M	15	Idiopathic	+	?	+	Anticonvulsant
	8	M	10	Idiopathic	+	Sudden mvt	+	Anticonvulsant
	9	F	8	Idiopathic	+	Sudden mvt	+	Anticonvulsant
	10	F	15	Idiopathic	–	Sudden mvt	+	PHY
Perez-Borja et al. (1967) [39]	1	F	6	Idiopathic	–	Sudden mvt	–	Anticonvulsant
DeBolt (1967) [40]	1	M	?	Idiopathic	?	Sudden mvt	?	PHY
	2	M	?	Idiopathic	?	Sudden mvt	?	PHY
Kato and Araki (1969) [32]	1	F	8	Idiopathic	+	Sudden mvt	+	Carbamaz
Horner and Jackson (1969) [41]	1	M	?	Idiopathic	+	Sudden mvt Hyperventilation	+	
	2	M	23	Idiopathic	+	During sleep	–	PHY, phenobarb
	3	M	8	Idiopathic	+	During sleep, later daytime, sudden mvt	+	PHY, phenobarb

Tassinari and Fine (1969) [42]	1	M	11	Idiopathic	–	Sudden mvt	+	PHY
Morley (1970) [43]	1	M	2	Idiopathic	–	Sudden mvt	+	Carbamaz
	2	M	20	Idiopathic	+	Hypnogenic	–	PHY
	3	M	13	Idiopathic	+	Sudden mvt	+	PHY
Burger et al. (1972) [13]	1	M	15	Idiopathic	–	Movement	–	PHY
	2	M	12	Idiopathic	–	Sudden mvt	–	PHY, phenobarb
Jung et al. (1973) [44]	1	M	8	Idiopathic	+	Sudden mvt Vig activity	+	PHY, phenobarb
	2	M	15	Idiopathic	+	Sudden mvt	+	Anticonvulsant
	3	M	16	Idiopathic	–	Vig activity	+	PHY
	4	M	16	Idiopathic	–	Sudden mvt	?	PHY
Loong and Ong (1973) [45]	1	M	19	Idiopathic	?	Sudden mvt	?	PHY, L-dopa
Waller (1977) [46]	1	F	8	Idiopathic	–	Sudden mvt	+	PHY
Goodenough et al. (1978) [47]	1	M	2	Idiopathic	–	Sudden mvt	+	PHY
	2	M	14	Idiopathic	–	Sudden mvt	–	PHY
	3	M	16	Idiopathic	–	Sudden mvt	–	PHY
Watson and Scott (1979) [48]	1	M	14	Idiopathic vs brain stem atrophy	–	Sudden mvt	–	
Kinast et al. (1980) [49]	1	M	11	Idiopathic	–	Sudden mvt	–	PHY
	3	M	16	Idiopathic	–	Sudden mvt	–	PHY
	5	M	17	Idiopathic	–	Sudden mvt	+	PHY
Homan et al. (1980) [50]	1	M	2	Idiopathic	+	Sudden mvt	–	PHY
	2	F	4	Idiopathic	–	Sudden mvt	+	PHY
	3	F	7	Idiopathic	+	Sudden mvt	–	PHY
	4	M	12	Idiopathic	+	Sudden mvt, ethanol	–	PHY
	5	M	8	Idiopathic	–	Sudden mvt	+	PHY

(continued)

Table 2.2 (continued)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Suber and Riley (1980) [51]	1	F	5	Idiopathic	+	Sudden mvt	–	Valproate
Przuntek and Monninger (1983) [52]	1	F	?	Idiopathic	?	Sudden mvt	?	Carbamaz
	2	M	?	Idiopathic	?	Sudden mvt	?	Carbamaz
	3	F	?	Idiopathic	?	Sudden mvt	?	Carbamaz
Zacchetti et al. (1983) [53]	1	M	13	Idiopathic	?	Sudden mvt	+	PHY
Garello et al. (1983) [54]	1	M	4	Idiopathic	+	Sudden mvt	+	Phenobarb
	2	M	6	Idiopathic	+	Sudden mvt	+	Phenobarb
Franssen et al. (1983) [55]	1	M	17	Idiopathic	–	Sudden mvt	–	
Bortolotti and Schoenhuber (1983) [56]	1	M	13	Idiopathic	+	Sudden mvt	–	Carbamaz
	2	M	40	Idiopathic	+	Sudden mvt	–	Remission
Plant (1983) [57]	1	M	6	Idiopathic	+	Sudden mvt	–	PHY
	2	M	14	Idiopathic	+	Sudden mvt	+	PHY
	3	M	15	Idiopathic	–	Sudden mvt	–	PHY
	4	M	11	Idiopathic	–	Sudden mvt	–	PHY
Boel and Cassaer (1984) [58]	1	M	10	Idiopathic	+	Sudden mvt	+	PHY
Lang (1984) [59]	1	F	22	Idiopathic	–	Sudden mvt	–	
Nardocci et al. (1989) [60]	1	M	10	Idiopathic	+	Sudden mvt	–	
Lou (1989) [61]	1	F	2	Idiopathic	–	Sudden mvt	–	Flunarizine
Hirata et al. (1991) [62]	1	M	13	Idiopathic	–	Sudden mvt	–	PHY, clonaz
Nair et al. (1991) [63]	1	M	21	Idiopathic	–	Sudden mvt	–	

Abbreviations used: + present or yes, – absent or no,? no information given
Triggers: mvt, movement; excite, excitement
Treatment: PHY, phenytoin; AMPH, amphetamine; anticonvul, anticonvulsants; phenobarb, phenobarbital; carbamaz, carbamazepine; clonaz, clonazepam

Table 2.3 Early reports of idiopathic paroxysmal non-kinesigenic dyskinesia (PNKD) (formerly called PDC)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Mount and Reback (1940) [24]	1	M	Infancy	Idiopathic	+	ETOH, caffeine, fatigue	+	Antimusc
Forssman (1961) [25]	1	M	6	Idiopathic	+	Cold, stress, fatigue, ETOH, lack of sleep	+	
Lance (1963) [4]	3	M	13	Idiopathic	–	Startle	+	
	4	M	22	Idiopathic	+	Relaxed, startle	+	
	5	M	2	Idiopathic	+	Excite, ETOH, fatigue	+	
	6	F	2	Idiopathic	+	Excite, fatigue	+	
	7	M	2	Idiopathic	+	Excite, fatigue	+	
	8	M	9	Idiopathic	+	Excite, fatigue	+	Anticonvulsant
Weber (1967) [30]	1	M	12	Idiopathic	+	Excite	+	
	3	M	22	Idiopathic	+	Excite	+	
	4	F	19	Idiopathic	+	Nervousness	–	
Perez-Borja et al. (1967) [39]	1	F	6 months	Idiopathic	–	Anxiety	–	Chlordiaz
	Case 1 reported 11 years later by Bird et al. (1978) [64] as familial							
Richards and Barnett (1968) [26]	1	F	Infancy	Idiopathic	+	Stress, caff	?	
	2	F	Child	Idiopathic	+		–	Phenobarb
	3	F	Sister of case 2; no details given					
	4	M	Brother of case 2; no details given					
	5	M	Infancy	Idiopathic	+		–	
	6	M	Child	Idiopathic	+	Excite, fatigue	–	Phenobarb
	7	M	Infancy	Idiopathic	+	ETOH	+	
	8	F	1	Idiopathic	+	Excite, fatigue	–	
	9	F	2 months	Idiopathic	+		–	

(continued)

Table 2.3 (continued)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Lance (1977) [16]	First pedigree							
	I.2	Same as Lance (1963) [4] case 4						
	II.4	Same as Lance (1963) [4] case 5, later developed writhing mvts						
	II.5	M	?	Idiopathic	+	ETOH	?	
	III.2	Same as Lance (1963) [4] case 6; age at onset now listed at 6 weeks of life						Clonazepam
	III.3	M	13	Idiopathic	+	ETOH, fatigue	+	Clonazepam
	III.4	Same as Lance (1963) [4] case 7						
	III.5	Same as Lance (1963) [4] case 8						
	IV.2	M	2 months	Idiopathic	+	Fatigue	?	
Tibbles and Barnes (1980) [65]	1	M	4	Idiopathic	+	Ethanol, chocolate, caffeine	+	Clonazepam
Kinast et al. (1980) [49]	4	M	8	Idiopathic	–		+	Carbamaz
Coulter and Donofrio (1980) [66]	1	M	19	Idiopathic	+		–	Haloper
	2	F	12	Idiopathic	+		–	Haloper, carbamaz
Dunn (1981) [67]	1	M	2	Idiopathic	–		–	
Walker (1981) [68]	1	M	Infancy	Idiopathic	+	Caffeine, ETOH, fatigue, exercise	–	Chlordiaz
	2	F	Infancy	Idiopathic	–	Caffeine, ETOH, fatigue, exercise	–	Chlordiaz
Mayeux and Fahn (1982) [69]	1	M	10	Hered ataxia	+		–	Acetazol, clonazepam
Przuntek and Monninger (1983) [52]	4–18	6M, 9F	?	Idiopathic	+	ETOH	+	Valproate, DOPA → worse in 1; haloper ➔ better in 7
Kurlan and Shoulson (1983) [70]	1	M	20	Idiopathic	+		+	Oxazepam
	2	F	24	Idiopathic	+		?	Oxazepam

Table 2.3 (continued)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Jacome and Risko (1984) [71]	1	F	Teens	Idiopathic	+	Stress	–	
Kurlan et al. (1987) [72]	III4	F	6	Idiopathic	+	Cold, long exercise	–	Quinine
	IV6	M	15	Idiopathic	+	As above, heat	–	Benzodiaz, L-trypt
	V25	F	23	Idiopathic	+	Cold, exert, long exercise	–	Benzodiaz, L-trypt
	Cases IV6 and V25 were reported by Kurlan and Shoulson [70] above							
Bressman et al. (1988) [31]	1	F	3	Idiopathic	–	Stress	–	Carbamaz
	2	M	6	Idiopathic	–	Laughing	–	Carbamaz
	3	F	14	Idiopathic	–	Fatigue	–	Acetazol
	4	M	18	Idiopathic	–	ETOH, stress, fatigue, heat	–	Acetazol (unsustained)
	5	M	27	Idiopathic	–	Awakening	–	
	6	F	29	Idiopathic	–		–	Remission
	7	F	30	Idiopathic	–	Fatigue, stress	–	Clonazepam
Nardocci et al. (1989) [60]	2	M	1	Idiopathic	–		–	Clonazepam
Hughes et al. (1991) [73]	1	M	16	Idiopathic	–	Tiredness, anxiety, fasting, ETOH, eating	+	
	2	M	20	Idiopathic	–		–	
Byrne et al. (1991) [74]	III3	M	40	Idiopathic	+	Excite, tension	+	
	III4	F	10	Idiopathic	+	Tension, excite, ETOH	+	
	IV2	M	13	Idiopathic	+	Emotion	?	
	V1	M	14	Idiopathic	+	?	?	

Abbreviations used: + present or yes, – absent or no,? no information given
Etiology: hered, hereditary
Triggers: ETOH, alcohol; excite, excitement; caff, caffeine
Treatment: antimusc, antimuscarinic; anticonvul, anticonvulsants; chlordiaz, chlordiazepoxide; phenob, phenobarbital; carbamaz, carbamazepine; haloper, haloperidol; acetazol, acetazolamide; benzodiaz, benzodiazepines; L-trypt, L-tryptophan

Table 2.4 Early reports of symptomatic paroxysmal kinesigenic dyskinesia

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Arden (1953) [75]	1	M	13	Hypoparathy	–	Sudden mvt	–	Calciferol
Matthews (1958) [34]	1	F	48	Mult scler	–	Sudden mvt	+	Phenobarb
	2	F	27	Mult scler	–	Sudden mvt	–	
	4	F	42	Mult scler	–	Sudden mvt	+	PHY
Whitty et al. (1964) [12]	3	M	13	Head injury	–	Sudden mvt	+	Anticovul
Rosen (1964) [29]	1	M	12	Perinatal hyp	–	Movement, startle plus body contact	–	Antimusc, antihist
Tabaee-Zadeh et al. (1972) [76]	1	M	19	Hypoparathy	–	Vig activ	–	Calciferol
Robin (1977) [33]	1	M	33	Head injury	–	Sudden mvt	+	PHY
Kinast et al. (1980) [49]	2	M	5	Hemiatrophy	–	Anticip mvt	–	PHY
Gilroy (1982) [77]	1	M	5	Unknown	–	Sudden mvt	–	Carbamaz
Huffstutter and Myers (1983) [78]	2	F	4	Infant hemi	–	Sudden touch	+	Anticonvul
Berger et al. (1984) [79]	1	M	27	Mult scler	–	Sudden mvt	+	PHY
	4	F	24	Mult scler	–	Sudden mvt	–	Remission
	5	M	16	Mult scler	–	Sudden mvt	+	PHY
Drake et al. (1980) [80]	1	M	22	Head injury	–	Sudden mvt	–	Phenobarb
	2	M	30	Head injury	–	Sudden mvt	–	Lorazepam
Adam and Orinda (1986) [81]	1	F	56	PSP	–	Sudden mvt	–	Carbamaz
Merchut and Brumlik (1986) [82]	1	F	33	Putam infarct	–	Sudden mvt	+	Carbamaz
Richardson et al. (1987) [83]	1	M	18	Head injury	–	Sudden mvt	–	Carbamaz
Barabas and Tucker (1988) [84]	1	M	12	Hypoparathy	–	Sudden mvt	–	Calciferol
Camac et al. (1990) [85]	1	F	53	Thal infarct	–	Sudden mvt	+	PHY
George et al. (1990) [86]	1	M	33	Head trauma	–	Touch	–	Diazepam

Table 2.4 (continued)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Verheul and Tyssen (1990) [36]	1	F	28	Mult scler	–	Hypervent	–	Carbamaz
Roos et al. (1991) [87]	1	F	35	Mult scler	–	Emotion, movement, speaking, writing	–	PHY
Fuh et al. (1991) [88]	1	F	52	Stroke	–		+	Diazepam
Burguera et al. (1991) [89]	1	M	26	Mult scler	–	Hypervent, writing, standing	+	Carbamaz
Sethi et al. (1992) [90]	1	F	30	Mult scler	–	Sudden mvt, hypervent	+	Acetazol
	2	M	44	Mult scler	–	Hypervent	–	Acetazol
	3	F	36	Mult scler	–	Hypervent	+	Acetazol + carbamaz

Abbreviations used: + present or yes, – absent or no, ? no information given
Etiology: hypoparathy, idiopathic hypoparathyroidism; mult scler, multiple sclerosis; perinatal hyp, perinatal hypoxia; infant hemi, infantile hemiplegia; PSP, progressive supranuclear palsy; putam, putaminal; thal, thalamic
Triggers: mvt, movement; vig, vigorous; anticip mvt, anticipation of movement; hypervent, hyperventilation
Treatment: phenob, phenobarbital; PHY, phenytoin; carbamaz, carbamazepine; anticonvul, anticonvulsants; antimusc, antimuscarinic; antihist, antihistaminic; acetazol, acetazolamide

Table 2.5 Early reports of symptomatic paroxysmal non-kinesigenic dyskinesia

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Matthews (1958) [34]	3	F	26	Mult scler	–		+	
Joynt and Green (1962) [35]	1	M	19	Mult scler	–		+	PHY
	2	F	39	Mult scler	–		+	PHY
	3	M	29	Mult scler	–		–	Remission
	4	M	31	Mult scler	–	During sleep	–	PHY
Lance (1963) [4]	1	F	12	Perinatal hyp	–	Fright (bouts also occur during sleep)	+	Anticonvul
	2	F	47	Mult scler	–		–	

(continued)

Table 2.5 (continued)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Mushet and Dreifuss (1967) [18]	1	M	0.5	Encephalitis	–	Startle, excite, sudden mvt	?	Antimusc
Cavanagh et al. (1974) [91]	1	M	4	Cystinuria	+		–	
	2	M	4	Cystinuria	+		–	
Soffer et al. (1977) [92]	1	F	17	Hypoparathy	–		–	Vit D, Ca++
Fischbeck and Layzer (1979) [93]	1	F	34	Thyrotoxic	–		–	Propyl-thiouracil
Margolin and Marsden (1982) [94]	1	M	51	Trans ischem	–		–	
	2	M	61	Trans ischem	–		–	
	3	M	57	Trans ischem	–		–	
	4	M	74	Trans ischem	–		–	
Huffstutter and Myers (1983) [78]	1	F	4	Infant hemi	–		+	Anticonvul
	2	F	4	Infant hemi	–	Sudden touch	+	Anticonvul
Perlmutter and Raichle (1984) [95]	1	M	50	Head injury	–	Stress	–	PHY plus trihexy
Newman and Kinkel (1984) [96]	1	F	45	Hypoglycemia	–		–	Glucose
Berger et al. (1984) [79]	2	F	55	Mult scler	–		+	Clorazepate
	3	M	45	Mult scler	–		+	Remission
	6	M	17	Mult scler	–		–	Carbamaz
	7	F	41	Mult scler	–	Hypnogenic	–	Carbamaz
	8	F	38	Mult scler	–		–	Remission
Sunohara et al. (1985) [97]	1	M	61	Stroke	–	Any mvt	–	Clonazepam & 5-HTP
Kawazawa et al. (1985) [98] (Translated by Yamamoto and Kawazawa, 1987)	1	F	38	Hypoparathy	–	Emotion, caffeine, fatigue	–	Vit D, Ca++

Table 2.5 (continued)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Drake et al. (1986) [80]	3	M	18	Head injury	–		–	Phenobarb
Micheli et al. (1986) [99]	1	F	37	BG calcif	–		+	Clonazepam
Nath et al. (1987) [100]	1	F	32	AIDS	–		?	
Erickson and Chun (1987) [101]	1	F	16	Perinatal hyp	–		–	PHY
	2	M	4	Perinatal hyp	–		–	Clonazepam
	3	F	15	Perinatal hyp	–	Excite	–	PHY
Micheli et al. (1987) [102]	1	M	16	DA blockers	–	Stress	–	Trihexy
Haan et al. (1988) [103]	1	F	80	Diabetes	–		–	
Bressman et al. (1988) [31]	1	M	7 months	Perinatal hyp	+	Sleep	–	Carbamaz
	2	F	8	Perinatal hyp	–		–	
	3	M	12	Perinatal hyp	–		–	
	4	M	24	Anoxia	–		–	
	5	M	28	Encephalitis	–		–	Clonazepam
	6	F	39	Ischemia	–		–	
	7	F	61	Meningioma	–		–	
Bressman et al. (1988) [31]	1	F	11	Psychogenic	–		–	Faith
	2	F	16	Psychogenic	–		–	Hypnother
	3	M	22	Psychogenic	–		–	
	4	F	31	Psychogenic	–		–	
	5	F	32	Psychogenic	–		–	
	6	M	32	Psychogenic	–		–	
	7	M	34	Psychogenic	–		–	Placebo
	8	F	35	Psychogenic	–		–	psychoRx
	9	F	36	Psychogenic	–		–	
	10	F	42	Psychogenic	–		–	Placebo
	11	F	49	Psychogenic	–		–	Placebo

(continued)

Table 2.5 (continued)

Authors (Year)	Case	Sex	Age at onset	Etiology	Family history	Trigger	Sensory Aura	Treatment
Bennett and Fox (1989) [104]	1	F	82	Trans ischem	–		–	Aspirin
Winer et al. (1990) [105]	1	F	58	Hypoglycemia	–	Exercise, fasting	–	
Fahn and Williams (1988) [106]	11	F	25	Psychogenic	–	Walking	–	psychoRx
	13	F	30	Psychogenic	–		–	psychoRx
	14	F	31	Psychogenic	–		–	
	15	M	33	Psychogenic	–	Walking, various sudden stimuli	–	Placebo
	16	F	36	Psychogenic	–		–	Placebo
	17	F	36	Psychogenic	–		–	Suggestion, psychoRx
	19	F	41	Psychogenic	–	Walking	–	Suggestion, placebo

Abbreviations used: + present or yes, – absent or no, ? no information given
Etiology: mult scler, multiple sclerosis; perinatal hyp, perinatal hypoxia; trans ischem, transient ischemic attack; infant hemi, infant hemiplegia; hypoparathy, hypoparathyroidism; BG calcif, basal ganglia calcification; AIDS, acquired immune deficiency syndrome; DA blockers, dopamine blockers
Triggers: mvt, movement; excite, excitement
Treatment: PHY, phenytoin; anticonvul, anticonvulsants; antimusc, antimuscarinic; Vit D, vitamin D; Ca++, calcium; trihexy, trihexyphenidyl; carbamaz, carbamazepine; 5-HTP, 5-hydroxytryptophan; phenob, phenobarbital; hypnother; hypnotheraphy; psychoRx, psychotherapy

As has been elaborated in other chapters (cfr. Chap. 1), the classification of the paroxysmal dyskinesias has evolved beyond the one proposed by Lance in 1977. Instead of Lance's proposed classification based on duration of the attacks, the classification scheme that has been adopted is the one based on precipitating factors suggested by Demirkiran and Jankovic [108] and using the term "dyskinesia" to replace the more cumbersome terms of dystonic choreoathetosis.

Early Reports of Paroxysmal Hypnogenic Dyskinesia

Horner and Jackson [41] described two families in which several members of the family had attacks of involuntary movement that occurred during sleep. These appear to be the first cases of hypnogenic paroxysmal dyskinesia reported. Family "W" is of particular interest because some affected members had classical

paroxysmal kinesigenic dyskinesia, some hypnogenic, and others a combination. Case 3 in this family began with the hypnogenic variety at age 8. By age 11, daytime attacks also occurred, sometimes triggered by sudden movement. Gradually the hypnogenic episodes disappeared, leaving him with kinesigenic dyskinesia that responded to anticonvulsants. Lugaresi and his colleagues [109, 110] independently rediscovered and eventually popularized the syndrome of hypnogenic paroxysmal dyskinesia.

Lugaresi and Cirignotta [109] described five patients with onset of hypnogenic dystonia at ages 5, 7, 26, 30, and 40. The attacks occurred almost every night during sleep, with the onset occurring in stages 2–4 of sleep. The attacks last 15–45 s, and several attacks can occur in the same night. The attacks can awaken the patient who may even emit a cry. The movements appear to be a mixture of dystonia, athetosis, and some more rapid flinging movements. The EEG is normal during sleep and while awake. Carbamazepine was effective therapy. In their next paper, Lugaresi et al. [110] described the movements as choreoathetosis and ballism in addition to dystonia. Maccario and Lustman [111] emphasized that tachycardia is a characteristic occurrence during these episodes.

In addition to the above short-duration attacks, long-duration hypnogenic attacks were reported by Lugaresi et al. [110]. Such long duration attacks occur in a minority of individuals with hypnogenic paroxysmal dyskinesia. These longer attacks last from 2 to 50 min and do not respond to medication, including anticonvulsants, tricyclics, benzodiazepines, and antipsychotics.

The disorder was originally described in nonfamilial cases but has since been reported to occur in three members of a family [112]. Other sporadic cases have since been reported [113–116] including a case with a concurrent reflex dystonic reaction provoked by stimulation of the right foot [117]. Besides the paper by Horner and Jackson mentioned above, another link with PKC is suggested by the report of Morley [43] who described a father as having hypnogenic dyskinetic attacks while his son had PKC. Both individuals responded to phenytoin.

There has long been considerable speculation as to whether the short-duration hypnogenic attacks could be a manifestation of epilepsy since they respond so well to anticonvulsants. The lack of abnormal EEG findings during the attack was against this concept. Tinuper et al. [118] described three patients with this disorder who did have EEG evidence for frontal lobe seizures as a cause of these attacks. Sellal et al. [119] and Meierkord et al. [120] studied a series of patients with hypnogenic dystonia and have concluded that these represent seizure disorders, particularly of frontal lobe epilepsy. It appears that the short-lasting attacks could be either seizures or could be more akin to the paroxysmal dyskinesia. Montagna et al. [121] described paroxysmal arousals during sleep. These can occur frequently and may be associated with complex movements.

Nowadays, most hypnogenic dyskinesias are considered epileptic in origin. This was reviewed by Fish and Marsden [122] and supported by Lűders [123], who found the origin to be in the supplementary sensorimotor area. A cyclic alternating EEG pattern is believed to be a provocative factor [124].

Early Reports of Transient Paroxysmal Dystonia/Torticollis in Infancy

Snyder [125] introduced a new type of paroxysmal dyskinesia that he called "paroxysmal torticollis in infancy." He described 12 cases of intermittent head tilting in young infants. The age at onset was between 2 and 8 months of age, except for three cases whose first attacks occurred at 14, 17, and 30 months. The attacks would occur about two to three times a month and last from 10 min to 14 days, usually 2–3 days. The head would tilt to either side and often rotate slightly to the opposite side. There is no distress unless a parent attempts to straighten the head, upon which the baby cries. In some cases the head tilting is associated with vomiting, pallor, and agitation for a short period. The infant is normal between attacks, and they disappear after months or years, usually around age 2 or 3 years. Subsequently, a number of similar cases have been described [126–128], including familial cases [129]. Sanner and Bergstrom [127] reported a patient whose father had a similar condition in early infancy, indicating that this disorder is hereditary.

The clinical picture of paroxysmal torticollis in infancy that has evolved is that the trunk can also be involved with lateral curvature concave to the same side as the head tilting and the ipsilateral leg can be flexed. Onset can be as early as the first months of life and recur every couple of weeks until they disappear before the age of 2 years. Each attack can last a couple of hours to a couple of weeks. In between attacks, the child is normal. The main differential diagnosis is a posterior fossa tumor and Sandifer's syndrome [130] .

In 1988, the clinical spectrum expanded with the report by Angelini et al. [131] under the title of "transient paroxysmal dystonia in infancy." They described nine patients who had onset of the paroxysmal dyskinesia between 3 and 5 months of age, except for one with an onset at 1 month. Three had a history of perinatal brain damage; nine did not. The attacks consisted of opisthotonus, increased muscle tone with twisting of the limbs, and in three, with neck and trunk twisting, thereby linking this with "paroxysmal torticollis in infancy." The attacks last several minutes, with a maximum of 2 h in one patient. They would occur from several attacks per day to once a month. Remission occurred between the ages of 8 and 22 months, with two not yet having reached a remission.

Dunn [67] described an infant with head turning and posturing of the right arm lasting 45 min to 18 h. There were six attacks from age 26 months to age 40 months. The author did not mention the possible diagnosis of paroxysmal torticollis in infancy and made a diagnosis of paroxysmal dystonic choreoathetosis instead. One should consider the possibility that PDC may occur in infancy and disappear over several months. If so, then the paroxysmal torticollis in infancy of Snyder and the paroxysmal dystonia in infancy of Angelini [131] may represent the lowest age spectrum of PDC and a benign form of the disorder.

This disorder should not be confused by the syndrome referred to as "benign paroxysmal tonic upgaze of childhood" [132–134], which is a sustained tonic conjugate upward deviation of the eyes beginning in infancy and eventually

disappearing in childhood. Ataxia may be present. They lessen in the morning hours and disappear with sleep. Acetazolamide is not effective. Perhaps calling it tonic upgaze with diurnal fluctuations would be a better term than "paroxysmal." Another paroxysmal ocular disorder was described in brain-damaged infants, known as "paroxysmal ocular downward deviation" [135]. The ocular displacement was accompanied by closure of the upper eyelids, and the episode would last seconds.

Early Reports of Paroxysmal Ataxias and Tremor

Intermittent ataxia has been reported with metabolic defects such as Hartnup disease [136], pyruvate decarboxylase deficiency [137–139], and maple syrup urine disease [140]. Fever often triggers the attacks of ataxia. In one case with pyruvate decarboxylase deficiency [138], choreoathetosis tended to accompany the chorea. Paroxysmal ataxia and dysarthria have also been reported to occur in multiple sclerosis [141–145], which, as remarked above, is a disorder that also can cause paroxysmal choreoathetosis/dystonia. The attacks of paroxysmal ataxia due to multiple sclerosis last seconds, much shorter than the attacks described below. They also can respond to carbamazepine.

In 1946, Parker [146] described six patients in four families with idiopathic familial paroxysmal ataxia, which he labeled as periodic ataxia. The age at onset ranged from 21 to 32 years. The attacks affected gait and speech and lasted from 30 s to 30 min. There could be several attacks per day, or there could be interval-free periods of several weeks. Vestibular symptoms occurred in some of the patients. Progressive cerebellar ataxia developed in some members.

In 1963, Farmer and Mustian [147] reported another family with idiopathic paroxysmal ataxia. The major clinical differences from Parker's cases were the high frequency of accompanying vestibular symptoms of vertigo, diplopia, and oscillopsia and the lack of speech involvement. They labeled their family as vestibulocerebellar ataxia. The age at onset ranged from 23 to 42 years. The attacks ranged from a few minutes to 2 months. The brief episodes may occur daily, but free intervals could last a year or more. Some affected members also developed progressive ataxia.

Hill and Sherman [148] described another family but with onset in childhood in many of the affected and no development of progressive ataxia. Another family of childhood onset and benign course was described by White [149]. All the families showed autosomal dominant inheritance.

An important advance was the discovery by Griggs et al. [150] that acetazolamide can effectively prevent attacks. These authors showed this benefit in one kindred with familial paroxysmal ataxia. Donat and Auger [151] the following year had similar results in another kindred. Fahn [152, 153] reported a woman who had paroxysmal tremor, both intention and resting, associated with ataxia and postural instability during the attack; acetazolamide eliminated the attacks. Factor et al. [154] reported an infant who had three attacks of coarse tremor and an orofacial

dyskinesia that resembled that seen with tardive dyskinesia. Each attack lasted several hours, before spontaneously clearing. Tetrahydrobiopterin, the cofactor for the enzymes tyrosine hydroxylase and phenylalanine hydroxylase, was reduced. The child responded to levodopa.

Mayeux and Fahn [69] reported a patient with PDC in a background of hereditary ataxia. Onset of PDC was at age 10; onset of ataxia was age 19. During an attack, which lasted 10 min to 4 h, there was also an accompanying increase of ataxia. Initially there was an 8-month response to acetazolamide. After the drug was no longer effective, the patient's PDC responded to clonazepam. It is possible that this patient might be a link between familial PDC and paroxysmal ataxia.

Several other reports of acetazolamide-responsive familial paroxysmal ataxia have been reported [155–157]. Although CT has been normal, magnetic resonance imaging studies have revealed selective atrophy in the anterior cerebellar vermis [158].

Families with a combination of periodic ataxia and persistent, continuous electrical activity in several muscles, reported as either myokymia [159–162] or as neuromyotonia [163], have been described. Descriptions of the attacks, which are of brief duration and are sometimes preceded by sudden movement, include dyskinetic movements and sustained posturing, as well as ataxia, dysarthria, and vertigo.

The initial classification of hereditary episodic ataxias was proposed by Gancher and Nutt [161] who classified them into three syndromes. The first group are those with attacks of ataxia (with or without interictal nystagmus and with or without persistent ataxia), responding to acetazolamide or amphetamines. The attacks are precipitated by exercise, fatigue, stress, and occasionally by carbohydrate or alcohol ingestion. In addition to ataxia, the attacks are accompanied by vertigo, headache, nausea, and malaise. The attacks last for several hours or until the patient falls asleep. In recent years additional families have been reported with these features [164–166]. The siblings reported by Bain et al. [165] had persistent diplopia due to superior oblique paresis as part of the syndrome. Using [31P] nuclear magnetic resonance spectroscopy, Bain and his colleagues [167] found the pH levels in the cerebellum to be increased in untreated subjects with acetazolamide-responsive paroxysmal ataxia; the pH dropped to normal with treatment.

The second group is associated with persistent myokymia or neuromyotonia. Attacks are precipitated by fatigue, excitement, stress, and physical trauma, but the family reported by Vaamonde et al. [163] had attacks triggered by sudden movement. There is no dizziness nor vertigo. The attacks last 2 min or less. Acetazolamide and anticonvulsants are ineffective.

The third group is that in which the attacks are induced by sudden movement, i.e., kinesigenic. Typical PKC can occur in some members of the family. The attacks of ataxia last minutes to hours, while the PKC lasts seconds. The disorder can resolve with time. Acetazolamide appears to be ineffective, but phenytoin is effective for both the kinesigenic ataxia and the PKC.

The classification of episodic ataxias has expanded as more cases and the genetics of these paroxysmal ataxias have been uncovered.

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Chapter 3
Paroxysmal Kinesigenic Dyskinesia

Katarzyna Smilowska, Roberto Erro, and Kailash P. Bhatia

Paroxysmal kinesigenic dyskinesia (PKD) is considered the most frequent type of paroxysmal dyskinesia (PxD). The incidence rate is estimated as 1/150000 [1].

Following earlier reports that referred to this disorder as paroxysmal kinesigenic choreoathetosis (PKC) or some other terms [1–4] (cfr. Chap. 2), the currently used term PKD was suggested by Demerkirin and Jankovic who proposed a classification of the PxD based on their triggers, encompassing four main forms: paroxysmal kinesigenic (PKD), non-kinesigenic (PNKD), exercise-induced (PED), and hypnogenic dyskinesia (PHD) [2]. However, PHD, in which attacks occur during sleep without a clear trigger, has been subsequently recognized as a form of autosomal dominant, nocturnal frontal lobe epilepsy (ADNFLE) [3] in the majority of cases (cfr. Chap. 1).

Over the years several families with PKD have been described [4, 5] and clinical diagnostic criteria proposed by Bruno and colleagues:

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-53721-0_3) contains supplementary material, which is available to authorized users.

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_3

Diagnostic Criteria for PKD

1. Attacks provoked by kinesigenic trigger
2. Short duration of attacks (<1 min)
3. No loss of consciousness or pain during attacks
4. No evidence of other organic diseases and normal neurological examination between the attacks
5. Good control of the attacks with phenytoin or carbamazepine
6. Age of onset between 1 and 20 years, if there is no family history of PKD

Modified from Bruno et al. [5]

Thus, PKD is defined by attacks of dystonia, chorea, or both, which are specifically triggered by sudden movements. Attacks are very brief in duration, usually lasting less than 1 min (Video 3.1). Interestingly, it was noted that there was often an autosomal dominant family history for PKD or epilepsy, namely, benign familial infantile seizures (BFIS), and that the two conditions could overlap in single patients, in the so-called infantile convulsion with choreoathetosis (ICCA) syndrome [6]. The term ICCA has been subsequently replaced with PKD with infantile convulsions (PKD/IC) to uniform terminology.

Further advances have been driven by elucidation of the genetic causes of PKD. In 2011, Chen et al. reported that mutations in the proline-rich transmembrane protein 2 (*PRRT2*) gene were related to most of the PKD cases [7], opening the way to the identification of *PRRT2* mutations as the main cause of PKD, BFIS, and ICCA cases. However, the prevalence of *PRRT2* mutations ranges from 40% to 90% of PKD patients, depending on case ascertainment [3, 6], therefore suggesting genetic heterogeneity. Recently, several other genetic disorders have been in fact suggested to be an alternative cause of the PKD syndrome including, but not limited to, those associated with *SCN8A*, *ADCY5*, and *SCL16A2* mutations [8]. On the other hand, *PRRT2* genetic screening in other episodic neurological disorders has largely broadened its clinical spectrum [6, 9, 10].

This chapter will be therefore structured in two main paragraphs: PKD associated with *PRRT2* mutations and PKD due to other genetic conditions. Recent proposals have in fact suggested that the classification of PxD in general, including PKD, should be based on two axes: the first dealing with the clinical features and the second based on the etiology, namely, the genetic determinants, if known (Table 3.1). This chapter will not focus on acquired forms, which will be covered altogether in a dedicated chapter (cfr. Chap. 6).

PRRT2-Related PKD

The onset of PKD in patients with *PRRT2* mutations is typically in childhood or adolescence and only rarely after 18 years of age [3, 6]. Patients with PKD/IC usually develop epilepsy within the first 2 years of age and subsequently attacks of

Table 3.1 Diagnostic criteria for paroxysmal dyskinesia

Axis I: Clinical characteristics
(A) Inclusion criteria (1 plus one of 2)
1. Paroxysmal attacks of dystonia, chorea, ballism (or a mixture of those) with sudden onset, and variable duration (seconds to hours)
2. Classification based on the precipitating factor (trigger) (a) Paroxysmal kinesigenic dyskinesia (PKD): attacks are triggered by sudden movements, acceleration, or intention to move (b) Paroxysmal non-kinesigenic dyskinesia (PNKD): attacks are triggered by coffee, alcohol, and other non-kinesigenic precipitants (c) Paroxysmal exercise-induced dyskinesia (PED): attacks are triggered by prolonged exercise
(B) Exclusion criteria
1. Symptoms are caused by another neurological condition
2. Symptoms are functional (psychogenic)
Axis II: Genetic characteristics
1. Mutations identified in one of the known genes (i.e., *PRRT2*, *MR-1*, *KCNMA1*, *SLC2A1*, etc.)
2. No mutations in one of the known genes or genetic testing not been performed (undetermined forms)

Revised from Erro et al. [3]

PKD. The majority of PKD cases are inherited in an autosomal dominant mode, but about 10–30% are sporadic, suggesting a de novo origin of the mutations [6, 11]. There is a male predominance with a male-to-female ratio of about 2:1.5 [10, 12].

By definition, PKD is characterized by sudden attacks precipitated by voluntary actions such as transition from sitting to standing position, intention to move, or accelerating from walking to running. Virtually all *PRRT2* cases have a kinesigenic trigger for the attacks, although additional triggers can be observed including loud sounds, emotional stress, startle, or hyperventilation [3, 4, 13, 14]. Characteristically, the duration of the attacks is shorter than 1 min, a point of difference with PNKD and PED, even though they can rarely last longer [3, 5], and their frequency ranges from one in few weeks to over 100 per day [3, 6, 15, 16]. A sensory aura preceding the attacks is reported by a large part of *PRRT2* patients [3, 5, 6]. It may manifest with paresthesia, stiffness, or a "fluttery feeling" usually in the body part where PKD develop. The aura may sometimes be reported as a non-localized, indescribable sensation [17]. Some patients indicate that the attack can be minimized by suppressing or slowing the movements when the aura appears [5].

Among the phenomenology of the attacks, the most common for *PRRT2*-related PKD and PKD/IC cases is dystonia, followed by chorea and athetosis [5, 6]. Infrequently, attacks can manifest with ballism or hemiballism [18–22].

The attacks can be uni- or bilateral and might alternate from one to the other body side. The face and tongue may also be involved, and speech impairment has been also reported [16, 23, 24]. Severity of the attacks may differ across the episodes. Mild attacks may be limited to a sensory aura followed by slight dystonic or choreic movements, whereas severe episodes mild result in falls and injuries [23].

Another important diagnostic clue is that *PRRT2*-PKD usually responds well to antiepileptic drugs (AED). Carbamazepine (CBZ) is the drug of choice. Sufficient

dosages are typically lower than those used in epilepsy (e.g., 50–200 mg), and a combination of two or more anticonvulsants is rarely necessary [3, 6, 10]. Other AED have been also reported as effective in *PRRT2* patients including oxcarbazepine, lamotrigine, levetiracetam, and topiramate [6]. Interestingly, it was shown that response to CBZ may differ between patients who carry the mutation in *PRRT2* gene and those without the mutation [25]. Since *PRRT2*-PKD is more frequent in individuals of Asian descent [3], it should be noted that in this population CBZ has been associated with hypersensitive reaction, including Stevens–Johnson syndrome and toxic epidermal necrolysis [26]. This is attributed to *HLA* allele *B*1502*, which is a marker of CBZ -related hypersensitivity [27, 28]. It is recommended by FDA to screen all Asian patients for the presence of this allele [26].

In most cases, the frequency of attacks decreases with age. Complete remissions typically occur in the third and fourth decades of life [5]. The tendency for improvement in the number and severity of attacks was also noted during pregnancy and was observed in 50% of affected woman [5].

It should be remarked that *PRRT2* mutations could also account for BFIS and the coexistence of epilepsy and PKD, in the so-called PKD/IC (formerly known as ICCA) syndrome. Therefore, the history of epilepsy in an individual with PKD or in his/her family makes the suspicion of *PRRT2* mutation more likely. BFIS is characterized for self-limiting afebrile focal seizures, typically occurring in the first years of life [29].

Interestingly, *PRRT2* cases can rarely develop attacks during sleep [4, 30], as recently identified in two patients with isolated PHD [2, 31]. Additional phenotypes related to *PRRT2* mutations have been also reported, including episodic ataxia and migraine, especially of the hemiplegic subtype, which should be therefore considered whenever present in a patient or in the family as clues to suspect *PRRT2* mutations [6, 10, 32–35].

PKD Associated with Other Genetic Conditions

After the discovery of *PRRT2* mutation as the leading cause of PKD, it has been also possible to demonstrate that up to 30–40% of PKD patients do not carry such gene variants, suggesting genetic heterogeneity [36].

Mutations in *SCN8A*, which encodes the sodium voltage-gated channels alpha subunit 8, have been reported to be another cause of the PKD/IC syndrome [36, 37]. The identical missense mutation in *SCN8A* was identified in three unrelated families, who fulfilled the diagnostic criteria for PKD/IC syndrome. However, the definition of PKD in this report has been subsequently questioned since in one of these cases video EEG showed cortical discharges during a “PKD” attack, pointing to an epileptic nature of the event [38]. Moreover, it should be noted that, at variance with *PRRT2* mutations, *SCN8A* mutations produce epileptic seizures that are usually refractory to AED and might be associated with neurodevelopmental delay [39].

Mutations of *ADCY5*, which encodes for the adenylate cyclase 5, have been reported to produce a whole spectrum of movement disorders such as dystonia,

chorea, myoclonus, and PxD [40–42] (cfr. Chap. 9). Usually, there is marked pleiotropy of PxD-*ADCY5*, which might be also of the kinesigenic type [8]. One important clue as regards the diagnosis of *ADCY5* is the presence of bouts of nocturnal paroxysmal dyskinesia (often painful). In addition, it is important to note that, unlike most cases with *PPRT2* mutations, interictally *ADCY5* carriers almost invariably will have other findings (cfr. Chap. 9).

SLC16A2 encodes the monocarboxylate transporter type 8 (MCT8), deficiency of which known as Allan–Herndon–Dudley syndrome, and is transmitted in an X-linked fashion (cfr. Chap. 9) [43, 44]. Although in a subset of patients with *SLC16A2* mutations a particular type of PKD attacks can occur (i.e., induced by passive movements; cfr. Chap. 9) this entity is clearly different from *PRRT2* mutations and does not enter in the differential diagnosis.

PKD, with or without epilepsy, has been further anecdotally reported in the context of ARSACS, primary familial brain calcification, *KCNA1* mutations (usually associated with episodic ataxia type 1; cfr. Chap. 11), and in association with *DEPDC5* and *CHRNA4* mutations [36, 45–49]. However, the latter two genes are also a cause of ADNFLE, and it remains to be seen whether these episodes of paroxysmal dystonia are epileptic in nature or not. Additionally, *PNKD* (formerly known as *MR-1*) and *SLC2A1* mutations, which are the leading cause of PNKD and PED, respectively (cfr. Chaps. 4 and 5), have been very rarely reported to induce attacks resembling PKD [10, 36]. Altogether, this evidence brought some authors to suggest that single gene testing might not be cost-efficient and that next-generation sequencing techniques should be preferred instead [50].

Conclusions

In recent years, the elucidation of different genes associated with the clinical syndrome of PKD has led to a better understanding of PxD in general and has further challenged the “one-gene, one-phenotype” paradigm. Whereas in the last years we have witnessed a great advance in the understanding of the pathophysiological mechanisms of *PRRT2* mutations (cfr. Chap. 8), there are still knowledge gaps about what influences the clinical phenotype. Moreover, a number of PKD cases do not carry mutations in either of the aforementioned genes, suggesting that other causes have yet to be discovered, which implies that current classification systems would require to be accordingly updated.

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Chapter 4
Paroxysmal Non-kinesigenic Dyskinesia

Zain Guduru and Kapil D. Sethi

Introduction

Paroxysmal non-kinesigenic dyskinesia (PNKD) is a rare movement disorder characterized by the recurrent attacks of dystonia, chorea, athetosis, ballism, or a combination. It can be idiopathic, genetic - and in both cases either sporadic or familial- or secondary due to a known etiology. The attacks usually range in duration from minutes to hours and are often precipitated by consuming alcohol, coffee, or tea, psychological stress or excitement, and fatigue. PNKD was earlier referred to as paroxysmal dystonic choreoathetosis (PDC), familial paroxysmal choreoathetosis [1]. Longer duration of attacks, smaller frequency of the attacks, and a host of different precipitants of the attacks differentiate it from paroxysmal kinesigenic dyskinesia (PKD). This chapter will focus on those forms formerly known as "primary" PNKD (i.e., idiopathic and/or genetically determined) where these attacks occur out of a background of normal motor behavior.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-53721-0_4) contains supplementary material, which is available to authorized users.

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_4

Epidemiology

PNKD is a rare disorder, occurring at an estimated prevalence of around one in a million people [2]. Familial cases of "primary" PNKD still greatly outnumber sporadic cases. Sporadic form may actually be underreported as it may be difficult to differentiate these attacks from a functional (psychogenic) etiology. When familial, PNKD is inherited as autosomal dominant trait, and the gene involved is myofibrillogenesis regulator-1 (*MR-1)*, now called *PNKD* gene. More males than females are affected (1.4:1), although the preponderance is not as striking as PKD (M:F, 3–4:1). Age of onset can be from 1 to 20 years; mean age of onset is 12. Attacks tend to diminish with age [1]. In sporadic cases, age of onset tends to be higher [3].

History

Paroxysmal dyskinesia (PxD) was first reported in 1892 by Shuzo Kure in a 23-year-old Japanese man, who had frequent movement-induced paroxysmal attacks from the age of 10 years. At that time the diagnosis was referred to as atypical Thomsen's disease [4]. Later, Gowers (1901) described a similar child, but he considered this movement disorder an epileptic phenomenon [5]. Wilson (1930) described a 5-year-old boy who had brief attacks of unilateral torsion and tonic spasm that lasted up to 3 min and were precipitated by fright or excitement, without loss of consciousness. Initially they were labeled as reflex epilepsy [6].

In 1940, Mount and Reback reported an index case who was a 23-year-old man with small (lasting 5–10 min) and long attacks (lasting up to 2 h) with retrocollis, eyes rolling, and abnormal movements of the face and hands. The onset of the attacks was in infancy. Twenty-seven other family members over five generations appeared to be similarly affected with an autosomal dominant pattern of inheritance. They labeled this condition familial paroxysmal choreoathetosis [7]. Forssman (1961) [8], Weber (1967) [9], Lance (1963) [10], and Richard and Barnett (1968) [11] reported similar large family cases series. Weber described families with this condition as familial paroxysmal dystonia. In 1967, Kertesz first differentiated the kinesigenic variant from that described by Mount and Reback, Forssman, and Lance, which were not aggravated by movement but by alcohol, caffeine, and fatigue [12]. Richard and Barnett coined the term paroxysmal dystonic choreoathetosis (PDC), which was later adopted by Lance in 1977. The classification of PxD was first proposed by Lance in 1977, based on the duration of the paroxysms, precipitating factors, and phenomenology of abnormal movements [13]. Later, this classification was replaced with the one proposed by Demirkiran and Jankovic, who used a generic term "dyskinesia" rather than dystonia, chorea, or choreoathetosis.

Their major classification was based solely on precipitating factors of the attacks, and they further subclassified based on duration of attacks and etiology. Their observation supports the conclusion that the precipitant of an attack is the major contributor of the future course [14] (cfr. Chaps. 1 and 2). More recently, Erro and Bhatia reviewed 500 cases and proposed a new classification of genetically determined PxD based on two axes. Axis one encompasses clinical characteristics and axis two the genetic findings [15].

Genetics

The mode of inheritance in PNKD was recognized as autosomal dominant, with a high but incomplete penetrance [16]. Initial reports of PNKD were familial, with hereditary transmission being autosomal dominant. A linkage study on an Italian family with PNKD by Fink et al. in 1996 [17] first mapped the disease allele to chromosome 2q35, but the disease-causing gene (*MR-1*) was not identified until 2004 [18, 19], and it is now referred to as the *PNKD* gene. The encoded PNKD protein associates with membranes and is expressed in neurons where it enriches in pre- and postsynaptic preparations [19, 20]. The *PNKD* gene has at least three alternate splice forms, which encode proteins of 385, 361, and 142 amino acids. The long isoform of PNKD (PNKD-L) is specifically expressed in CNS, while the medium isoform (PNKD-M) and short isoform (PNKD-S) are ubiquitously expressed [19]. Two missense mutations (Ala to Val), located at amino acids 7 or 9 of PNKD-L and PNKD-S, were found in most patients, and a third mutation (Ala to Pro) at position 33 was reported in one family [21]. Both PNKD-L and PNKD-M have a putative catalytic domain that is homologous to hydroxyacylglutathione hydrolase (HAGH), a member of the zinc metallo-hydrolase enzyme family, which contains β-lactamase domains. HAGH functions in a pathway to detoxify methylglyoxal, a compound present in coffee and alcoholic beverages and produced as a by-product of oxidative stress [22]. This could explain the attacks provoked particularly by caffeine, alcohol, and stress [23]. Shen et al. [24] have shown that PNKD interacts with the synaptic active zone proteins RAB-interacting molecule (RIM) 1 and RIM 2 and modulated neurotransmitter release. The mutant protein is less effective at inhibiting exocytosis. Based on these findings, altered release of synaptic neurotransmitter vesicles and increased neuronal hyperexcitability have been postulated as the main disease mechanisms in PNKD. *PNKD*-positive PNKD is also categorized as DYT8 [25]. However, the authors of this chapter do not agree with the inclusion of paroxysmal dyskinesia in the classification of dystonia.

MR-1 (*PNKD* gene) negative sporadic and familial PNKD cases have also been reported (Table 4.1). Paroxysmal non-kinesigenic dyskinesia with or without generalized epilepsy (PNKD3) is an autosomal dominant neurologic disorder due to a pathogenic variant ion the *KCNMA1* gene.

Table 4.1 *PNKD (MR1)* gene-negative sporadic and familial PNKD cases, reported in the literature

Case/ Family	Gene mutation	Accompanying feature	Mutation DNA and amino acid	Reference #
One Family	*PRRT2*	Migraine	c.649C > T (p.Arg217X)	[26]
One case	*PRRT2*	PKD	c.649C > T (p.Arg217X)	[27]
Five cases	*PRRT2*	PKD	c.884G>A and c.649C > T	[28]
Four cases	*PRRT2* (biallelic)	Seizures in all patients, PKD in one patient	c.649dupC/ c.649dupC	[29]
Two cases	*PRRT2*	–	Unknown	[30]
One family	Gene locus at *2q31*	Migraine in three patients and seizures in two patients	–	[31]
One family	*SLC2A1* gene on chromosome 1-encoding glucose transporter (GLUT-1)	Spastic paraparesis	–	[32]
One family	*KCNMA1*	A few had epilepsy	p.D434.G	[33]
Two unrelated children	*KCNMA1*	Developmental delay	p.E884K and p.N1053S	[34]
One case	*KCNMA1*	PKD	c.1534A>G (p.I512V)	[35]

Clinical Features

PNKD typically begins in childhood (mean age is 12 years), and only a few patients have the onset after 18 years of age. They are precipitated by consuming alcohol, coffee, or tea and also by psychological stress or excitement and by fatigue. Attacks may begin with premonitory symptoms (41% of *MR-1* gene-positive cases) such as a sensation of tightness (80% of those) in one limb, involuntary movements of the mouth, or anxiety [36]. The attacks of PNKD consist of any combination of dystonic postures, chorea, athetosis, and ballism (Video 4.1). They can be unilateral – always on one side or on either side – or bilateral, and unilateral episodes can be followed by a bilateral one. They can affect a single region of the body or be generalized [1]. Attacks have never been associated with loss of consciousness or with seizures and never reported to occur during sleep. Sleep aborts the episodes. Speech is often affected, with inability to speak due to dystonia, but there is never any alteration of consciousness, and there is no pain during the episodes. Attacks may diminish spontaneously with age [3, 13]. Attacks lasts for minutes to hours, sometimes longer than a day. Usually they range from 5 min to 4 h. However, they are much more infrequent than PKD and occur a few times a day to only a few times a year [2, 7, 19]. There is no consistent correlation between duration and frequency.

PNKD differs from PKD by longer duration of attacks, smaller frequency of the attacks, and different precipitants of the attacks (cfr. Chap. 3).

Patients with PNKD who do not carry a *MR-1 (PNKD* gene*)* mutation are more variable in their age of onset, provoking factors, and response to medication (Table 4.2). The clinical characteristics of PNKD with *MR-1* (*PNKD* gene) mutations are more uniform. The *MR-1* (*PNKD* gene) mutation-positive individuals have the precipitation of attacks by caffeine and alcohol in nearly 100% of instances. Sleep benefit (attack resolving if the patients went to sleep during their attacks) was a characteristic for PNKD previously reported and was found in patients both with and without the *MR-1 (PNKD* gene) mutations. The prevalence of migraine was high in the mutation carriers, reported in 47% of the patients [33]. In summary, the patients with MR-1 (*PNKD* gene) mutations have three distinguishing features: (1) onset of attacks in infancy or early childhood; (2) precipitation of attacks by caffeine and alcohol in nearly 100% of patients; and (3) a favorable response to benzodiazepines and sleep [19].

In sporadic cases, onset age tends to be even higher; many of the sporadic PNKD patients in fact have a functional (psychogenic) movement disorder [3]. Conversely, PNKD may be mistakenly diagnosed as a functional disorder as stated above.

Table 4.2 Summary of clinical characteristics for *MR-1* mutation-positive and mutation-negative patients in PNKD

	MR-1 mutation positive	*MR-1* mutation negative
Number of patients	49	22
Male	27	14
Female	22	14
Age at onset	4.0 ± 4.6	12.3 ± 10.8
Premonitory sensation	41%	63%
Precipitants		
Alcohol	98% ($n = 44$)	0% ($n = 6$)
Caffeine	98%	38%
Exercise	12%	68%
Fatigue	12%	32%
Emotional stress	82%	27%
Sleep benefit	70%	36%
Attack phenomenology		
Dystonia	12%	36%
Chorea	–	18%
Combination of dystonia and chorea	88%	27%
Ballism	–	18%
Typical attack duration (minimum and maximum)	10 min to 1 h	10 min to few hours

From Bruno et al. [36]. Reprinted with permission from Wolters Kluwer Health, Inc.

Acquired PNKD might have interictal neurologic abnormalities reflecting the underlying disorder, as opposed to "primary" PNKD with normal neurologic examination between the paroxysms. Onset of symptoms of acquired PNKD has a wider range (2.5–79 years), with a peak in the twenties when caused by trauma and a mean age of 60 years when a result of vascular events [37] (cfr. Chap. 6).

KCNMA1 gene mutation-induced PNKD cases are characterized by absence seizures, generalized tonic-clonic seizures, and paroxysmal non-kinesigenic dyskinesia. Onset is usually in childhood. Patients may have seizures only, dyskinesia only, or both.

ADCY5-induced choreoathetosis can be jerky or twitchy, and trigger factors are drowsiness and intercurrent illness. Episodes mostly occur at the initiation of sleep (with prolonged sleep latency) or waking up from sleep. Initially the disorder can be episodic and progressively becomes constant. Usually the onset is in the infancy with delayed milestones. The movements can be initially episodic lasting for minutes to hours and even up to days during intercurrent illness. Interictal examination often shows hypotonia and movement disorders such as chorea. The exacerbating factors could often be identified, and they lacked the stereotyped trigger and duration of many paroxysmal movement disorders, leading to prefer the term episodic rather than paroxysmal (however, the dictionary meaning of episodic and paroxysmal is the same) [1]. A further important point differentiating *ADCY5* gene mutations from *PNKD* gene mutation-positive PNKD is the presence of a normal neurological examination between episodes in the latter [38]. Onset in the first months of life and relation to sleep is unusual in paroxysmal movement disorders due to *PRRT2*, *PNKD*, and *SLC2A1* mutations; thus, mutations in *ADCY5* should be considered in the differential of paroxysmal movement disorders with a very early onset even in the absence of a detectable chronic movement disorder [39].

Investigations

CT head, MRI brain, and ictal and interictal EEGs are generally normal. However, an invasive video-electroencephalographic study by Lombroso [40] demonstrated discharge from the caudate nuclei, whereas cortical recordings were normal. We do not recommend invasive investigations in this setting. SPECT scans have revealed hyperperfusion of the right caudate and thalamus [41]. Reduced density of presynaptic aromatic amino acid decarboxylase activity in the striatum and increased density of postsynaptic dopamine D2 receptors could be demonstrated by 18F-DOPA and 11C-raclopride PET [41]. This was thought to reflect chronic upregulation of postsynaptic dopaminergic receptors. 18FDG and [11C] dihydrotetrabenazine (DTBZ) PET did not show any metabolic abnormalities or abnormal binding [42]. It has been suggested that dopaminergic abnormalities, if present, may be a result of altered regulation of dopamine release or of postsynaptic mechanisms, rather than

of an altered density of nigrostriatal innervation. Animal models with PNKD have demonstrated dopamine dysregulation in the basal ganglia [43]. Lance [13] mentioned that autopsies performed on two patients with PNKD revealed no pathology. In acquired PNKD, abnormal EEG, MRI brain, and laboratory investigations may be noted.

Treatment

Avoidance of the precipitating factors such as alcohol or caffeine can be helpful. Unlike PKD, PNKD does not readily respond to anticonvulsants, and medical treatment is less rewarding. However, anticonvulsants should be tried in every case, and an occasional patient may respond to carbamazepine (200–400 mg/day). Clonazepam (0.25 mg BID), as introduced for PDC by Lance [13], appears to be the most successful agent, for both idiopathic and symptomatic PDC. Other drugs that have been tried including diazepam (2 mg, 2–3 times/day), haloperidol, alternate-day oxazepam [44], and anticholinergics such as benztropine and trihexyphenidyl (up to 20 mg total daily dose) and levetiracetam (500 mg BID) [45, 46], however, without consistent success. Van Rootselaar reported successful treatment of two children with PNKD from a large kindred with sublingual lorazepam. Benzodiazepines appeared to be of some benefit in one-third to three-fourths of patients with PNKD [2].

Deep brain stimulation (DBS) is also being explored as a potential therapeutic option in the treatment of medically refractory severe PNKD. Loher et al. [47] have assessed the effect of chronic stimulation of the ventrointermediate (Vim) thalamus for treatment of dystonic PNKD. Chronic stimulations through a stereotactically implanted monopolar electrode in the left Vim resulted in a decrease of the frequency, duration, and intensity of the dystonic paroxysmal movement disorder, and the benefit of stimulation was maintained over 4 years of follow-up. Long-term follow-up was reported after 9 years and showed mild loss of stimulation effect. The effect was regained when the target was changed to the GPi [48]. Yamada et al. [49] presented a case of unilateral posttraumatic PNKD with complete suppression of abnormal movements after implantation of GPi DBS, and Kaufman et al. [50] reported a difficult case with a generalized movement disorder with superimposed bilateral PNKD which, although with atypical elements, showed a significant reduction in the frequency and intensity of the episodic dystonic episodes. Riaan van Coller et al. [51] reported successful treatment with chronic stimulation of bilateral globus pallidus in two patients.

Botulinum toxin has been tried by some, but the generalized nature of the movement disorder limits its usefulness [37]. In acquired PNKD the treatment of the underlying etiology is the most important.

Conclusion

Paroxysmal non-kinesigenic dyskinesia is a rare disorder, and the attacks are often precipitated by consuming alcohol, coffee, or tea and also by psychological stress or excitement and by fatigue. Genetically determined or idiopathic PNKD have normal interictal examination. PNKD differs from PKD by longer duration of attacks, lower frequency of the attacks, and a host of different precipitants of the attacks. Clonazepam is the treatment of choice. Further research into the mechanisms and pathophysiology of disease [52] will help to elucidate novel therapies for treatment and disease modification.

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Chapter 5
Paroxysmal Exercise-Induced Dyskinesia

Sara Scannapieco and Roberto Erro

Introduction

Paroxysmal exercise-induce dyskinesia (PED) is a clinical syndrome first described in 1977 by Lance, who reported on a family manifesting with recurrent attacks of dystonia lasting between 5 and 30 min that were provoked by sustained exercise [1]. These two latter features (i.e., duration and trigger of the attacks) ostensibly differentiated this variant from the two other previously described (i.e., PKD and PNKD, cfr. Chaps. 1, 3 and 4), but it took about 30 years before the genetic underpinnings of this clinical syndrome were elucidated. In 2008, two independent research groups identified *SLC2A1* mutation as the cause of PED [2, 3]. However, over the years it has become clear that only about 30–40% of patients with PED carry a *SLC2A1* mutation [4, 5], implicating other disorders, genetic or otherwise, in this clinical syndrome. This chapter will focus on the different disorders that can produce PED, recognition of which is critical as management heavily depends on the underlying etiology.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-53721-0_5) contains supplementary material, which is available to authorized users.

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_5

SLC2A1 (GLUT1)-Related Paroxysmal Dyskinesia

SLC2A1 encodes for the glucose transporter type 1 that facilitates glucose entry across the blood-brain barrier and the astrocyte membrane [2–4]. *SLC2A1* mutations can cause a broad variety of neurological disorders, ranging from severe encephalopathies with learning disability and epilepsy to isolated PED [6, 7]. This phenotypic variability would be owing to the specific type of genetic mutation, with splice site, nonsense, insertions, and deletions (i.e., loss of function mutations) being associated with a severe clinical phenotype of GLUT1 deficiency syndrome encompassing epilepsy, hypotonia, spasticity, ataxia, and developmental delay [4, 6, 7]. On the other hand, missense mutations more commonly present with PED, isolated or otherwise [4–6]. However, there might be clinical heterogeneity that is not caused by mutation type alone. *SLC2A1*-PED usually manifest during childhood, but onset can be in early adulthood (>18 years of age) in about 5% of patients with *SLC2A1* mutations and PED [8]. Most *SLC2A1* cases presenting with PED are de novo, with only 10% having a positive family history [3, 8]. Although autosomal recessive transmission has been described in rare cases of GLUT1 deficiency syndrome [9], this has not been reported in patients with PED. It is important to remark that while PED is the most common type of paroxysmal dyskinesia reported in *SLC2A1* cases, other non-kinesigenic triggers (fasting, sleep deprivation, stress, and anxiety) have also been described [8, 10], and patients can manifest other episodic neurological disorders including episodic ataxia, aberrant gaze saccades, oculogyric crisis, epilepsy, transient weakness, dysarthria, recurrent impaired vigilance, and migraine [10–13].

Typically, PED episodes last from 15 to 40 min but can more rarely be shorter (Video 5.1) or as long as several hours [8]. Frequency of attacks can vary from several per day to one per month [8].

Regardless of the specific phenotype, in patients carrying *SLC2A1* mutations, a ketogenic diet should be attempted to treat the underlying neuroglycopenia. In this regard, good outcomes have been reported with early dietary treatment [14], even though PED might occasionally worsen with this type of diet [2]. Compliance to this type of diet is however poor, and the modified Atkins diet, which has a less strict fat-to-non-fat ratio as well as no restriction of food or fluid intake, has been proposed as alternative, with good results on PED and other paroxysmal disorders [15]. Occasionally, acetazolamide [16] and L-dopa [17] have been reported to ameliorate the attacks.

GCH1-Related Paroxysmal Dyskinesia

GCH1 encodes for the GTP cyclohydrolase I, a rate-limiting enzyme in the synthesis of tetrahydrobiopterin from GTP, mutations of which account for about 50% of dopa-responsive dystonia (DRD) [18]. While the commonest phenotype associated with *GCH1* mutations is that of (early-onset) non-intermittent dystonia, a few patients have been described with a phenotype consistent with PED. In 2010, Dale

and colleagues described a family with two affected members with isolated PED [19]. Attack duration was about 5 min, and PED episodes never occurred at rest or during movement initiation [19]. The notion that *GCH1* mutations can produce isolated PED has been further confirmed by Erro et al., who found 2 *GCH1* carriers (12.5%) in a series of 16 consecutive patients with PED [5]. In all reported cases, L-dopa treatment markedly improved PED attacks.

The diagnosis relies on the genetic analysis of *GCH1*, which can be pursued if CSF examination reveals a specific pattern, featuring low levels of tetrahydrobiopterin, homovanillic acid, and 5-hydroxyindoleacetic acid [5, 19].

ECHS1-Related Paroxysmal Dyskinesia

ECHS1 encodes for the mitochondrial short-chain enoyl-CoA hydratase protein, mutations of which have been reported to typically cause early-onset Leigh syndrome (or an atypical Leigh-like syndrome that is often milder and with later onset) [20, 21]. However, *ECHS1* mutations have been further associated with paroxysmal dyskinesia, which can be either isolated or combined with lactic acidosis, encephalopathy, deafness, epilepsy, optic atrophy, and cardiomyopathy [22–24]. Thus, *ECHS1* mutations have been associated with intermittent episodes of long-duration (30–50 min) opisthotonus with no identifiable trigger [21], thus falling into the PNKD rubric. Another report labeled the episodes of paroxysmal dystonia as "kinesigenic" [22]. However, a careful analysis of the original case description reveals that the attacks were actually triggered by "physical strain" [22] and would be therefore better labeled as PED. Two more recent reports have confirmed that *ECHS1*-related paroxysmal dyskinesia is more likely to be in the form of PED [23, 24].

The diagnosis relies on genetic analysis, but T2 MRI pallidal hyperintensity as well as raised serum and/or CSF lactate levels represent clues to suspect the disorder. Despite there not being a specific treatment, a partial benefit has been reported with ketogenic diet and/or a mitochondrial cocktail including thiamine, riboflavin, carnitine, coenzyme Q-10, vitamin B6, and vitamin C [22, 24].

Pyruvate Dehydrogenase Deficiency

The mitochondrial pyruvate dehydrogenase complex (PDC) catalyzes the rate-limiting step in the aerobic glucose oxidation and comprises multiple copies of three subunits: pyruvate dehydrogenase (E1, encoded by the *PDHA1* gene), dihydrolipoamide transacetylase (E2, encoded by the *DLAT* gene), and dihydrolipoamide dehydrogenase (E3), as well as an E3 binding protein (also known as component X and encoded by the *PDHX* gene) [25]. Deficits in either subunit have been reported to cause paroxysmal dyskinesia that are usually, but not always, part of a complex neurologic syndrome. Similarly to *ECHS1* mutations, PDC deficiency

causes an early encephalopathy with lactic acidosis and/or Leigh syndrome, but some cases might have milder phenotypes, which include episodes of ataxia, recurrent acute flaccid paralysis, and/or paroxysmal dystonia [25]. The latter, which can be either isolated or combined with the aforementioned phenotypes, is generally brought on by prolonged exercise, thus meeting the criteria for PED [26], or without any clear trigger, thus falling into the PNKD category [27]. Attacks are sometimes reported to be hemi-dystonic.

Raised (serum or CSF) lactate and/or pyruvate levels along with pallidal hyperintensity suggesting striatal necrosis are important clues to suspect PDC deficiency [25–27], but it is important to recognize that these might be lacking, and, therefore, this condition should be considered in the differential diagnosis of isolated PED/PNKD even in the absence of any detectable biochemical or imaging abnormality.

PDC is, at least partially, a treatable condition that responds to thiamine supplementation [28]. In other cases, beneficial outcomes have been also reported with a ketogenic diet [29].

Early-Onset Parkinson's Disease

In contrast to the disorders discussed above that generally present during infancy or childhood, there have been a few reports describing PED as the presenting feature in patients with early-onset Parkinson's disease (PD) [5, 30, 31]. In a series of 16 patients with PED, Erro et al. identified 4 patients (12.5%) with early-onset PD, of whom one carried *parkin* mutations [5]. Invariably, the age at onset was in early adulthood, although a patient with *parkin* mutations who developed PED at the age of 8 years has recently been reported on [32]. In such cases, only the foot is affected with PED (Video 5.2), and the dystonia tends to progress over time to the stage that it is brought on by minimal exercise or is even present at rest. L-dopa supplementation might be useful in these patients, but anticholinergic drugs and/or botulinum toxin injections might be needed [5, 30, 31].

Conclusions

PED is a clinical syndrome with different possible etiologies (Table 5.1). Prompt recognition of the underlying disorder is crucial because most of them are treatable, and misdiagnosis can possibly lead to inappropriate management of these patients.

A syndromic approach that considers age at onset, inheritance pattern if any, and the presence of associated features might help clinicians to suspect a particular disorder. However, it should be noted that there are no reliable clinical features aiding the differential diagnosis, especially in patients with isolated PED [5]. As such, a systematic diagnostic workup is advisable when facing with patients presenting with PED. In the classic scenario, age at onset is during infancy or childhood, and

Table 5.1 Summary of the clinical features of the main conditions producing PED

	SLC2A1 (GLUT-1)	*GCH-1*	*ECHS-1*	PDC deficiency[a]	Early-onset PD
Inheritance	Autosomal dominant/ sporadic	Variable	Variable	Autosomal recessive/ X-linked	Autosomal recessive (*parkin*)/ sporadic
Age at onset	Usually <18 year adult onset is possible	Usually <18 year	Usually <18 year	Variable	Early adulthood Childhood is possible
Associated features	Isolated ± episodic ataxia, oculogyric crisis, epilepsy, transient weakness, and migraine	Isolated	Isolated ± Leigh syndrome	Isolated ± ataxia, recurrent acute flaccid paralysis, and/ or paroxysmal dystonia	Isolated ± parkinsonism
Investigations	CSF (low glucose)	CSF (low levels of tetrahydrobiopterin, homovanillic acid, and 5-hydroxyindoleacetic acid	MRI (pallidal hyperintensity) CSF and/or serum (raised lactate)	Serum or CSF (raised lactate and/or pyruvate) and MRI (pallidal hyperintensity)	DatScan
Therapy	Diet [2] L-dopa Acetazolamide	L-dopa	Ketogenic diet Mitochondrial cocktail [24, 26]	Thiamine suppl. [30] Ketogenic diet [31]	L-dopa Anti-cholinergic drugs Botulinum toxin injections

[a]Pyruvate dehydrogenase deficiency (see text for details)

we would advocate CSF investigations for glucose, lactate, pterins, and dopamine metabolites, to be mandatory.

A low glucose CSF/serum ratio (≤25th percentile) is present in the majority of patients with *SLC2A1* mutations [33]. Raw CSF glucose levels are instead below the 10th percentile for all patients with *SLC2A1* mutations if age-specific reference values are applied, suggesting that this index can be more sensitive than glucose CSF/serum ratio [33]. Raised lactate levels should prompt additional investigations for PDC deficiency and *ECHS1* mutations [20, 25], while alterations in the pterins and dopamine pathway would suggest *GCH1* defects [18].

On the other hand, if onset is in adulthood, one might consider to request a functional imaging of the nigrostriatal dopaminergic pathway before CSF investigations and to further perform the latter only in the case of normal dopaminergic imaging [5]. At this stage, genetic testing can be tailored based on the results of the aforementioned investigations and should be pursued to reach a definitive diagnosis, which is critical for subsequent management, prognosis, and genetic counseling of these patients. It should be noted, however, that a certain degree of clinical overlap

has been also demonstrated among the three main genes responsible for PKD, PNKD, and PED (i.e., *PRRT2*, *PNKD*, and *SLC2A1*, respectively) [8, 10], which led some authors advocating the use of comprehensive gene panels in contrast to single gene testing [34].

Finally, although the number of conditions associated with PED has been increasing during the last years, for a number of patients, it is not possible to reach a definitive diagnosis, suggesting that other disorders have yet to be implicated with the clinical syndrome of PED.

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Chapter 6
Acquired Paroxysmal Dyskinesia

Harsh Vardhan Gupta, Shyamal H. Mehta, and Kapil D. Sethi

Introduction

According to Fahn [1], acquired paroxysmal dyskinesia (PxD) was first reported by Sterling in 1924 in patients with epidemic encephalitis. He termed it extrapyramidal epilepsy. Lance questioned the term due to the long duration (up to 6 h) of the attacks. Spiller [2] published a case with a vascular etiology.

Many of the reports in the modern era focused on idiopathic or genetically determined PxD. Lance proposed a classification scheme proposed for PxD based on duration and precipitating factors [3]. Goodenough proposed a classification that included etiology [4]. A widely utilized classification of PxD was proposed by Demirkiran and Jankovic which is based on the precipitating factors of the attack and etiology [5] (cfr. Chap. 1). Once the PxD has been classified based on the precipitating factor, further distinction is made based on the underlying etiology [4]. This chapter will focus on acquired ("secondary") paroxysmal dyskinesia (i.e., paroxysmal dyskinesia because of an underlying lesion/disorder).

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-53721-0_6) contains supplementary material, which is available to authorized users.

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_6

Clinical Features

Paroxysmal dyskinesia can manifest themselves as attacks of chorea or dystonia, and some reports describe attacks of ballism and athetosis [6, 7]. Since a combination of movements of varying phenomenology can be seen, it is preferred to use the term dyskinesia [7].

Acquired paroxysmal dyskinesia may be provoked by sudden movement (paroxysmal kinesigenic dyskinesia-PKD), or these may be unrelated to movement (paroxysmal non-kinesigenic dyskinesia-PNKD) [8]. A minority of the patients can have a mixed form. The distribution of movements may be unilateral, bilateral, or axial. Some patients can have an aura as well [8]. Initially, there were some reports of migraine headache leading to paroxysmal dyskinesia, but now it is believed that those patients may have had a genetically determined form of paroxysmal dyskinesia, and the same genetic defect is responsible for causing both the migraine and the paroxysmal dyskinesia. The clues to a PxD (paroxysmal dyskinesia) being acquired as opposed to genetically determined (or idiopathic) include late age of onset, absent family history, sudden onset, abnormal neurological examination in between the episodes, pain during the attacks, lack of robust response to anticonvulsants, abnormal laboratory or imaging findings, and unusual precipitating factors [4, 8, 9]. The attacks in acquired paroxysmal dyskinesia may be painful which is not seen with genetically determined PxD [8]. There can be some latency between the onset of abnormal movements and responsible CNS insult [8].

Etiology

There are a variety of underlying disorders that can lead to paroxysmal dyskinesia. These are summarized in Table 6.1. The cases published from the beginning of 2000s have been summarized in Table 6.2.

Table 6.1 Acquired causes of paroxysmal dyskinesia

Autoimmune/ inflammatory	Sjögren's syndrome [10], multiple sclerosis [11, 12], neuromyelitis optica [13], antiphospholipid syndrome [14], Hashimoto encephalopathy [15], systemic lupus erythematous [16], voltage-gated potassium channel complex antibodies [17, 18], ADEM [19]
Vascular	Stroke [20, 21], transient ischemic attack [22–24], moyamoya disease [25–27], severe carotid stenosis or occlusion [28, 29], AV malformation [30]
Infectious	HIV encephalitis [31], CMV encephalitis [8], syphilis [8], subacute sclerosing panencephalitis [32], H1N1 infection [33], streptococcal infection [34, 35]
Neoplastic/ paraneoplastic	CNS lymphoma [36]
Degenerative	Parkinson's disease [37], Fahr's disease [38], progressive supranuclear palsy [39]
Traumatic	Traumatic brain injury or peripheral injury [40–42]
Endocrine/ metabolic	Hypoglycemia [43–45], hyperglycemia [46, 47], thyrotoxicosis [15, 48, 49], hypoparathyroidism, pseudohypoparathyroidism [50–53]
Others	Gluten intolerance [54], cervical cord lesion [55, 56], cerebral palsy [57, 58], neuroacanthocytosis [59], Wilson's disease [60], kernicterus [8], anoxic brain injury [61], Arnold-Chiari malformation with syringomyelia [62], parasagittal meningioma [63], methylphenidate treatment [64], cystinuria [65]

Table 6.2 Cases of acquired paroxysmal dyskinesia

Cases	*Etiology*	*Location and type*	*Duration*	*Frequency*	*Precipitant*
See SJ 2003 [66]	ADEM?	Dystonic posturing of right side	5–20 s	10–15 attacks in a day	Sudden movements
Kowacs 2004 [23]	Carotid stenosis	Case 1: rapid shaking of the left arm	Case 1: daily attacks lasting a few seconds	Case 1: NA	Case 1: NA
		Case 2: right leg shaking	Case 2: NA	Case 2: NA	Case 2: change in position from supine to standing
Puri V 2004 [67]	Hyperthyroidism	Left side or right side dystonic attacks and occasionally bilateral	20–30 s	Several attacks in a day	Sudden voluntary activities
Spengos K 2004 [68]	Moyamoya disease	Bilateral choreiform movements	NA	NA	Coitus, hyperventilation, and movement
Gálvez-Jiménez N 2002 [69]	Patient 1: carotid stenosis	Patient 1: right hand shaking	Patient 1: 2 min	NA	Patient 1: NA
	Patient 2: right vertebral artery high-grade stenosis	Patient 2: right hand tremor and ataxia	Patient 2: 20 min		Patient 2: physical exercise
	Patients 3, 4, and 5: transient ischemic attack	Patient 3: right hand tremor and dystonic posturing	Patient 3: 30 min		Patient 3: NA
		Patient 4: left upper extremity dystonic movements	Patient 4: 18 h		Patient 4: NA
		Patient 5: right leg jerking associated with dystonia	Patient 5: 3 minutes		Patient 5: NA
Warner GT 2003 [70]	Bilateral globus pallidus injury	Right upper extremity dystonic posturing and occasionally left upper extremity dystonic posturing	2 h	2–3 times in a week	Alcohol
Zorzi G 2003 [58]	Patient 1: multiple sclerosis	Patient 1: focal dystonia	Patient 1: 1–2 min	Patient 1: 4–5/day	NA
	Patient 2: cerebral palsy	Patient 2: generalized dystonia	Patient 2: 10–20 min	Patient 2: 2–4/month	
	Patient 3: cerebral palsy	Patient 3: unilateral dystonia	Patient 3: 10–20 min	Patient 3: 1–2/day	
	Patient 4: brain hemiatrophy	Patient 4: focal dystonia	Patient 4: 2–15 min	Patient 4: 2–4/month	
	Patient 5: basal ganglia stroke	Patient 5: unilateral choreoathetoid movement	Patient 5: 1–30 min	Patient 5: 10–20/day	

(continued)

Table 6.2 (continued)

Gonzalez-Alegre P 2003 [71]	Moyamoya disease	Patient 1: unilateral choreoathetoid movement	Patient 1: 1 min	Patient 1: 10/day	Patient 1: walking or swimming
		Patient 2: unilateral choreoathetoid movement	Patient 2: 30 min to several hours	Patient 2: 5/day	Patient 2: None
Garcia-Ruiz PJ 2003	Subthalamic lesion (unknown etiology)	Unilateral dystonic attacks	Few seconds	1 attack/day	NA
Baba Y 2003 [72]	Osmotic demyelination	Unilateral dystonic attacks	2–5 min	NA	Standing up from a prolonged sitting position
Thomas R 2002 [53]	Hypoparathyroidism	Dystonic posturing of the bilateral upper extremities and face	15–30 s	NA	Walking from a sitting position
Bonev VI 2002 [73]	Cryptogenic myelitis	Spasm in bilateral upper and lower extremities	10–30 s	Many times a day	Passive or volitional movement of the limbs
Dale RC 2002 [35]	Post-streptococcal	Dystonic posturing of the face, hands, and trunk	10 min to 4 h	1–4 attacks/day	Stress and anxiety
Huang CW 2005 [74]	Pseudohypoparathyroidism	Dystonic posturing in the bilateral upper extremities	1 min	NA	Running
Mahmud FH 2005 [75]	Pseudohypoparathyroidism	Choreoathetoid movements in the hands and feet	1 min	NA	NA
Engelen M 2005 [14]	Antiphospholipid antibody	Choreiform movements on the right side	Several hours to a day	NA	Stress
Shimizu T 2001 [76]	Bilateral carotid artery stenosis	Alternating shaking of the extremities	30 min	2–3 attacks/day	No
Volonté MA 2001 [77]	Hypoparathyroidism	Right side dystonic posturing	10–20 s	10 attacks/day	Running, walking, and standing up
Irani SR 2011 [17]	Autoimmune	Faciobrachial dystonic seizures (always unilateral but may involve either side)	Very brief (less than 3 s)	50 attacks/day	Auditory and high emotions
Carnero Contentti E 2016 [78]	Autoimmune (neuromyelitis optica)	Paroxysmal painful tonic spasms (PPTS)	20–45 s	NA	NA

Table 6.2 (continued)

Hur YJ 2013 [33]	H1N1 infection	Bilateral dystonic posturing of the hands	Less than 1 min	Several attacks in a day	Sudden standing, stress, and anxiety
Sethi KD 2002 [79]	Carotid stenosis	Right upper and lower extremity dystonic posturing	1–2 min	Around 3 attacks in a day	Hyperventilation while sitting, standing from sitting, and yawning
Ondo WG 2002 [32]	SSPE	Dystonic posturing of the arms, legs, neck, and lower face	5–10 s	NA	NA
Bozi M 2003 [37]	Parkinson's disease	Left lower extremity dystonic posturing	NA	NA	Running
Alonso-Navarro H 2009 [10]	Sjögren's syndrome	Dystonic posturing of the right arm	2 min	3–4 attacks/day	NA
Waubant E 2001 [80]	Multiple sclerosis	Right side segmental dystonia	15–30 s	100 times a day	Hyperventilation
Thomas KP 2010 [81]	Pseudohypoparathyroidism	Left foot and both hands dystonic posturing	10 s	10 times a day	Running or walking
Hall DA 2007 [54]	Celiac disease	Dystonic posturing of the upper body and left leg	5–30 min	200 attacks/day	No
Liu MY 2012 [15]	Hashimoto encephalopathy	Left side choreiform movements	NA	120–150 times/day	Always induced by a sudden movement
Kim SM 2012 [13]	Neuromyelitis optica	Bilateral or unilateral PTS	NA	NA	Variable (may be precipitated by sudden movement)
Benz R 2012 [55]	Spinal cord lymphoma	Bilateral upper extremities dystonic posturing	30–40 s	Occurred every 1–60 min	None
Montilla-Uzcátegui V 2016 [38]	Fahr's syndrome	Bilateral dystonic and choreoathetoid movements	30 min to 3 h	NA	None
Peila E 2015 [82]	Post-streptococcal	Bilateral choreiform	20 min	3–4 attacks/day	None
Kwon YJ 2015 [83]	Pseudohypoparathyroidism	Bilateral dystonic posturing	5–10 s	4–5 attacks/day	Sudden movements (physical exercise)

(continued)

Table 6.2 (continued)

Sorgun MH 2013 [21]	Ischemic stroke	Left-side hemidystonia	10–30 s	5–50 times/day	None
Jin D 2012 [84]	Hypoparathyroidism	Dystonia and choreoathetosis on the right	Few minutes	Several times a day	Standing up or walking
Zittel S 2012 [85]	Multiple sclerosis	Unilateral dystonic attacks	1 min	2–15 times/day	Sudden movements or hyperventilation
Chung EJ 2012 [86]	Fahr's disease	Bilateral dystonic movements (right>left)	5–10 s	20–30 attacks/day	Standing suddenly from a seated position
Debruyne F 2009 [87]	Insulinoma	Bilateral choreoathetoid	30 min	NA	Psychological stress and fatigue
Aradillas E 2011	Autoimmune (VGKC antibody)	Bilateral dystonic	30 s	40–50 attacks/day	Change of position, startle, lack of sleep, and stress
Yulug B 2008 [56]	Spinal cord compression	Choreiform movements in right upper extremity	15–30 s	NA	Movement of the right arm
Tschopp L 2008 [59]	Neuroacanthocytosis	Choreiform and dystonic movements in all four extremities, trunk, and neck	Seconds to several minutes	NA	Stress and cold
Bonakis A 2009 [88]	Cerebral palsy	Hemidystonic spasm	1 min	10–20 episodes/day	Loud noise and touch
Chiesa V 2008 [42]	Post-traumatic	Hemidystonia	NA	30 attacks/day	Movement of the left limb or rising from the chair
Alemdar M 2008 [89]	Fahr's disease	Left-sided choreiform	3 min	NA	NA
Diaz GE 2010 [90]	Bilateral striopallidodentate calcinosis	Bilateral dystonic episodes	2–5 min	3 times/week	Standing up from a seated position
Hopkins RS 2007 [91]	Hypothyroidism	Bilateral choreoathetoid movements	1 min	NA	NA
Lyoo CH 2007 [92]	Moyamoya disease	Unilateral dystonic and choreiform movements	30 min to 4 h	1 attack every 10 days	Walking for long distance
Senbil N 2008 [93]	Post-streptococcal	Generalized dystonic movements	2–3 min	30–40 attacks/day	Psychological stress

Table 6.2 (continued)

Alemdar M 2007 [94]	Hypoparathyroidism	Dystonic movements in the neck and bilateral choreiform movements	10 s to 3 min	130 attacks/day	NA
Prashantha DK 2009 [95]	Pseudohypoparathyroidism	Bilateral choreiform and dystonic movements	8–10 h	2–3 times a month	Hyperventilation
Lee SS 2009 [96]	Neuromyelitis optica (NMO)	Right-side choreiform movements	15–30 s	NA	NA
Pop R 2017 [97]	Multiple sclerosis	Right upper extremity dystonic and choreiform movements	30–40 s	50 attacks/day	Sudden or voluntary movements
Ciampi E 2017 [98] (seven patients reported)	Multiple sclerosis	Dystonic episodes in the face (1), leg (2), arm, and leg (4)	Seconds	More than 10 times a day (four patients)	Hyperventilation (six patients)
Yeghiazaryan NS 2010 [99] (4 patients reported)	Intracranial calcification	Dystonic posturing and choreiform movements of the head, limbs, and trunk	5–30 s	1 attack/year	Fever, fasting, and stress
Fragoso YD 2006 [100]	Multiple sclerosis	Case 1: right leg cramps, right arm dystonic posturing	1 min	2 attacks/day	Movements such as walking
		Case 2: painful cramps in her right wrist, fingers, ankle, and toes.	2 minutes	30 times/day	Any sudden movement, startling noise, or repetitive movements (such as brushing teeth or combing hair)
Cases	*Aura*	*Pain*	*Imaging*	*Treatment*	*Latency*
See SJ 2003 [66]	Yes	NA	Internal capsule and globus pallidus	Phenytoin (marked improvement)	NA
Kowacs 2004 [23]	NA	NA	Case 1: right internal carotid artery 95% stenosis	Case 1: carotid endarterectomy (improvement)	NA
			Case 2: left internal carotid artery critical stenosis	Case 2: left carotid stenting	

(continued)

Table 6.2 (continued)

Puri V 2004 [67]	No	No	Normal	Carbamazepine and carbimazole	NA
Spengos K 2004 [68]	Yes	No	Right basal ganglia and parieto-occipital cortex	NA	NA
			Angiography showed findings consistent with moyamoya disease		
Gálvez-Jiménez N 2002 [69]	No	No	Patient 1: high-grade left carotid stenosis on MR angiogram	Patient 1: left carotid endarterectomy	NA
			Patient 2: MR angiogram showed high-grade stenosis of right vertebral artery	Patient 2: right vertebral artery balloon angioplasty	
			Patient 3: head CT showed chronic ischemic changes and old lacunar infarcts	Patient 3: aspirin 325 mg (no further episodes)	
			Patient 4: Brain MRI showed old left ACA/MCA watershed infarct	Patient 4: warfarin (no further episodes reported)	
			Patient 5: CT scan showed an old infarct in the posterior limb of right internal capsule, and brain MRI was normal	Patient 5: aspirin 325 mg daily	
Warner GT 2003 [70]	No	No	Brain MRI showed bilateral globus pallidus hyperintensity	NA	NA

Table 6.2 (continued)

Zorzi G 2003 [58]	No	No	NA	Patient 1: acetazolamide (marked improvement)	NA
				Patient 2: carbamazepine (no improvement)	
				Patient 3: clonazepam (no improvement)	
				Patient 4: carbamazepine and acetazolamide (no improvement)	
				Patient 5: clonazepam (no improvement)	
Gonzalez-Alegre P 2003 [71]	No	No	Patient 1: angiogram revealed findings consistent with moyamoya disease	Patient 1: external carotid-internal carotid artery bypass	NA
			Patient 2: angiogram showed findings consistent with moyamoya disease	Patient 2: phenobarbitone (improved)	
Garcia-Ruiz PJ 2003 [101]	No	Yes	Brain MRI showed increased signal in the subthalamus	Valproic acid (no effect) and carbamazepine (improved)	NA
Baba Y 2003 [72]	No	Yes	Brain MRI showed area of hyperintensity in the pons	Subsided without any treatment	2 months after the insult
Thomas R 2002 [53]	No	No	Brain MRI and head CT showed bilateral calcification of the cerebellum, thalamus, globus pallidus, and caudate nucleus	Vitamin D3 and calcium carbonate	NA

(continued)

Table 6.2 (continued)

Bonev VI 2002 [73]	Yes	Yes	C-spine MRI showed T2 hyperintensity from C2 to C6	Carbamazepine (improvement)	NA
Dale RC 2002 [35]	No	No	Brain MRI was normal	Chlorpromazine (no effect) and carbamazepine (moderate improvement)	NA
Huang CW 2005 [74]	No	No	Brain MRI showed symmetric calcification of bilateral putamen and dentate nucleus	Vitamin D and calcium (marked improvement)	NA
Mahmud FH 2005 [75]	No	No	Brain MRI was reported normal	Vitamin D and calcium (marked improvement). There was some improvement with carbamazepine	NA
Engelen M 2005 [14]	No	No	Brain MRI showed multiple hyperintensities in the basal ganglia	Anticoagulation led to a significant reduction in her symptoms	NA
Shimizu T 2001 [76]	No	No	Brain MRI showed white matter changes and angiogram showed marked stenosis of bilateral internal carotid arteries	Bilateral carotid endarterectomy led to a complete resolution	NA
Volonté MA 2001 [77]	Yes	No	Brain MRI showed hyperintensity on T1 sequence in bilateral basal ganglia	Vitamin D3 and calcium led to a complete resolution of episodes	NA
Irani SR 2011 [17]	NA	No	Brain MRI normal if there is no cognitive impairment	Immunotherapy (excellent response)	NA
Carnero Contentti E 2016 [78]	NA	Yes	Spine MRI showed LETM (longitudinally extensive transverse myelitis)	Carbamazepine (satisfactory response) Phenytoin, pregabalin, and gabapentin was not effective	Mean time from relapse to PPTS was 30 days, and mean time from the diagnosis of NMO was 7 months

Table 6.2 (continued)

Hur YJ 2013 [33]	No	No	Brain MRI showed venous angioma in the left basal ganglia	Levodopa and carbamazepine helped significantly	NA
Sethi KD 2002 [79]	No	No	MR angiography showed complete occlusion of the left internal carotid artery and near total occlusion of the right internal carotid artery	NA	NA
Ondo WG 2002 [32]	No	No	Brain MRI was normal	Carbamazepine (moderate improvement)	NA
Bozi M 2003 [37]	No	No	NA	NA	NA
Alonso-Navarro H 2009 [10]	No	No	Brain MRI showed chronic ischemic changes	Carbamazepine, gabapentin, valproic acid, phenytoin, lamotrigine, and topiramate were not effective. Clonazepam was moderately effective	NA
Waubant E 2001 [80]	NA	NA	Brain MRI showed enhancement in the left internal capsule	Acetazolamide (dramatic improvement)	NA
Thomas KP 2010 [81]	No	No	Brain MRI showed hyperintensity of bilateral basal ganglia	Vitamin D3 and calcium administration led to dramatic improvement	NA
Hall DA 2007 [54]	No	No	Brain MRI was normal	Carbamazepine, gabapentin, acetazolamide, phenytoin, clonazepam, and levodopa (no benefit). Gluten-free diet showed marked improvement	NA
Liu MY 2012 [15]	No	No	Brain MRI was normal	Steroids led to a marked improvement	NA

(continued)

Table 6.2 (continued)

Kim SM 2012 [13]	Variable (may be preceded by paresthesia)	Yes	Spine MRI showed LETM	Phenytoin, carbamazepine, gabapentin, and pregabalin were effective	The onset of PTS occurred after a month of myelitis episode
Benz R 2012 [55]	NA	NA	Spine MRI showed intramedullary T1 contrast enhancement	Carbamazepine (minor and short-lived effect). Pregabalin, levetiracetam, and benzodiazepines (no effect)	NA
Montilla-Uzcátegui V 2016 [38]	NA	NA	Head CT showed symmetric hyperdense lesion in the basal ganglia, thalamus, and cerebellum	Carbamazepine (excellent response)	NA
Peila E 2015 [82]	NA	NA	Brain MRI was normal	Penicillin, valproic acid, and clonazepam (mild improvement)	NA
Kwon YJ 2015 [83]	No	No	In one patient, head CT showed calcification in the basal ganglia, while in other it was normal	Both patients were treated with oral calcium leading to improvement	NA
Sorgun MH 2013 [21]	No	No	Brain MRI showed an infarct in right putamen	Carbamazepine led to an excellent response	NA
Jin D 2012 [84]	No	No	Brain MRI and head CT were reported normal	Oral calcium led to an improvement	NA
Zittel S 2012 [85]	No	No	Brain MRI in patient 1: left thalamic lesion and left mesencephalic peduncle in patient 2	Anti-inflammatory treatment led to the disappearance of symptoms	NA
Chung EJ 2012 [86]	No	No	Head CT showed calcification in the dentate nucleus and basal ganglia	Carbamazepine caused a marked improvement in symptoms	NA

Table 6.2 (continued)

Debruyne F 2009 [87]	No	No	Brain MRI and head CT were reported normal	Removal of insulinoma	NA
Aradillas E 2011	No	No	Brain MRI showed left caudate and left putamen hyperintensity	Intravenous immunoglobulin and plasma exchange (resolved completely)	NA
Yulug B 2008 [56]	No	No	Spine MRI showed cord compression at C5–C6 level	Carbamazepine led to a remarkable improvement	NA
Tschopp L 2008 [59]	No	No	Brain MRI was normal	Carbamazepine led to a dramatic improvement	NA
Bonakis A 2009 [88]	No	No	Brain MRI showed left basal ganglia and parietal lobe ischemic lesion	Phenytoin monotherapy led to a dramatic decrease in the number of episodes	18 years
Chiesa V 2008 [42]	No	No	Brain MRI showed atrophy	Carbamazepine led to improvement	1 month
Alemdar M 2008 [89]	No	No	Head CT showed symmetric calcification of the basal ganglia, cerebellum, and thalamus	Oxcarbazepine led to resolution of the attacks	NA
Diaz GE 2010 [90]	No	No	Brain MRI showed mineral deposition in the basal ganglia and dentate nucleus bilaterally	Carbamazepine caused an improvement	NA
Hopkins RS 2007 [91]	No	No	Brain MRI was reported normal	Levothyroxine led to improvement	NA
Lyoo CH 2007 [92]	No	No	Angiography showed findings consistent with moyamoya	The patient refused surgical treatment	NA
Senbil N 2008 [93]	No	No	Brain MRI was reported normal	Haloperidol and penicillin partially helped	NA

(continued)

Table 6.2 (continued)

Alemdar M 2007 [94]	No	No	Head CT showed massive bilateral calcification in the basal ganglia, thalamus, and brain stem	Vitamin D3 and calcium did not improve these spells. Levetiracetam reduced the frequency of episodes	NA
Prashantha DK 2009 [95]	No	No	Head CT showed bilateral calcification in the basal ganglia, thalamus, and dentate nuclei	Calcium, Vitamin D3, and carbamazepine led to resolution of these episodes	NA
Lee SS 2009 [96]	No	No	Spine MRI showed LETM	Clonazepam and steroids led to a gradual reduction of these episodes	NA
Pop R 2017 [97]	No	No	Brain MRI showed demyelinating lesion in the left basal ganglia and left midbrain	Intravenous steroids led to resolution of these spells	NA
Ciampi E 2017 [98]	No	No	Brain MRI showed demyelinating lesion in contralateral thalamus (two patients) and contralateral cerebellar peduncle (four patients)	Steroids (no improvement), acetazolamide (six patients – improvement), clonazepam (one patient – improvement), and levetiracetam (one patient – improved)	4–60 months from the diagnosis
Yeghiaza-ryan NS 2010 [99]	No	No	Three out of four patients had intracranial calcification on head CT	NA	NA
Fragoso YD 2006 [100]	Case 1: no	Case 1: yes	Brain MRI showed demyelinating plaques in both cases	i.v. steroids, glatiramer	NA
	Case 2: yes (prickly sensation in the right arm and leg)	Case 2: yes		Oral steroid, glatiramer	NA

Autoimmune/Inflammatory

Multiple sclerosis and related disorders are the most common cause of acquired PKD and PNKD. Initially the brief attacks occurring in multiple sclerosis (MS) and neuromyelitis optica (NMO) were termed tonic spasm or tonic seizures [102]. The first case of tonic seizures (paroxysmal dyskinesia) was published in a patient with multiple sclerosis in 1962. Interestingly, it first occurred during the night. Occasionally, this may be the presenting feature of the disease [11].

Paroxysmal dystonia in MS typically affects one side of the body. However, in some, the attacks are generalized [12]. In patients with NMO, these attacks are occasionally confined to the trunk bilaterally [13]. The attack may occur without any precipitating factor or may be provoked by sudden movement. However, in the clinic, brief hyperventilation has been the most frequently described triggering maneuver [12].

During an episode, there is a painful posturing of the upper and lower limbs on one side of the body with or without involvement of the face lasting from seconds to minutes [13]. These attacks may occur up to several times a day. Sometimes we have observed transient neurologic findings such as an inability to elevate one eye (Video 6.1) only during an attack [103]. In one published case of acute disseminated encephalomyelitis, dyskinesia was accompanied by laughing [19].

The occurrence of these attacks does not necessarily imply an exacerbation of the underlying demyelinating disease. These attacks run their own course even when the underlying disease continues to worsen [13].

Unilateral attacks can occur due to lesions anywhere in the motor pathway including the corona radiata, internal capsule, cerebral peduncle, or spinal cord. Bilateral attacks without facial involvement likely have a spinal origin [12, 104]. These were described frequently in the Japanese population [105]. In unilateral attacks imaging often shows a plaque that involves the motor pathway at the level of the posterior limb of the internal capsule or the cerebral peduncle on the contralateral side [80, 106, 107]. Despite the difficulty with localization as eluded by Mathews that "tonic seizures form very unpromising material for any attempt to determine the site of the responsible central lesion or the nature of the central mechanism involved" [108], we think that the most frequent imaging abnormality is seen in the contralateral cerebral peduncle (Fig. 6.1 and Video 6.1).

Since MS causes numerous plaques, attributing a clinical finding to a specific lesion can be difficult. If a demyelinating plaque involves an area where motor fibers are close, then a greater number of axons would be involved, which is the most important underlying anatomic factor.

The pathophysiology of paroxysmal dystonia in MS likely involves ephaptic transmission of the electrical impulse at the site of demyelination [109]. This phenomenon has been described in other conditions such as hemifacial spasm. In MS it has been shown that the prolonged latency of visual evoked responses is shortened by hyperventilation [110]. This suggests an improved conduction in demyelinating optic pathways because of transient alkalosis induced by hyperventilation. In the case of paroxysmal dystonia, the improved conduction in the motor pathways

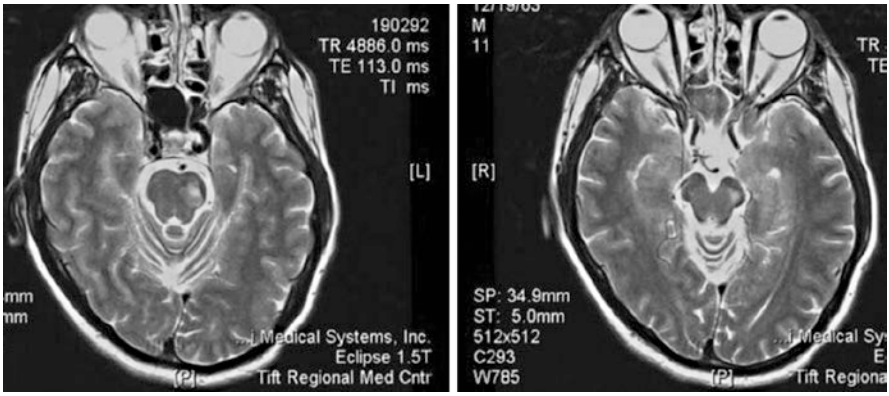

Fig. 6.1 Brain MRI T2 axial sequence shows hyperintensity in the left cerebral peduncle

induced by hyperventilation may facilitate the radial spread of impulses resulting in an attack. This hypothesis is supported by the reported robust efficacy of acetazolamide [103].

Usually, the first line of therapy is anticonvulsants such as carbamazepine and oxcarbazepine which have shown some effectiveness in the treatment of this condition [13, 111]. Some patients may respond to gabapentin, pregabalin, and phenytoin as well [78]. Acetazolamide alone or as an adjunct to carbamazepine is remarkably effective [103]. How long the therapy should be continued is unclear. We usually try and taper the drug off after 3–6 months of therapy. The underlying disease should be managed by immunomodulatory treatment as indicated.

Endocrine/Metabolic

Hypoparathyroidism and Pseudohypoparathyroidism (HP and PHP)

Both HP and PHP can lead to seizures, paresthesias, and psychiatric symptoms. In addition, mental retardation or dementia may occur. The psychiatric manifestations may include hallucinations [112].

HP can be iatrogenic or of unknown etiology. A wide variety of movement disorders have been described in association with both HP and PHP. These include chorea, athetosis, dystonia, oculogyric crises, parkinsonism, and cerebellar ataxia and paroxysmal dyskinesia [50, 51]. The incidence of movement disorders in HP is reported to be 4–12.5% [52]. Both PKD [53] and PNKD [94] have been described in HP and PHP (Videos 6.2, 6.3, and 6.4). One report described apraxia of eyelid opening and faciobrachial movements with hypoparathyroidism [53].

Oculogyric crises have not traditionally been classified under PxD. However, these may be intermittent and can occur in numerous other conditions apart from HP [113].

CT scan of the head may or may not show calcification of the basal ganglia, and this finding can be difficult to detect on a brain MRI (Fig. 6.2) [114]. Impaired basal

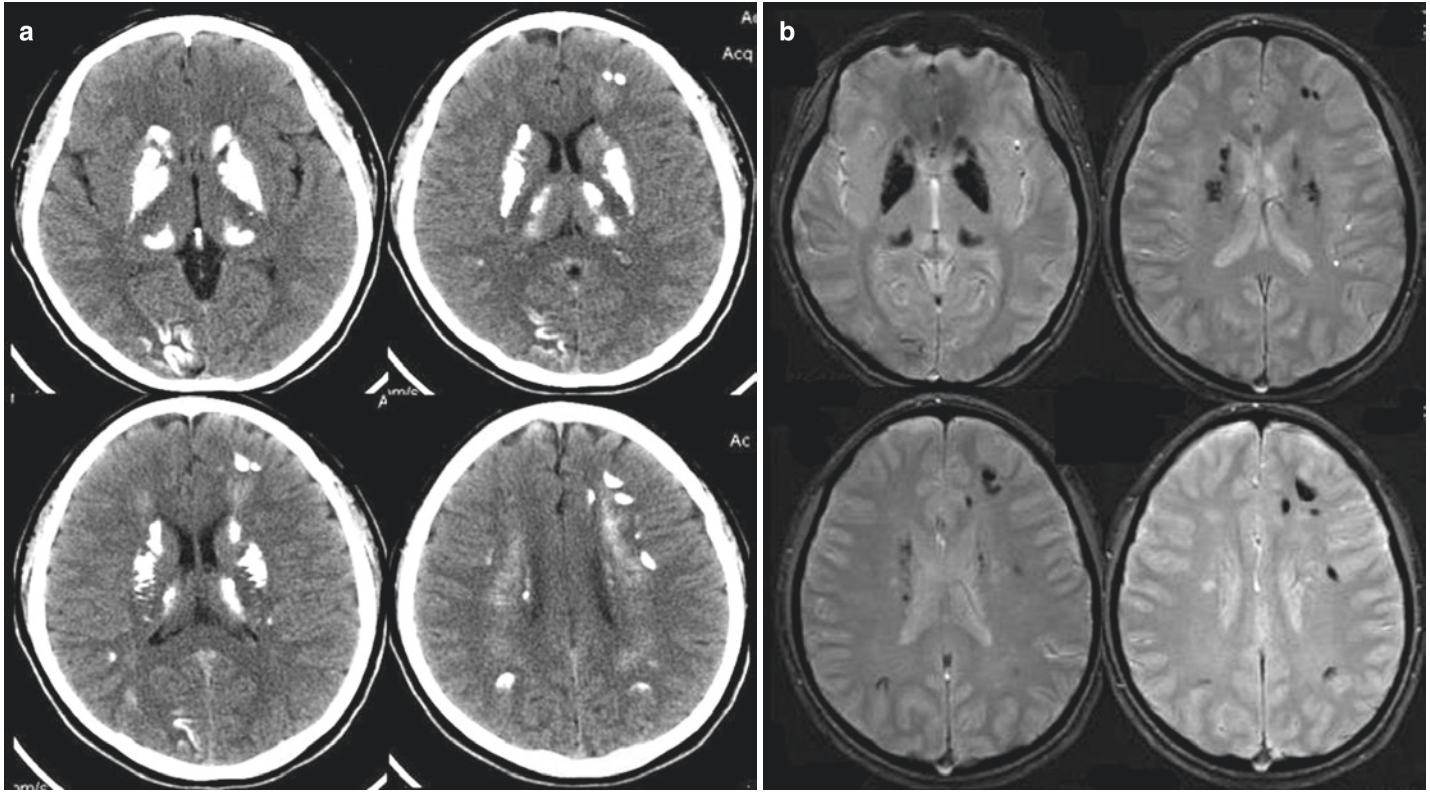

Fig. 6.2 (**a**, **b**) MRI and CT of the brain in a patient with mixed PKD and PNKD in pseudohypoparathyroidism (Video and image courtesy: Anthony Lang, MD). Head CT shows calcification, and brain MRI is suggestive of mineral deposition

ganglia function due to hypocalcemia may be the mechanism that leads to neurological manifestations. A significant hypometabolism of the ventral putamen and inferior caudate on [18F]-FDG PET has been described in one report. The symptoms disappeared following calcium/calcitriol therapy, and the abnormality on FDG-PET disappeared as well. The deposits of calcium were still present on the follow-up scan which suggests that hypocalcemia, and not calcium deposits, is responsible for the altered function of the basal ganglia [77].

The PxD associated with HP and PHP usually responds well to calcium and Vitamin D supplementation (Fig. 6.3) [81, 115]. As mentioned above the cerebral calcifications remain unchanged [77].

Hyperthyroidism

Hyperthyroidism is a well-known cause of exaggerated physiological tremor. Albeit rare, persistent chorea, generalized, or hemichorea has been known to occur in hyperthyroidism [116]. There are some reports of PKD in hyperthyroidism [48]. The underlying cause could be excessive thyroid hormone supplementation [49] or autoimmune thyroiditis [15]. The discontinuation of exogenous thyroid hormone or treatment with antithyroid drugs resulted in amelioration of the paroxysms [49]. There is one case report of spasmodic flexion of the trunk associated with hyperthyroidism, but this does not fit the phenomenology of dyskinesia [117].

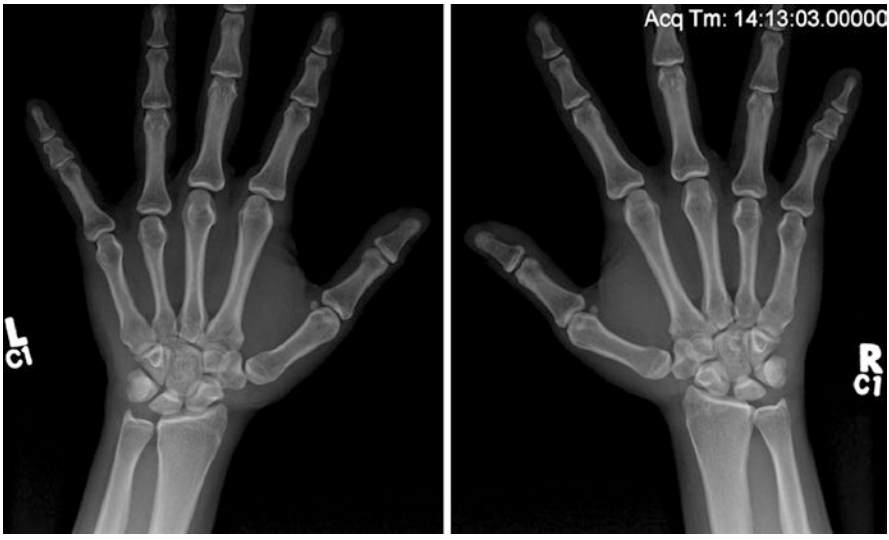

Fig. 6.3 X-ray of the patient above showing shortening of the fourth metacarpal consistent with the diagnosis of pseudohypoparathyroidism

Disorders of Glucose Metabolism

Both hypoglycemia and hyperglycemia may result in paroxysmal dyskinesia. Hypoglycemia may be due to overzealous treatment of diabetes mellitus or due to an insulin-secreting tumor. Recurrent choreoathetosis due to iatrogenic hypoglycemia may result in dyskinesia, and these patients almost always display an altered awareness during the episodes, a feature not seen in PxD due to GLUT1 deficiency [43–45].

Mechanistically hypoglycemia and GLUT 1 deficiency are similar. GLUT1 deficiency is a genetic disorder due to *SLC2A1* gene mutation (cfr. Chap. 5). It results in cerebral hypoglycemia due to an impaired glucose transport from the blood to the brain. In its milder form, it may manifest as PED [118].

Hypoglycemia may present as paroxysmal exercise-induced dystonia [119], but it may also manifest as PNKD (Video 6.5) [87].

Hyperglycemia can lead to a variety of neurological manifestations such as confusion, coma, epilepsia partialis continua (EPC), hemichorea/hemiballism, and biballism [46]. EPC in hyperglycemia may be confused with a PxD [120]. EPC may manifest as negative myoclonus (asterixis) which can be confused with PKD or PNKD [47]. Contrary to a commonly held belief, EPC may disappear during sleep, further highlighting the fact that it may be confused with a movement disorder [121]. Diabetes mellitus may present as PKD [122].

Both PKD and PNKD have been reported with hyperglycemia [46]. In some cases, an underlying structural abnormality of the putamen may predispose patients to develop a movement disorder secondary to hyperglycemia [123].

Autoimmune Disorders

There are a variety of movement disorders that occur in the setting of autoimmune diseases. These include stiff person syndrome (SPS) and its variants such as progressive encephalomyelitis with rigidity and myoclonus (PERM), ataxia, chorea, parkinsonism, and progressive supranuclear palsy phenotype [124]. Paroxysmal worsening of the SPS (spasms) is not included under secondary PxD [125]. However, tonic spasm (paroxysmal dystonia) has been described in systemic lupus erythematosus and antiphospholipid antibody syndrome. Sometimes, this is due to a lacunar infarct in the putamen and not a direct result of the antibody-mediated injury [16]. Faciobrachial dystonic seizures (FBDS) are a relatively recently recognized entity that is discussed below.

Faciobrachial Dystonic Seizures (FBDS)

This disorder is recognized as an autoimmune movement disorder rather than autoimmune epilepsy [126, 127]. FBDS is characterized by transient unilateral arm posturing and ipsilateral face involvement (Video 6.6). However, despite

what the name suggests, leg and trunk involvement may occur. Occasionally, the attacks change sides [126]. Bilateral attacks are well described. The episodes typically occur without any provoking factors, so these should be included under PNKD. However, in some cases auditory stimuli and high emotion may bring upon an attack [17]. The attacks occur several (30–50 or more) times per day, and each attack lasts only for a few seconds. Majority of the patients do not have an EEG correlate with the attacks, and patients generally remain alert during the attack. However, altered awareness is reported by the patient or caregivers in some instances [126]. FBDS must be differentiated from non-LGI1 insular seizures [128]. The response to antiepileptics is poor, and many patients develop a skin rash after the administration of anticonvulsants [17]. Another clue to the underlying etiology is the presence of hyponatremia due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [17]. The antibody responsible for this syndrome is a LGI1 (leucine-rich glioma inactivated-1) antibody. LGI1 is a component of the voltage-gated potassium channel (VGKC). It has to be emphasized that the VKGC antibodies may be negative, and the LGI1 antibodies are the specific antibody that should be tested [18].

Immunotherapy is the treatment of choice. If the disorder is not promptly recognized and treated, the patients may go on to develop limbic encephalitis (Fig. 6.4) [17].

Vascular

Cerebrovascular vascular disease has rarely been reported as a cause of PxD. Lacunar infarcts in the putamen may result in PKD [20] or PNKD [21] (Video 6.7). Diffuse white matter disease is another reported cause [129] although this cause needs further investigation. Painful tonic spasms in a patient with putaminal lacunae were discussed above [16]. PKD episodes involving face and speech have been described with thalamic infarct as well [130]. One report of focal PxD precipitated by swallowing has been reported because of an old hemorrhage in the medulla [131]. An important entity that has been termed limb shaking transient ischemic attack (LSTIA) may be confused with a seizure and carries a substantial risk of a future stroke. These attacks occur upon sitting or standing and usually affect one leg but may involve the arm as well [22–24]. In the only video example that we have been able to review, there appears to be a temporary lapse of tone (asterixis) rather than a myoclonic jerk that is responsible for the limb shaking [28] (Video 6.8). The investigations demonstrate severe stenosis of the contralateral internal carotid artery (ICA) (Fig. 6.5). Revascularization of the carotid artery in these cases leads to an improvement in the symptoms [28]. In addition to LSTIA, paroxysmal arm dystonia has also been described in a patient with severe contralateral ICA disease leading to stroke [29]. Another rarely described entity is orthostatic paroxysmal dystonia. This was seen in a patient with severe bilateral inoperable intracranial lesions of both ICAs and was precipitated by standing up (Video 6.9) [79].

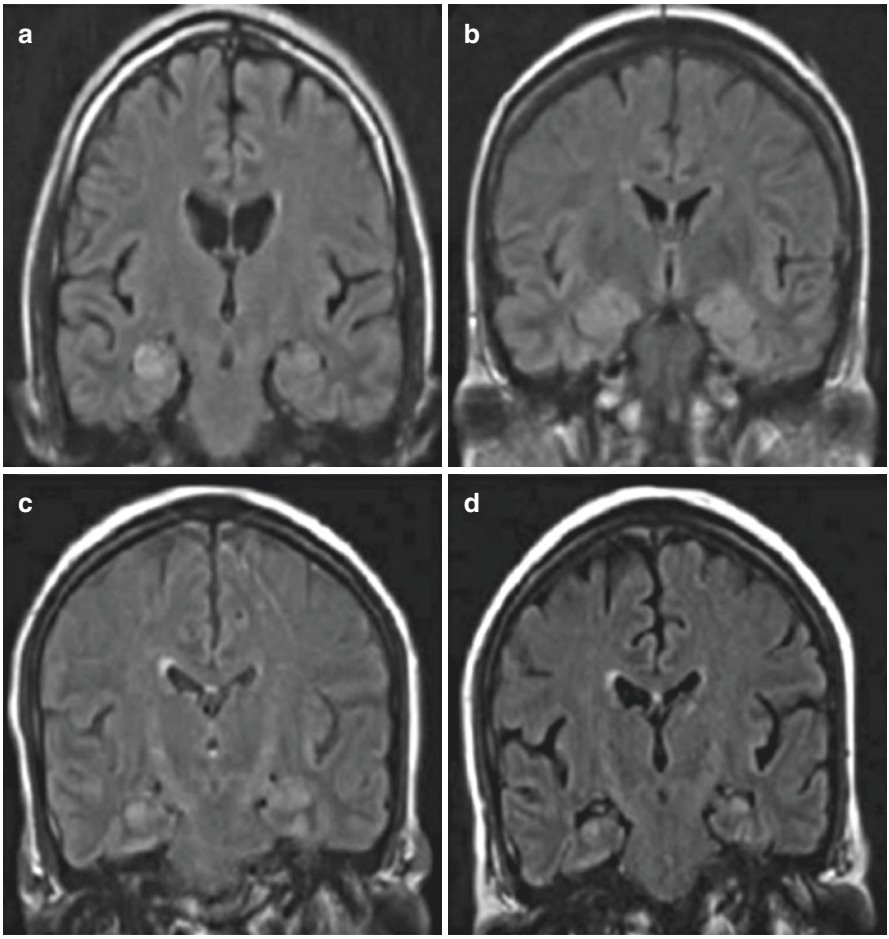

Fig. 6.4 (**a**–**d**) Brain MRI in faciobrachial dystonic seizures shows FLAIR hyperintensity in medial temporal lobes which can progress to atrophy (**d**) over a period of time. (From Irani et al. [17]. Reprinted with permission from John Wiley and Sons)

Moyamoya disease results in progressive narrowing of the ICA resulting in occlusion and the formation of fine collateral vessels in the basal ganglia and the cortex. Hemichorea and rarely generalized chorea have been described in moyamoya disease [25]. Other movement disorders include LSTIA [26] and recurrent torticollis [27]. PKD, PNKD [71], and PED [92] have been described in moyamoya disease as well. In one patient the PxD initially appeared during and after coitus [68]. Eventually, the attacks started while running or climbing stairs [68]. Another patient had attacks of chorea induced by singing [132]. Ingestion of hot food can also cause paroxysmal chorea in moyamoya disease [133]. The common element in both these reports is hyperventilation that results in hypocarbia and

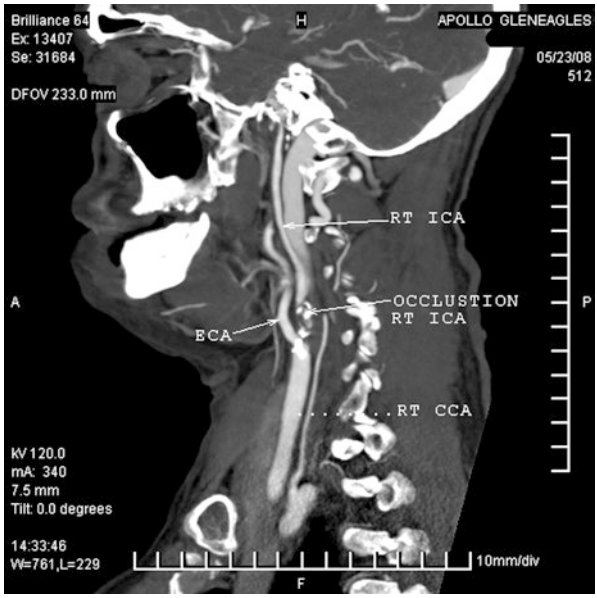

Fig. 6.5 CT angiogram shows severe stenosis of the right internal carotid artery

cerebral ischemia in the setting of a compromised vascular system [25]. Encephaloduroarteriosynangiosis results in amelioration of the PxD [25].

Trauma

Both central [40, 41] and peripheral trauma [42] have been shown to cause paroxysmal dyskinesia (Video 6.10). There may be some latency between the onset of abnormal movements and trauma [8]. Traumatic injury leading to paroxysmal dyskinesia may be diffuse [40, 41] or focal (basal ganglia) [134]. The delayed onset of symptoms could be due to changes in CNS plasticity and time taken for synaptic reorganization.

One reported patient fell from a height and sustained mild trauma to his head and neck. This trauma was shortly (within minutes) followed by the development of paroxysmal intermittent dystonic posturing of his right face, forearm, hand, and foot, with weaker contractions of the left foot. Neurological examination between spells was normal. A head CT scan (initially and 4 weeks later) was normal. However, positron emission tomographic (PET) scanning revealed abnormalities in the left basal ganglia region, including decreased oxygen metabolism, decreased oxygen extraction, increased blood volume, and increased blood flow [135].

However, in many cases of trauma, the situation is complicated by the presence of litigation, thus raising the possibility of malingering or a psychogenic movement disorder.

Spinal Cord Lesions

Bilateral tonic spasms (paroxysmal dystonia) or those involving the trunk often have a spinal origin. These are even more common in neuromyelitis optica spectrum disorders (NMSOD) as compared to MS [13]. In one study the tonic spasms were more common in aquaporin-4 antibody-positive patients as compared to myelin oligodendrocyte glycoprotein antibody-positive cases [136]. Other spinal cord lesions such as glioma, lymphoma [55], and cervical disc [56] have been reported to result in secondary PxD. A case of paroxysmal kinesigenic myoclonus has been described in a patient with slow-growing spinal cord tumor [137] (Video 6.11 and Fig. 6.6).

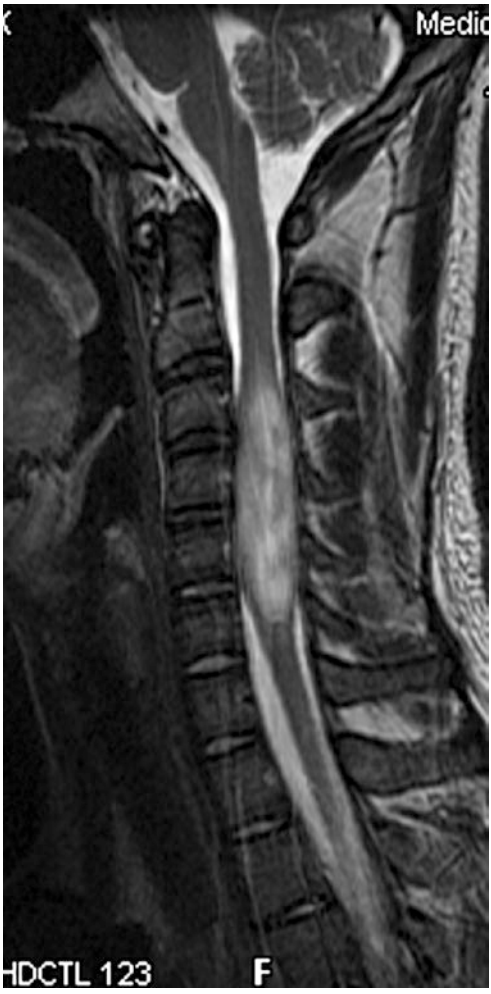

Fig. 6.6 Spine MRI shows intramedullary T2 hyperintensity suggestive of a spinal cord tumor

Functional (Psychogenic) Paroxysmal Dyskinesia

This group probably represents the most common known etiology of PxD (Video 6.12) [8]. Many patients are referred to a movement disorders specialist from their epilepsy colleagues after the video EEG fails to show abnormality. In one series of 26 patients, the mean age at onset was 38.6 years which is much later than genetically determined PxD. Females were predominantly affected (73%). Most subjects (88.4%) had long attacks, and unlike genetically determined PxD, there was very high within-subject variability for attack phenomenology, duration, and frequency. Dystonia was the single most common movement disorder presentation, but 69.2% of the patients had mixed or complex PxD. In half of the attacks, unusual triggers could be identified, and nearly the same percentage had unusual relieving strategies. These patients may have other supportive signs such as give way weakness, non-physiologic sensory loss, and an unusual gait [138, 139].

As in non-epileptic seizures (NES) that may be superimposed on a background of organic seizures, functional (psychogenic) PxD may co-occur in a patient who has PxD due to other etiologies (Video 6.13) [140].

These patients may be hard to diagnose and manage, and usually an interdisciplinary approach with the involvement of psychiatrist, psychologist, physical therapist, and the neurologist is required (cfr. Chap. 10). There are no adequate biomarkers to identify these patients, and no controlled trials exist to evaluate available approaches to therapy.

Miscellaneous Causes

PxD have been described in multiple other disorders such as human immunodeficiency virus infection, other CNS infections, progressive supranuclear palsy, and methylphenidate administration [31, 34, 39, 64].

Cerebral palsy is another cause of delayed onset of paroxysmal dyskinesia [57, 58].

Self-stimulatory behavior is seen in the pediatric age group. It occurs in a specific body position and is characterized by stiffening of the legs and rocking of the pelvis. It can mimic paroxysmal dyskinesia [141].

Sandifer syndrome leads to paroxysmal dystonic movements of the head, neck, or trunk. These movements are prominent during or after feeding. The neurological examination and other investigations such as brain MRI and EEG often show normal results. These movements are considered as a manifestation of gastroesophageal reflux disease (GERD), and treatment of GERD usually leads to an improvement in these movements [142].

Investigations

All patients with suspected paroxysmal dyskinesia should undergo a comprehensive metabolic testing including but not limited to ionized calcium, glucose, and thyroid hormone levels. A brain MRI should be performed in all suspected cases of acquired dyskinesia, and spine MRI should be considered where the cranial MRI is normal. MRI of the brain may miss cerebral calcifications, and a head CT may be necessary. In selected cases routine EEG or video EEG monitoring should be performed to rule out ictal or interictal discharges which may be suggestive of epilepsy as an underlying cause of the symptoms. Cerebrospinal fluid must be obtained in patients where CNS infection is suspected such as transplant recipients or patients receiving chemotherapeutic agents or immunosuppressive drugs. The testing for human immunodeficiency virus (HIV) and CD4 count should be done on a case to case basis. Some patients with moyamoya disease and carotid artery stenosis may have normal brain imaging, so CT angiogram or MR angiogram is an appropriate test in this setting. Autoimmune or paraneoplastic causes must be considered in the differential and should be tested for based on the clinical description and index of suspicion.

Treatment

In addition to the symptomatic management of PxD, the treatment of acquired paroxysmal dyskinesia should be directed at the underlying cause. Symptomatic treatment often with anticonvulsants should be tried [8]. In demyelinating disease, phenytoin, carbamazepine, acetazolamide, clonazepam, and gabapentin are effective treatment options, but the mainstay of treatment remains immunomodulatory therapy to control the underlying disease process and progression [78]. In structural CNS lesions, symptomatic treatment with baclofen, clonazepam, tetrabenazine, botulinum toxin, levodopa, phenytoin, and phenobarbitone has shown some benefit. In a review by Blakeley and Jankovic, two patients improved with a combination of tetrabenazine and trihexyphenidyl [8]. In metabolic disorders such as hypoglycemia or hypocalcemia, correction of the underlying metabolic abnormality usually leads to excellent results [46, 48, 81, 115, 143]. Surgical revascularization has been the mainstay of treatment for paroxysmal dyskinesia related to carotid stenosis [23]. Some cases of paroxysmal dyskinesia secondary to moyamoya disease may undergo spontaneous resolution; otherwise encephaloduroarteriosynangiosis is the recommended treatment option [71, 92]. In cases of autoimmune or paraneoplastic etiology such as faciobrachial dystonic episodes, benefit is seen with immunotherapy rather than antiepileptic treatment [126, 127].

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Chapter 7
Pathophysiology of Paroxysmal Dyskinesia

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Abbreviations

GLUT1	Glucose transporter type 1
HAGH	Hydroxyacylglutathione hydrolase
KCNMA1	Ca^{2+}-activated K^+ channel subunit α
KO	Knockout
NT	Neurotransmitter
PED	Paroxysmal exercise-induced dyskinesia
PKD	Paroxysmal kinesigenic dyskinesia
PNKD	Paroxysmal non-kinesigenic dyskinesia gene
PNKD	Paroxysmal non-kinesigenic dyskinesia
PRRT2	Proline-rich transmembrane protein 2
PxD	Paroxysmal dyskinesia
SCN8A	Voltage-gated Na^+ channel type 8
SLC2A1	Solute carrier family 2 member 1 gene

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_7

Introduction

Paroxysmal dyskinesia (PxD) represents a heterogeneous group of rare neurological disorders characterized by sudden attacks of involuntary hyperkinetic movements including dystonia, chorea, athetosis, and ballism, isolated or in combination. Disorders can be either inherited or acquired and can also be linked to secondary causes [1]. Setting the secondary forms aside, these disorders display common physiopathological features, being characterized by overlapping genetic causes and a general status of neuronal hyperexcitability [2].

In 1995, Demirkiran and Jankovic proposed a PxD classification based on precipitant factors, duration, and etiology. This classification differentiated PxD in four categories: paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD), paroxysmal exercise-induced dyskinesia (PED), and paroxysmal hypnogenic dyskinesia, which is now considered a form of epilepsy (autosomal dominant nocturnal frontal lobe epilepsy), thus reducing the classification to three main forms of PxD (cfr. Chap. 1) [3].

In PKD, paroxysms are characterized by short duration, lasting from few seconds to few minutes, and are triggered by sudden voluntary movements (such as acceleration or change in movement direction) or startle. In PNKD, differently from PKD, the paroxysms are characterized by longer duration, lasting few minutes to hours, and are precipitated by caffeine, tea, alcohol, sleep deprivation, and stress. Finally, PED is calssically provoked by sustained exercise. All these forms of PxD can be classified as idiopathic (familial or sporadic), genetic or secondary to other neurological disorders/lesions [4] (Fig. 7.1).

Originally, idiopathic PxD-related disorders were generally thought to belong to "channelopathies" [5]. This hypothesis was corroborated by the discovery that mutations in genes encoding for ion channels are associated with PxD, epilepsy, or other episodic neurological disorders [5–7]. Indeed, PxD and epileptic seizures cooccur in the recently described mutations in Ca^{2+}-activated K^+ channel subunit α (*KCNMA1*) and in voltage-gated Na^+ channel type 8 (*SCN8A*) genes [8, 9]. In line with these associations, pharmacological studies showed the sensitivity of some subtypes of PxD to anticonvulsant drugs that, at low doses, are able to modulate the conductance of ion channels [5, 10].

In the last years, the advent of next-generation sequencing allowed the identification of several mutations in genes distinct from ion channels, opening a different interpretation of the possible physiopathological mechanisms causing these pathologies [11]. Interestingly, the epileptic phenotype is also present in many PxD patients with mutations in genes distinct from ion channels.

In this chapter, we discuss the main genes implicated in the various forms of PxD, in particular, proline-rich transmembrane protein 2 gene (*PRRT2*) for PKD, paroxysmal non-kinesigenic dyskinesia gene (*PNKD*) also called myofibrillogenesis regulator 1 (*MR-1*) for PNKD, and solute carrier family 2 member 1 gene (*SLC2A1*) encoding for the glucose transporter type 1 (GLUT1) for PED [12–16]. However, not all patients with PKD, PNKD, or PED have mutations in these genes,

Fig. 7.1 Venn diagrams of the three major PxD diseases with the main associated disorders and triggers (left) and of the genes mutated in these pathologies (right) with main pathophysiological mechanisms and current therapies

suggesting that other genes may be implicated in these pathologies. In addition, it is important to note that, in genetic cases, a direct correlation between genotype and clinical phenotype is not present. Indeed, the same mutation in the mentioned genes can generate different clinical phenotypes in various patients, ranging from diverse forms of motor disorders to epilepsy, defining in each patient a specific spectrum of neurological disorders. The presence of this marked pleiotropy suggests the implication of other factors in the modulation of clinical phenotype of PxD, such as modifier genes or the broad spectrum of interacting proteins. Overall, the general episodic nature of several PxD-related events suggests that they result from neuronal network alterations and/or hyperexcitability [17].

PRRT2

Mutations in *PRRT2* gene cause a spectrum of pathologies composed of PKD, benign infantile epilepsy, or a combination of both diseases called infantile convulsions with choreoathetosis that may associate with hemiplegic migraine (cfr. Chap. 3).

About 95% of the more than 70 different *PRRT2* mutations reported to date are nonsense or frameshift with variable penetrance. The majority of patients (80%) carry the same mutation (c.649dupC; p.Arg217Profs*8) that leads to a premature stop codon, generating a truncated protein, which is degraded. Therefore, most of the *PRRT2* mutations are predicted to be loss of function leading to haploinsufficiency [18].

PRRT2 encodes for a protein expressed in the neuronal membrane and enriched at synaptic level in various regions of the central nervous system such as the cerebellum, hippocampus, striatum, and cerebral cortex [19]. It was originally identified in a proteomic screening as a potential interactor for the presynaptic synaptosomal-associated protein 25 kDa (SNAP-25) [20].

The analysis of its exact topology revealed that PRRT2 is a single-pass type 2 membrane protein with a large N-terminal domain on the cytoplasmic side of the membrane and two sequential C-terminal membrane-associated domains very conserved in evolution. The more C-terminal domain spans the membrane completely and functions as an anchor, in analogy to the type II SNARE proteins VAMP/synaptobrevin and syntaxin-1 [21].

The intracellular location of the N-terminal domain suggests possible interactions with intracellular proteins at the synapse. Indeed, it was demonstrated that PRRT2 interacts with the other SNARE complex proteins such VAMP/synaptobrevin and Syntaxin1 in addition to SNAP-25 and with the calcium sensors synaptotagmins 1 and 2, suggesting a function of PRRT2 in the calcium-dependent neurotransmitter (NT) release machinery [22, 23]. In addition, proteomic analysis of the AMPA receptor subunit GRIA1 revealed PRRT2 as a potential interactor, suggesting also a possible postsynaptic function [24].

Interestingly, PRRT2 is expressed in both glutamatergic and GABAergic neurons, although it appears more reliably targeted to glutamatergic synapses. The protein was demonstrated to have a central role in synapse formation and maintenance, as

well as in the regulation of excitatory and inhibitory transmission. Indeed, acute silencing of PRRT2 in developing primary neurons or its constitutive inactivation in PRRT2 knockout (KO) mice decreases the density of excitatory synaptic connections and impairs glutamate release due to a sharp drop in release probability and calcium sensitivity [22, 25] (Fig. 7.2, left). The decreased glutamate release in response to single stimuli leads, in PRRT2 KO neurons, to a markedly strengthened facilitation during high-frequency activity, consistent with a decreased calcium sensitivity of release [22, 26]. On the other hand, the response of the inhibitory transmission in PRRT2 KO neurons is quite different. Indeed, while the spontaneous release is unaffected, the inhibitory strength evoked by single stimuli is increased due to a parallel rising of the release probability. This effect may reflect adaptive plasticity of the GABAergic synapses to the lack of PRRT2 and is associated with an increased depression during high-frequency activity [27]. The effects of PPRT2 deletion on short-term plasticity (increased facilitation of excitatory transmission and increased depression of inhibitory transmission) support the idea that an excitation/inhibition imbalance occurs in the short-term plasticity domain, generating a state of activity-dependent hyperexcitability observed in neuronal networks lacking PRRT2 [28, 29].

An additional mechanism leading to hyperexcitability in the absence of PRRT2 consists in the selective increase of surface expression of voltage-gated Na^+ channels in glutamatergic neurons. Indeed, PRRT2 is an important negative modulator of Nav1.2 and Nav1.6 channels, which show a strong expression in the axonal initial segment of glutamatergic neurons, but not of Nav1.1 channels that are more strongly expressed in GABAergic interneurons [30, 31]. In fact, when PRRT2 is expressed in cell lines stably expressing different Na_V subtypes, it interacts specifically with Nav1.2 and Nav1.6 subtypes leading to a lower surface expression of these channels and, in turn, decreasing Na^+ currents. Moreover, experimental recordings have shown that, in the presence of PRRT2, Nav1.2 and Nav1.6, but not Nav1.1, were

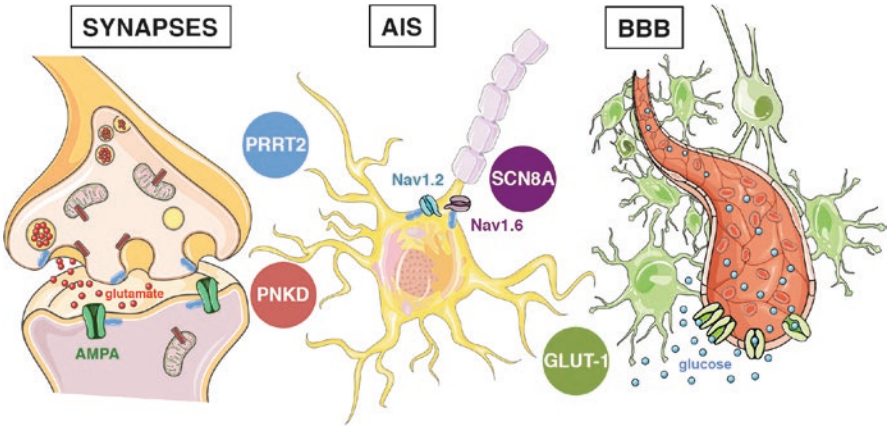

Fig. 7.2 Schematics of the three main pathomechanisms associated with PxD. Synaptic dysfunction is caused by both PNKD and PRRT2 mutations (left), Na+ channel trafficking and activity impairments at the axon initial segment (AIS) are due to mutations in PRRT2 or SCN8A (middle), and glucose transport failure across the blood-brain barrier (BBB) is due to GLUT1 mutation (right)

characterized by a slower recovery from inactivation. More importantly, increased Na^+ conductance and hyperexcitability were also observed in human neurons obtained by fibroblast-derived induced pluripotent stem cells from heterozygous and homozygous patients bearing the most common disease-causing mutation in PRRT2 [29].

Given the predominant paroxysmal character of PRRT2-linked diseases and the observation that Na^+ channel blockers (i.e., carbamazepine) are very effective in PKD, the network hyperexcitability by the lack of the PRRT2-mediated negative modulation of Na^+ channels appears a reliable pathogenetic mechanism of PRRT2-linked diseases (Fig. 7.2, middle).

PRRT2 Mice

To model the disorders and investigate the underlying neurobiological alterations, a PRRT2 KO mouse was recently characterized, and the PRRT2 regional expression was also mapped [32]. At the behavioral level, the PRRT2 KO mouse recapitulates many of the phenotypic features of the human PRRT2-linked disorders, showing abnormal motor behaviors and abnormal motor/epileptic-like responses to environmental stimuli (Fig. 7.3). The motor phenotype appears early in the postnatal life and persists in the adult mice. PRRT2 KO animals display gait abnormalities and a

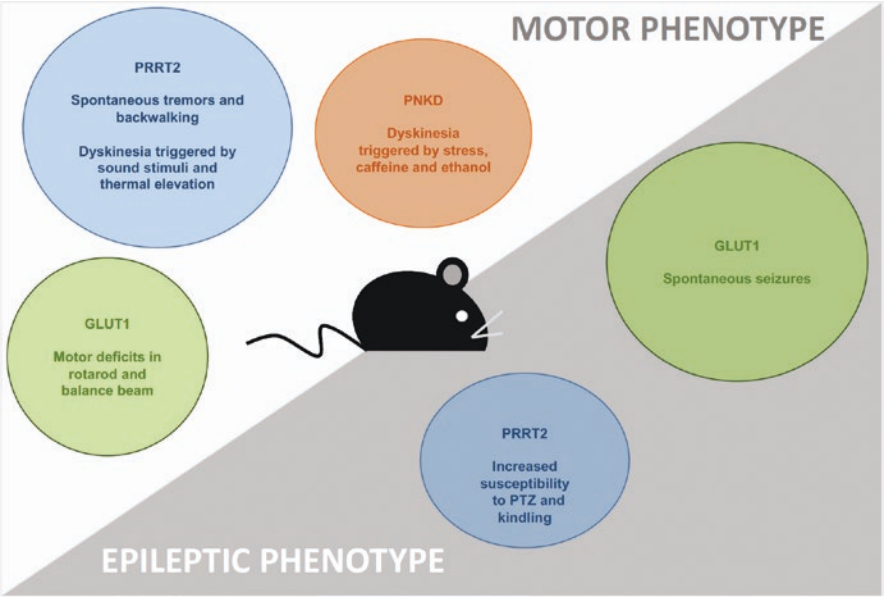

Fig. 7.3 Summary of the motor and epileptic phenotypes recapitulated by animal models of PxD. As in humans, the dual phenotype is observed in PRRT2 and GLUT1 mice, while the PNKD mouse displays only motor dyskinesia in response to various triggers

peculiar paroxysmal back walking, a phenotype that becomes dramatic in response to the administration of convulsants, such as pentylenetetrazole, or after audiogenic stimulation, which trigger wild running, back walking, and jumping. In both kinds of provocations, however, the seizure propensity is not severe, consistent with the mild epileptic phenotype of patients bearing PRRT2 mutations [19, 33]. The authors also showed that PRRT2 mRNA expression was not widespread but rather concentrated at restricted brain areas, such as the cerebral cortex, hippocampus, claustrum, and dorsal horns of the spinal cord, all brain regions involved in processing sensory information and elaborating motor responses. However, the most intense staining is present in the cerebellum, a brain area involved in the generation of motor phenotypes and in which altered synaptic plasticity at the parallel fibers-Purkinje cells synapse has been found [32].

To investigate in depth the role of the cerebellum in the pathogenesis of PxD, Tan et al. generated a PRRT2 mutant with a nonsense mutation (PRRT2-Stop) and various PRRT2 conditional KO animals [34]. Interestingly, they observed spontaneous dyskinesia attacks in some PRRT2-Stop mice under natural conditions but also attacks induced by hyperthermia, kindling, or pentylenetetrazole induction, confirming a susceptibility of these animals to specific triggers. Interestingly, specific deletion of PRRT2 in cerebellar granule cells is sufficient to induce the dyskinetic phenotype in mice, while the ablation of PRRT2 in the forebrain is apparently ineffective.

Overall, the constitutive and conditional PRRT2 KO mouse lines generated in different laboratories reproduce the paroxysmal traits described in PRRT2 patients and suggest the cerebellum as a key region for the pathogenesis of the PRRT2-related dyskinesia.

PNKD

Patients with mutations in the *PNKD* gene experience paroxysmal attacks characterized by dystonic and choreic features that are often generalized [10, 35]. Attacks are precipitated by fatigue, stress, hunger, and consumption of coffee or alcohol, and patients are completely normal between attacks (cfr. Chap. 4).

The *PNKD* gene has three splicing forms *PNKD-L*, *PNKD-M*, and *PNKD-S*. *PNKD-L* encodes for a protein of 385 amino acids specifically expressed in the central nervous system, whereas the other two forms of 361 and 142 amino acids, respectively, are ubiquitously expressed. PNKD-L isoform is a neuron-specific and membrane-associated protein also expressed at synapses.

PNKD mutations show nearly complete penetrance, and most patients carry the missense mutations Ala6>Val or Ala9>Val, while only in one family a third mutation was identified (Ala33>Pro).

PNKD shares high homology (≈40%) with the gene codifying the enzyme hydroxyacylglutathione hydrolase (HAGH; [13]). As HAGH is involved in the detoxification of methylglyoxal, a by-product of oxidative stress present in coffee

and alcoholic beverages, it was suggested a mechanism whereby alcohol, coffee, and stress act as precipitants of attacks in PKND-linked paroxysmal disorders [13]. However, experiments conducted on cultured cells from transgenic animals showed that PNKD protein did not restore the altered levels of HAGH in vivo, suggesting that PNKD may play different roles [36].

More recently, Shen et al. demonstrated a localization of PNKD at presynaptic boutons, where it interacts with the C-terminal domain of RIM1/2, a protein involved in the calcium-dependent NT release and in the modulation of various forms of neuronal plasticity [37, 38]. Interestingly, if PNKD carries both mutations found in patients (Ala6>Val and Ala9>Val), the binding becomes much weaker, suggesting that the lack of interaction between PNKD and RIM at synapses is crucial for the development of the disease. At the synaptic level, PNKD may stabilize RIM1/2; indeed, the decreased localization of RIM1/2 at synaptic terminals observed in PNKD KO mice affects both excitatory synaptic strength and short-term plasticity properties [37].

In primary neuronal cultures, an overexpression of PNKD inhibits synaptic vesicle release, suggesting the possibility of a gain-of-function mechanism for PNKD mutations (Fig. 7.2, left).

PNKD Mice

Other hints about PNKD function came from the study of PNKD mutant animal models. In 2012, Lee et al. showed that, while the null mouse has no phenotype, the transgenic knock-in PNKD mouse model carrying both human mutations (Ala6>Val and Ala9>Val, mut-Tg animals) recapitulates the human phenotype, confirming a gain-of-function mechanism [39]. Mut-Tg mice display dyskinesia after handling or caffeine/ethanol injections. Dyskinetic attacks approximately start 10–15 min after treatment and persist for 2–4 h. Interestingly, basal ganglia neurons are specifically activated in mut-Tg mice after induction of attacks, as observed by the increase in c-Fos immunoreactivity in the globus pallidus, subthalamic nucleus, and substantia nigra reticulata after caffeine or ethanol injections. The authors also suggest the pathogenetic role of a dysregulation of adenosine-dopamine signaling in PNKD. In support of this theory, neuropharmacological experiments showed that the dyskinetic phenotype observed in mut-Tg mice in response to stress, caffeine, and ethanol can be reproduced in these animals after injection of the selective Adenosine A_{2A} or Dopamine D_2 receptor agonists, two receptors that colocalize in the medium spiny neurons of the indirect pathway of the striatum. In support of a crucial role of the dopamine system in the pathology, reduced extracellular dopamine levels in the striatum and a proportional increase of dopamine release in response to caffeine and ethanol treatments were observed in mut-Tg mice [39]. Overall, transgenic mice carrying mutations equivalent to those found in patients with PNKD recapitulate the human phenotype (Fig. 7.3), and alterations in dopamine signaling seem to play a key role in the generations of behavioral phenotype. However, further studies are

needed to better understand the synaptic role of PNKD under physiological conditions and the contribution of PNKD mutations to pathophysiology.

GLUT1

Mutations in *SLC2A1* gene, encoding for the glucose transporter GLUT1, are the main cause of PED but can also manifest as PNKD and episodic ataxia (cfr. Chap. 5) [2, 40]. GLUT1 is a key glucose transporter across the blood-brain barrier [14]. Consequently, its deficiency caused by mutations in the *SLC2A1* gene produces hypoglycorrhachia, a key diagnostic feature of the phenotypic spectrum. Hence, the PED phenotype is caused by the reduced glucose availability occurring when the energy demand of the brain overcomes the glucose supply throughout the blood-brain barrier, such as after prolonged period of exercise (Fig. 7.2, right). De novo heterozygous mutations have been reported for the majority of patients, although in familial cases, an autosomal dominant inheritance pattern has also been reported [41]. A fine correlation between genotype and phenotype is missing to date. Indeed, the milder versions are often associated with missense mutations resulting in a reduction of 50–70% of GLUT1 function, while severe forms are associated with mutations that induce a reduction of GLUT1 of about 50% [42, 43]. In this context, the phenotypic spectrum of the disease has markedly expanded over the last years ranging from mild forms (isolated PED, migraine, seizures) to severe forms with delayed development, acquired microcephaly, spasticity, and refractory seizures [44, 45]. Ketogenic diet, inducing a change from glucose to ketone body metabolism, was used as first therapeutic choice, although it has little effect on the severe forms [40, 46, 47].

Glut1 Mice

In the context of PED, a mouse model for GLUT-1 haploinsufficiency was first described in 2006 by Wang et al. [48]. Homozygous GLUT-1 mice (GLUT-$1^{-/-}$) show embryonic lethality, while heterozygous GLUT-1 mice (GLUT-$1^{+/-}$) display impaired motor performance and spontaneous seizures, recapitulating the human phenotype (Fig. 7.3). A consistent reduction in the motor performance of the GLUT-$1^{+/-}$ mice was detected by the rotarod and beam walking tests starting at 4 weeks of age and worsening thereafter. Motor deficits in GLUT-$1^{+/-}$ mice were also confirmed by Nakamura et al. [49], who showed the positive effects of gene therapy in these animals [49]. Consistent with the observation that epileptic features often appear in PED, Wang et al. identified, by electroencephalographic analysis, several patterns of electrographic seizures in GLUT-$1^{+/-}$ mice, including generalized or partial seizures, bilateral generalized slow spike and wave pattern without behavioral abnormalities, and frequent brief bilateral rhythmic spike discharges

accompanied by periods of behavioral arrest in the fasting state. However, no generalized tonic–clonic seizures are observed [48]. In line with the normal magnetic resonance imaging findings in GLUT-1 patients [50], no alterations in brain structure are present, despite the smaller brain size measured in GLUT-$1^{+/-}$ mice. A decreased glucose uptake was found in the brain of GLUT-$1^{+/-}$ mice, and these findings are in line with the data collected in GLUT-1 patients by positron emission tomography scan [51]. Overall, the GLUT-$1^{+/-}$ mouse represents a model for the study of pathophysiology of GLUT-1 deficiency syndrome and an opportunity to evaluate new treatment strategies.

Other "Dyskinetic" Genes

SCN8A

The *SCN8A* gene encodes the α-subunit of voltage-gated Na^+ channel $Na_V1.6$ that is clustered at axon initial segment and is responsible for initiation and propagation of the axon potential [31]. Several mutations were identified in *SCN8A*, leading to both loss of function associated with impaired cognition or gain-of-function phenotype associated with epileptic encephalopathy [52, 53].

At the preclinical level, a knock-in mouse carrying the human mutation associated with epileptic encephalopathy was behaviorally characterized [54]. These animals display both epileptic and motor phenotypes starting at 3 weeks of age. Interestingly, the disease severity is directly correlated with dosage of the mutant *SCN8A* allele, and the presence of the wild-type allele partially attenuates the phenotype.

Recently, a heterozygous missense mutation in *SCN8A* has been found in three families with PKD associated with benign infantile epilepsy, negative for PRRT2 mutations [9]. Interestingly, the mutation (c.4447G>A) hits the inactivation gate of the $Na_V1.6$ α-subunit, suggesting an impaired channel inactivation. The clinical phenotype of these patients is arguably similar to patient carrying PRRT2 mutations. The selective interaction of PRRT2 with this Na^+ channel subtype that modulates its surface expression and activity [29] explains why mutations in these genes cause similar phenotypes that respond well to Na^+ channel blockers.

KCNMA1

The *KCNMA1* gene encodes the α-subunit of the large conductance, voltage- and Ca^{2+}-sensitive K^+ channel which plays an important role in neuronal excitability. The activation of the KCNMA1 channel promotes a more rapid repolarization and faster recovery of Na^+ channels from inactivation leading to higher firing frequency [55]. Heterozygous mutations in *KCNMA1* were first described in a large family

with generalized epilepsy and PNKD, with alcohol as possible trigger [8]. The presence of epilepsy differentiates the clinical phenotype of these patients from patients with classical PNKD. The mutation carried by these patients hits the domain of the channel that couples calcium binding to channel opening and leads to an increase in the calcium sensitivity and opening probability. These functional changes lead to a gain of function of KCNMA1 activity generating hyperexcitability [55]. More recently, different *KCNMA1* mutations have been described in patients with PNKD without epilepsy, confirming the implication of this gene in PxD and the complexity of the underlying pathomechanisms [56].

Conclusions

PRRT2, *PNKD*, and *SLC2A1* represent the main genes involved in the development of PKD, PNKD, and PED. The elucidation of the genetic causes of various PxD forms has led to better clinical definitions of genotype–phenotype correlations in the familial forms, despite the presence of a marked pleiotropy.

Notwithstanding the specific genetic and phenotypic traits identified in different PxD subtypes, this rubric of movement disorders shares typical common traits, i.e., the paroxysmal nature and the presence of triggering factors. Moreover, there is a phenotypic overlap among PxD with episodic ataxia, dystonia, and familial hemiplegic migraine. Common features and comorbidities suggest common pathophysiological mechanisms underlying PxD. As proposed by Erro et al., although PxD can be considered channelopathies, synaptopathies, or transportopathies, the final target is always represented by an alteration of neuronal excitability [11].

It is important to note that the hyperexcitability caused by these genetic alterations produces not only motor attacks but also epilepsy in PRRT2 and GLUT1 patients and animal models (Fig. 7.3). Interestingly, epilepsy and PxD share common traits, including their episodic nature, triggering factors, and therapeutic response to antiepileptic drugs. However, it is still unknown how the same mutation in a specific gene can cause both epilepsy and movement disorders. To date, the only strong evidence is that the motor and epileptic phenotypes represent two sides of the same coin. Future studies should address this issue by exploring the putative role of modifier genes, interacting proteins, and environmental factors on the phenotypic variability.

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Chapter 8
Neurophysiology of Paroxysmal Dyskinesia

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Abbreviations

CNV	Contingent negative variation
EEG	Electroencephalography
EMG	Electromyography
LICI	Long intracortical inhibition
MEG	Magnetoencephalography
MEP	Motor evoked potentials
PED	Paroxysmal exertion/exercise-induced dyskinesia
PHD	Paroxysmal hypnogenic dyskinesia
PKD	Paroxysmal kinesigenic dyskinesia
PNKD	Paroxysmal non-kinesigenic dyskinesia
PxD	Paroxysmal dyskinesia
SICI	Short intracortical inhibition
SNW	Slow negative wave
TMS	Transcranial Magnetic Stimulation
β-ERS	Beta event-related synchronization

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_8

Introduction

The aim of this chapter is to describe the various neurophysiological tests available to achieve a better diagnosis and pathophysiological investigation of paroxysmal dyskinesia (PxD). The correct choice of neurophysiological studies that can help with the diagnosis of PxD mainly depends on their clinical presentation [1]. The observed movement disorder can vary from dystonia to chorea or ballism, and the attacks might be induced by a variety of different triggers (cfr. Chap. 1). Thus, depending on the clinical presentation of PxD, a specific neurophysiological test might be better able to assist in its diagnosis [1].

This chapter will focus on the various neurophysiological tests and interpretation of their results for assisting the clinical diagnosis of PxD. It will further examine other neurophysiological techniques that have been used in research for a better understanding of their pathophysiological mechanisms.

Neurophysiology in the Diagnosis of Paroxysmal Dyskinesia

Various simple and accessible neurophysiological tests can be used to assist the diagnosis of PxD. These tests are primarily useful to confirm the clinical suspicion of PxD, excluding a wide range of neurological diseases that might induce episodic neurological dysfunction resembling PxD. They might be further helpful to rule out symptomatic causes of PxD [2]. The choice of which neurophysiological test should be performed first will depend in the individual cases on the clinical features of PxD as well as on associated (i.e., interictal) neurological findings or available instrumental results, for instance, imaging.

Electroencephalography

The results of EEG studies, including sleep EEG, are typically normal in patients with paroxysmal kinesigenic dyskinesia (PKD) [3, 4]. No ictal or interictal changes have been observed in EEG studies in general except for a few reported cases [5, 6]. In one report, transient epileptic discharges were found in 66.7% of the studied patients during the clinical course, and centro-midtemporal and frontal spikes were the abnormalities most often observed [5]. In one isolated patient, the ictal EEG of an afebrile convulsion showed a partial seizure with secondary generalization that originated from the frontal area [6]. It should be noted, however, that most of these evidences stem from research prior to the discovery of *PRRT2* mutations as the leading cause of PKD. *PRRT2* mutations can cause a broad spectrum of episodic neurologic disorders including seizures and the combination of epilepsy and PKD (cfr. Chap. 3), and, as such, it is difficult to ascertain whether the observed EEG

abnormalities in the aforementioned studies reflected the coexistence of epilepsy. It is currently construed that PKD attacks are not epileptic in nature, and EEG is unrevealing during such attacks.

EEG studies of paroxysmal non-kinesigenic dyskinesia (PNKD) are also generally normal both during the attacks and interictally [4]. However, an invasive video EEG study demonstrated ictal discharges originating in the caudate nuclei in a young patient with PNKD [7], which brought to the concept of PxD as "subcortical seizures." An argumentation of the latter point is beyond the aims of this chapter, and it should be remarked that EEG is uninformative in PNKD due to mutations in *PNKD* (formerly known as *MR-1*, i.e., the main gene for PNKD, cfr. Chap. 4). Conversely, the clinical syndrome of PNKD can be associated with epilepsy in *KNCMA1* carriers [2]. This implies that, in a patient with PNKD and with or without documented history of epilepsy, EEG abnormalities make the presence of *PNKD* mutations very unlikely, and clinicians should think of other conditions, including *KNCMA1* mutations.

As in most cases of PKD and PNKD, EEG fails to demonstrate ictal or interictal abnormalities in paroxysmal exercise-induced dyskinesia (PED) [4], unless concomitant epilepsy is present. The major gene accounting for PED is *SLC2A1* (cfr. Chap. 5), which encodes for the glucose transporter type 1 (GLUT1). In the case of severe mutations, the clinical phenotype can be complex and encompass epilepsy beyond PED. In such cases, EEG might show generalized spikes or spike wave, generalized slowing, and polyspikes [8]. Interestingly, PED attacks might be misdiagnosed as epileptic myoclonic seizures [9], which emphasizes the importance of EEG studies in PED and PxD in general.

More interesting findings are observed in patients with paroxysmal hypnogenic dyskinesia (PHD), where awake interictal discharges have been observed in some cases, where the use of zygomatic and sphenoidal electrodes has detected a mesial frontal lobe origin of attacks in some patients [10], suggesting that PHD could indeed represent a form of nocturnal frontal lobe epilepsy [3, 11].

In summary, EEG is a neurophysiological test that might be primarily used in the PxD diagnostic process. Although the results might be negative in most cases with isolated PxD, EEG studies, including extended registrations such as polysomnography, can be useful for the differential diagnosis of certain entities that need to be considered, such as juvenile myoclonic epilepsy, REM sleep behavior disorder, other parasomnias, and periodic limb movement syndrome [1, 3, 4].

Electromyography

As with EEG, EMG studies are generally uninformative in all forms of PxD and are of little utility in the differentiation among PxD subtypes. In most cases the neurological examination will be unrevealing and the suspicion based on the patients' description of the attacks [12]. As such, a number of conditions that can produce disordered movements resembling PxD, including tonic spasms, tetany,

neuromyotonia, periodic paralyses, startle syndromes, and episodic ataxias, should be considered, and obviously, in such cases, EMG findings will be very informative. One example would be interictal EMG findings of subtle myokymia in the face and hands, which is an important clue redirecting the clinical diagnosis toward that of episodic ataxia type 1 (cfr. Chap. 11) [1].

Depending on the clinical context, more advanced EMG studies, such as polymyographic or EEG-EMG recordings, might be required and will be discussed below.

Other Clinical Neurophysiology Studies

We have thus far described basic and isolated neurophysiological tests that may assist in the diagnostic workout of PxD. However, more complex neurophysiological studies might be needed in some cases. These include the concomitant EEG and EMG recording to explore the presence of the premotor potential (Bereitschaftspotential, BP) or to perform startle reaction studies [13–16]. Premotor potential studies are mainly used for the diagnosis of functional jerks or movement disorders that can resemble PxD. By triggering the EMG activity of affected muscles, the EEG activity before the onset of movement is averaged offline and might show the presence of the BP, which is suggestive of the functional nature of the attacks. A startle reaction study is aimed at the neurophysiological diagnosis of hyperekplexia or startle epilepsy [17]. Multi-EMG activity from various facial, neck, and upper/lower limb muscles is recorded after a sudden stimulus (auditory or electrical). Latency of evoked EMG responses, spread patterns, and attenuation at 5–10 stimuli are then analyzed. A patient with hyperekplexia will have sudden cramping movements induced by the startle, with short-lasting, generalized stiffening without loss of consciousness; in the case of startle epilepsy, an asymmetrical tonic epileptic seizure of brief duration is induced by a startle [17]. Conversely, startle response in patients with PxD will be normal [18].

Neurophysiology in the Pathophysiological Study of Paroxysmal Dyskinesia

Early studies using neurophysiological techniques in PxD focused on contingent negative variation (CNV). Franssen et al. observed that the slow negative wave (SNW) of the CNV repeatedly showed a remarkable enhancement in a patient with PKD. First described in 1964, CNV is a slow negative cortical wave appearing at the Cz position of the scalp within two consecutive stimuli (preparatory stimulus/S1 and imperative stimulus/S2), delivered at a fixed interval. Preparatory stimulus/S1 produces an alert state in the individual before the imperative stimulus/S2. After this second stimulus, the subject must perform a motor response in a reaction time paradigm. When recording cortical activity in the time lapse between S1 and S2, an

SNW is observed representing a readiness for the motor response [19]. The aforementioned result thus suggested possible enhanced cortical excitability (or reduced inhibitory mechanisms) in patients with PKD occurring before voluntary motor responses [20].

More recent evidence stems from newer neurophysiologic techniques such as magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS). Both techniques can evidence functional abnormalities in the cerebral cortex. MEG consists of the analysis of cortical event-related potentials induced by peripheral stimulation (preferably of the upper limbs). In the case of TMS, different paradigms can be applied to explore the excitability and inhibition mechanisms of different brain areas and of cortical-subcortical loops.

Magnetoencephalography

Various MEG studies have identified an aberrant gamma synchronization in the somatosensory cortex of patients with PxD. This abnormal gamma synchronization or altered inhibitory modulation in primary and secondary somatosensory cortices has mostly been studied in patients with PKD, probably because the clinical manifestations better fit with the framework of event/movement-related potentials and oscillatory activity change as recorded in MEG studies. Aberrant gamma synchronization in particular represents the attenuation of automatic cortical inhibition in sensory gating and might be a neurophysiological feature of PKD [21]. These results implicate abnormal sensory processing in patients with PKD, thus highlighting a key role for the primary somatosensory cortex in the pathogenesis of PKD [22]. Cortical inhibition mechanisms involved in sensory gating are closely related to GABAergic neurotransmission, which might be therefore implicated in PKD [23, 24]. Similarly, inhibitory motor pathway abnormalities have been implicated in PKD, arguably pointing at an involvement of the GABAergic system. Thus, reduced power and prolonged peak latency of post-movement beta event-related synchronization (β-ERS) were observed in patients with PKD, representing reduced inhibition of the motor cortex. This β-ERS is less extended in the contralateral hemisphere, indicating that post-movement inhibition is less affected in the contralateral hemisphere than in the ipsilateral one [25].

Transcranial Magnetic Stimulation

TMS studies have been conducted to observe cortical excitability of the stimulated area, cortical connectivity between various brain areas, and, in an indirect manner, the functionality of cortical-subcortical loops. Overall, TMS stimulation protocols produce reproducible motor peripheral responses that are specifically related to the activation of facilitatory or inhibitory synaptic activity mediated by various neurotransmitters.

One of the first studies using TMS in patients with PxD was conducted in a family with PED and benign epilepsy in combination with somatosensory evoked potentials and EMG recording [26]. The authors observed spontaneous EMG activity, combined with reduced somatosensory evoked potentials. This amplitude reduction is ascribed by some authors to gating of sensory inflow during active and passive movements [27, 28]. Different TMS abnormalities have been observed with significant facilitation of motor evoked potentials (MEPs), which would be related to reduced cortical inhibition in patients with PED compared with healthy participants. Apart from that hypothesis, an increase in the MEP amplitudes observed in these patients may also be explained by enhancement of spinal excitability (possibly by reduction of spinal GABA-mediated inhibitory mechanisms) related to proprioceptive inputs [29].

One of the most complete TMS studies in patients with PxD was conducted in 2005 on patients with PKD. Abnormalities in short intracortical inhibition (SICI) and early-phase transcallosal inhibition were observed in patients as compared with healthy individuals [18]. These results suggest (as observed in MEG studies) abnormalities in inhibitory mechanisms in patients with PKD, possibly related to GABAergic circuits. Intracortical inhibition and cortical excitability were also measured in a patient with PKD after TMS stimulation of the brachial plexus that induced dystonic attacks resembling those that patient had as part of his clinical situation [30]. In this report, disturbances in the intracortical inhibitory circuits and an enhanced excitability of motor area were observed immediately after the paroxysms, suggesting an abnormally common corticospinal drive to the motor neuron pools of antagonistic muscles. Similar conclusions had been reached in another TMS study, which evidenced long intracortical inhibition (LICI) abnormalities, which are also GABA-mediated mechanism [31].

More evidence suggesting aberrant central inhibitory circuits in patients with PxD have been obtained exploring the so-called surround inhibition. This phenomenon was studied in a group of patients with PKD revealing a clear disturbance/absence of the normal post-movement excitation of the surrounding muscles [32]. This observation was explained as a possible early termination of post-movement cortical and spinal activation or even as an increase of surround inhibition that suppresses post-movement activation. Although surround inhibition as a whole does not seem to be primarily disturbed in PKD, it appears that part of it (i.e., post-movement activation/enhancement) is altered in patients with PKD, probably acting as a compensatory mechanism for abnormal supraspinal inputs (including SICI, LICI, and transcallosal inhibition [18, 31, 33]) to the inhibitory spinal interneurons.

Other Research Neurophysiology Studies

Another inhibitory circuit possibly altered in patients with PxD is the reciprocal inhibition phenomenon produced by Ia interneurons of a reflex peripheral circuit at the spinal level. The reciprocal inhibition phenomenon is produced by electrical

nerve stimulation of agonist-antagonist muscles by paired-pulse protocol at various interstimuli intervals. In healthy individuals, at specific interstimuli intervals, there is a reduction in H reflex size (measured in the upper or lower limbs). This reduction in H reflex size can be observed in three different phases at short (around 0 ms), middle (20–30 ms), and long (100 ms) interstimuli intervals [34]. These observations are related to inhibitory spinal circuits originated in Ia interneurons and mediated by glycine or even GABA neurotransmitters at the spinal level [35].

Early and late phases of reciprocal inhibition from stimulation of the upper limbs in patients with PKD have been shown to be altered. Since similar abnormalities can be found in patients with hyperekplexia, which is linked by a well-known glycinergic spinal alteration [33], this would suggest a spinal glycinergic disturbance in patients with PKD. This disturbance in reciprocal inhibition, yet only of its early phase, was confirmed in another study on PKD patients, who further had a decreased level of both SICI and early-phase transcallosal inhibition [18]. These two observations would suggest a possible glycinergic defect associated with an abnormality of the GABAergic system in patients with PKD.

Conclusion

In summary, various neurophysiology techniques can help in clinical and research investigations of various subtypes of PxD. Classical neurophysiology tests, such as EEG, EMG, polysomnography, premotor potential (Bereitschaftspotential), startle reaction, and CNV studies, are useful in the diagnostic process given the high number of entities with clinical characteristics similar to PxD that need to be excluded. Other neurophysiological techniques such as MEG and TMS can be used to further explore the underlying pathomechanisms of PxD, especially after the discovery of the main genetic causes of PxD, as similar clinical phenomenon might be underpinned by different pathophysiological abnormalities.

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Chapter 9
Other Paroxysmal Movement Disorders

Roberto Erro, Kapil D. Sethi, and Kailash P. Bhatia

Introduction

Over the last years, a number of different genetic disorders have been reported to encompass recurrent episodes of dystonia, chorea, and/or myoclonus in their phenotype [1, 2]. Nonetheless, these disorders have escaped the classic definition of paroxysmal dyskinesia (PxD) and are not usually included in their classification (cfr. Chaps. 1, 3, 4, and 5). This probably owes to the fact that in these disorders the paroxysmal episodes of choreodystonia are usually embedded in complex neurological syndromes, which contrasts with the former diagnostic criterion for "*primary*" PxD requiring normal neurological examination between the attacks (cfr. Chap. 1). However, with the discovery of the genetic underpinnings of PxD, it has become clear that patients with the so-called "*primary*" PxD might in fact have interictal findings on examination or other associated features by history (PxD associated with *SCL2A1* mutations, for instance, cfr. Chap. 5). Therefore, additional (interictal) findings on examination should be no longer considered an exclusionary criterion for PxD [1] but should be instead carefully investigated as these might be helpful in guiding subsequent diagnostic workup.

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-53721-0_9) contains supplementary material, which is available to authorized users.

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_9

This also implies that the differential diagnosis in patients presenting with episodic choreodystonia should not only include the disorders associated with the three main form of PxD [i.e., kinesigenic (PKD), non-kinesigenic (PNKD), and exercise-induced (PED)] but also a number of different conditions, which can encompass paroxysmal choreodystonia in their phenotype. Differently from the main three forms of PxD, which are primarily characterized based on the specific triggers of the episodes, the ones covered in this chapter can also be defined by other features including the distribution of choreodystonia during the attacks.

ADCY5 Mutations

Mutations in *ADCY5*, encoding for the adenylate cyclase 5, can cause a spectrum of non-paroxysmal, childhood-onset, movement disorders that might include chorea, dystonia, and myoclonus, or a combination thereof, sometimes associated with axial hypotonia and also PxD [3, 4]. PxD does not always fit clearly within previously identified PxD subtypes. The myoclonus may involve the face, and the attacks can be painful [similar to alternating hemiplegia of childhood (AHC); see below], a point of difference from PxD due to *PRRT2*, *PNKD*, or *GLUT-1* mutations (i.e., the main causes of PKD, PNKD, and PED, respectively) [5, 6] Moreover, *ADCY5*-PxD may manifest within the same patient as multiple subtypes, including both PKD and PNKD [5, 6]. Two unrelated *ADCY5* carriers manifesting with attacks similar to those observed in AHC have been recently reported in the context of a more complex neurological picture including dysarthria, hypotonia, and *non*-paroxysmal choreodystonia [7], reinforcing the concept that episodic movement disorders due to *ADCY5* mutations can be quite variable.

Further at variance with other genetic disorders that can produce PxD, patients with *ADCY5* mutations characteristically develop PxD during sleep [6]. Nighttime dyskinesia (along with the presence of non-paroxysmal movement disorders) would therefore suggest *ADCY5* mutations. However, nighttime PxD (formerly referred as to paroxysmal hypnagogic dyskinesias, a fourth subtype of PxD; cfr. Chaps. 1 and 2) has been also rarely reported in association with *PRRT2* mutations [8], which should be therefore considered in such cases.

Treatment can be disappointing, but a partial benefit has been reported with both tetrabenazine [9] and deep brain stimulation [10].

ATP1A3 Spectrum Disorders

Mutations in the *ATP1A3* gene can cause a number of different clinical syndromes including AHC, rapid-onset dystonia parkinsonism, and cerebellar ataxia with pes cavus and optic neuropathy, although an increasing number of patients with

overlapping phenotypes have been recently described [11, 12]. In the context of this chapter, we will only cover AHC, which is classically a sporadic disorder with onset within the first 18 months, by definition [11, 12]. The misnomer AHC is explained by the first descriptions of this condition that focused on the occurrence of episodic hemiplegia. In fact, attacks of hemidystonia occur at least as commonly as the attacks of hemiplegia, may involve both sides of the body at the same time, and may encompass other paroxysmal neurological signs including nystagmus, anarthria, dysphagia, and seizures [11–13]. Paroxysmal eye movements are very characteristic. Attacks last from a few minutes, rarely, to several days, and episodes occur from repeatedly within a day to several times a month [11–13]. They are almost invariably triggered by emotional stressors, such as excitement, or less frequently by physical stressors, including hypo- or hyperthermia, respiratory tract infections and surgery [11–13]. Characteristically, there is a rostrocaudal gradient in the hemiplegic/hemidystonic episodes (face/neck>arm>leg). Episodes, either hemiplegic or hemidystonic, typically shift from one side of the body to the other and are typically ameliorated by sleep. Almost invariably the attacks are associated with other (interictal) features such as developmental deficits, muscular hypotonia, dysarthria, and ataxia [11–13]. However, "milder" forms with age at onset >18 months, with focal presentation of dystonic attacks (predominantly affecting the arm), and with no other associated signs either during the episodes or interictally (Video 9.1) have been recently reported [14]. Long duration of the episodes (up to days), painful dystonic posturing, and sleep-induced cessation of the attacks are clinical clues to suspect *ATP1A3* mutations.

Treatment consists of flunarizine (10–20 mg/day) as a prophylactic drug along with the avoidance of triggers [11–13]. Patients should be encouraged to sleep when attacks begin, using fast-acting benzodiazepines if necessary.

SCN8A Mutations

Mutations in *SCN8A*, encoding for sodium voltage-gated channel alpha subunit 8, have been recently reported to be an alternative cause of the ICCA syndrome (i.e., infantile convulsions with choreoathetosis, which is mostly associated with *PRRT2* mutations, cfr. Chap. 3) [15]. However, this proposal has been questioned [16] based on the evidence that, in one affected case, a "PKD" attack was recorded by video-electroencephalography and correlated to a cortical event, suggesting that these attacks might in fact be epileptic in nature. Moreover, in this single report where the term PKD was used, attacks were not induced by sudden movements [15]. We therefore feel that the term PKD in the context of *SCN8A* mutations is a misnomer. However, it has to be acknowledged that *SCN8A* mutations have been in other reports associated with episodic dystonia (with no kinesigenic triggers), although the term paroxysmal dyskinesia was not explicitly used [17]. As such, it is worth considering this condition in the differential diagnosis of childhood-onset

PxD, especially of the non-kinesigenic variant and, when associated with epileptic seizures, particularly those resistant to antiepileptic therapy and/or with neurodevelopmental delay [17].

CACNA1A Mutations

Mutations in the *CACNA1A* gene, which encodes for the calcium voltage-gated channel subunit alpha1 A, are associated with a number of phenotypes including SCA6, episodic ataxia type 2 (see Chap. 11), as well as familial hemiplegic migraine. More rarely, *CACNA1A* mutations have been associated with episodes of benign paroxysmal torticollis of the infancy (BPTI) [18, 19]. BPTI is characterized by attacks of head tilt with onset within the first 18 months of life with a tendency to remission with increasing aging [18, 19]. Episode duration ranges from 10 min to several days, and associated features can be vomiting, pallor, and ataxia [18, 19]. As mentioned above, BPTI usually resolves after infancy but can be sometimes replaced by paroxysmal vertigo and/or migraine [18, 19]. The co-occurrence of episodic ataxia, hemiplegic migraine, and paroxysmal tonic upgaze in a single subject or in the family are a clue to suspect *CACNA1A* mutations, even though in many BPTI cases the genetic cause is not found [20]. This condition is generally self-limiting, and usually no treatment is needed.

SLC16A2 Mutations

The monocarboxylate transporter type 8 (MCT8), encoded by *SLC16A2,* is required for transmembrane uptake of free triiodothyronine (fT3) from blood into neurons. MCT8 deficiency causes an X-linked disorder (also termed Allan-Herndon-Dudley syndrome), with onset in infancy and characterized by hypotonia with poor head control, generalized muscular hypotrophy, microcephaly, and marked developmental delay [21]. The disorder is progressive, and a different combination of spasticity, ataxia, and severe dysarthria usually develops and complicates the clinical syndrome. In a subset of cases, a specific sort of PKD is observed [21, 22]. Attacks are classically triggered by sudden passive movements such as changing of clothes or diapers or by lifting the children from one place to another [21, 22]. Attacks can further be triggered by excitement, happiness, or crying, thus falling into the PNKD subtype. Episodes are generally brief, lasting seconds to few minutes, and the main phenomenology is dystonia. The hallmark of MCT8 deficiency is raised serum concentration of fT3 [21]. At present, no treatment is available, and management is symptomatic and supportive.

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Chapter 10
Functional Paroxysmal Movement Disorders

Christos Ganos and Mark J. Edwards

Introduction

The spectrum of paroxysmal movement disorders encompasses conditions characterized by sudden onset hyperkinesias, for example, dystonia or chorea, with variable duration (typically ranging from seconds to minutes) and a range of specific triggers (also see Chaps. 3, 4 and 5). Electroencephalography during episodes of paroxysmally occurring movement disorders is normal. In older literature, paroxysmal movement disorders were classified as *primary*, which could be familial or sporadic and where routine clinical examinations were unrevealing, or secondary (i.e., acquired, see Chap. 6), typically as a result of another condition, most commonly lesions in the basal ganglia or brainstem [1]. More recently, a new classification scheme proposed a dual classification system with axes for clinical characteristics and aetiology [2]. Importantly, the clinical axis of this classification excludes patients with episodic hyperkinetic movements as a result of a functional disorder [2]. However, the diagnostic distinction between cases of paroxysmal movement disorders, for example, due to monogenic conditions, from functional paroxysmal movement disorders can be challenging. Here, we specifically focus on this latter category of cases, in order to provide a list of helpful clinical clues and signs that will aid the diagnostic process and guide the selection of appropriate treatments.

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_10

Phenotypic Characteristics

The clinical characterization of movement disorders is rooted in their phenomenological categorization and distinction. In the case of functional paroxysmal movement disorders, however, the clinical presentation is often variable, and core phenotypic presentations can be discerned only for a subset of cases (also see below) [3]. In other words, in functional movement disorders, any type of motor output – from functional paroxysmal tremor to functional paroxysmal gait disorder – can occur as a sudden, episodic event, and often more than one movement disorder patterns may occur [3]. Out of a sample of 26 well-characterized cases of functional paroxysmal movement disorders, only 8 patients (30.7%) presented with a single type of paroxysmal movement disorders, most commonly with movements resembling dystonia ($n = 4$), followed by paroxysmally occurring tremulous ($n = 2$) or jerky ($n = 2$) movements [3]. In seven cases, a combination of discernible movement disorder patterns (e.g. movements resembling dystonia with tremor) was observed, whereas in the majority of cases ($n = 11$), more complex paroxysmally occurring motor events were noted. In this latter group of patients, the exact phenotypic classification was challenging. Such cases are not rare and demonstrate that patients with functional paroxysmal movement disorders may also be frequently encountered in neurologic disciplines other than movement disorders, for example, epileptology and neuroimmunology. Indeed, patients with similar presentations may often be diagnosed with functional non-epileptic attacks [4], and we have recently also encountered several cases with functional paroxysmally occurring spasms being mislabelled as "seronegative" stiff-person variants. In these cases, lack of alteration of consciousness and absence of epileptic activity during motor events on EEG video telemetry (caveat, frontal seizures), as well as meticulous neurophysiological characterization from experienced clinicians (e.g. absence of continuous motor unit activity), are paramount to aid correct diagnostic classification (see section "Diagnosis and Treatment Approach" below).

However, despite the wide phenomenological variability among functional paroxysmal movement disorders, certain phenotypic presentations with distinctive clinical features are well recognized. For example, functional paroxysmal movement disorders affecting the cranial muscles typically involve the lower half of the face, characteristically the mouth [5]. In these cases, unilateral or predominantly asymmetric downward pulling of the lips, which may on occasion spread to involve the ipsilateral platysma with or without speech difficulties, is common [5–7]. Episodes may last between seconds to minutes or even hours, and some cases may report episodes lasting several days [5]. Symptoms remit during sleep, swallowing is typically unaffected, and brief periods of normal facial muscle activity may be interjected during the attacks. In cases where the entire side of the face is affected ("hemifacial spasm" mimic), there typically is lack of synchronicity between spasms of muscles of the lower and upper half of the face [5–7]. Also, bilateral tonic contractions of the lower face with unilateral spasms of the upper face might also be

observed. In addition, the "other Babinski sign" [8] is invariably absent, and the duration of muscle spasms is typically longer in paroxysmal movements of functional etiology than in patients with typical hemifacial spasm.

Beyond cranial involvement, some patients may present with functional paroxysmal movements of the trunk. Based on clinical phenomenology (typically flexor jerks of the trunk that may involve the upper or lower limbs), these patients are often misdiagnosed as having "propriospinal myoclonus", a clinical entity first described in 1991 by Brown et al. [9]. In fact, the majority of patients with the diagnosis of propriospinal myoclonus most likely have paroxysmally occurring axial jerks due to a functional etiology [10]. Indeed, a systematic re-evaluation of relevant cases published in the literature since 1991 ($n = 179$) highlighted that 58% fulfilled criteria of a functional movement disorder [10]. In many of these cases, electrophysiology (presence of a premotor potential preceding axial jerks) could be particularly helpful, as, indeed, aetiologic classification of axial jerks as either "organic" or "functional" based on clinical impression alone may be unreliable [11].

A different category of paroxysmally occurring motor events involves movements that phenomenologically resemble tics. These are usually movements that have the characteristics of voluntary actions but appear brief and repetitively, typically without appropriate social context. To date, there have been three case series that have specifically highlighted the clinical overlap of functional tic-like jerks and actual tic movements, as encountered in conditions such as Tourette syndrome, and also proposed criteria to aid diagnostic distinction between the two [12–14]. Certain clinical clues, for example, adult age at onset, absence or atypical descriptions of sensory phenomena preceding tics ("premonitory urge") and the inability to voluntarily control excessive movements (non-suppressibility), often characterize functional tic-like jerks [12]. However, it has become increasingly clear that in many cases this distinction may not be as straightforward, and, in fact, behaviours as striking as coprolalia or echolalia have now been identified in patients with functional paroxysmal movement disorders [14, 15]. In these particularly difficult cases, expertise in both tic disorders and functional tic-like disorders is crucial, in order to facilitate appropriate diagnostic labelling and therapeutic approach.

Associated Signs

The classic spectrum of paroxysmal movement disorders due to genetic mutations encompasses well-characterized phenotypes with young age of onset and well-defined associated features, including triggers (e.g. sudden movement in paroxysmal kinesigenic dyskinesia, or fatigue, caffeine and alcohol in paroxysmal non-kinesigenic dyskinesia). In contrast, patients with functional paroxysmal movement disorders typically develop the abnormal episodes at a later – characteristically adult – age (mean age of 38.6 years in our sample of 26 cases of functional paroxysmal movement disorders [3], contrasted to a mean of 9.9 years, 5 years and 8.6 years for patients with paroxysmal dyskinesia due to mutations in the PRRT2,

MR-1 and SLC2A1 genes, respectively [2]). Although functional paroxysmal movement disorders have been reported in children [16], this is particularly rare. Similarly, less than 5% of cases of paroxysmal dyskinesia due to the aforementioned mutations may first manifest in adult age [2]. Table 10.1 provides a list of main clinical features of the three prototypical paroxysmal dyskinesias contrasted to those of patients with functional paroxysmal movement disorders [3].

Table 10.1 Predominant clinical features of the main paroxysmal dyskinesia subtypes and functional paroxysmal movement disorders (FPMD)

Condition	PKD	PNKD	PED	FPMD
Age onset (years)	1–20	Infancy or early childhood	Usually childhood to early adulthood	Adulthood
Triggers	Kinesigenic (sudden movement, usually whole body)	Caffeine, alcohol, stress, excitement	Physical exertion	Diverse, often many different ones in the same patient
Duration	<1 min[a]	10 min–1 h +	15 min (<1 min–3 h)	Highly variable (seconds to hours or days)
Frequency	Daily	Variable, usually 1/week	Usually weekly	Highly variable, usually daily
Gene[a]	PRRT2	MR-1	GLUT-1	–
Phenomenology	Dystonia, chorea, ballism or mixed movement disorder. Uni-/bilateral or alternating	Dystonia, chorea or both	Choreoathetosis, dystonia or both Legs invariably affected. Lateralization common	Dystonia, tremor, jerks. Mixed presentations common. Predominant involvement of limbs bilaterally, followed by head/face and trunk
Level of responsiveness	Normal	Normal	Normal	Unresponsiveness possible
Pain	No	Possible	Usually none	Possible
Response to medication	Excellent to carbamazepine, phenytoin	Some comfort with benzodiazepines	Good response to ketogenic diet	Usually none. Some benefit from benzodiazepines or dramatic response to placebo
Associated features	ICCA, hemiplegic migraine, episodic ataxia	Migraine headache	Epilepsy, mental retardation, ataxia	Somatisations, unusual precipitants and stressors
Family history	Most likely	Yes	Possible	No

Adapted from Ganos et al. [3] (Elsevier OpenAccess)
ICCA infantile convulsions and choreoathetosis
[a]Typical genetic mutation for each phenotype

With regard to attack triggers, these can be particularly unusual and manifold in functional paroxysmal disorders. Although some patients might report that attacks could be elicited in association with increased stress, or caffeine and alcohol intake, they will also often report further triggers. These could range from exerting pressure at certain body parts (e.g. pressure on the middle of the quadriceps muscle may lead to paroxysmal spasms of the ipsilateral leg that may spread to involve the arm and/or face) to assuming certain postures or even being exposed to certain types of sounds [3]. Importantly, patients with functional paroxysmal movement disorders often experience a demonstrable aggravation of their attacks during clinical examination. Noteworthy is also the fact that the majority of patients will report a clear precipitant (physical or psychological) at the onset of their symptoms [3, 17].

Another salient feature related to functional paroxysmal movement disorders is attack duration. Indeed, attacks in these patients typically have great variability often ranging from few minutes to days or even weeks. In contrast, attack duration in the primary genetic paroxysmal movement disorders or also in symptomatic cases is typically less variable [2]. In addition, other symptoms and signs during attacks, for example, speech or swallowing difficulties, light-headedness and dizziness, may also be noted. Distractibility and/or entrainment, typical for functional movement disorders in general, can also be found in patients with functional paroxysmal, particularly jerky, movement disorders. Unusual alleviating factors, such as odd manoeuvres (e.g. rotation of the neck at a certain posture will lead to a cessation of the attack), may also be reported. For this reason, examination of a patient with suspected paroxysmal functional movement disorder during an attack is particularly useful.

Beyond the clinical features of the attacks, additional functional neurological signs may be further observed on *interictal* examination. Functional gait difficulties, give way weakness, non-anatomic sensory disturbance and other functional movement disorders, including fixed dystonic postures of the feet or hands, are such examples. Moreover, patients will often have a history of other medically unexplained somatic symptoms, including previous episodes of constant fatigue with overall weakness or "spells of weakness" ("stroke-like presentations"), sudden onset speech disturbance or blurred vision, diffuse abdominal symptoms, headaches, dizziness, swallowing difficulties and palpitations, just to name a few. However, caution needs to be exerted, as in some cases there is the dual presence of a primary movement disorder and a functional paroxysmal movement disorder.

Diagnosis and Treatment Approach

The spectrum of paroxysmal motor events, which encompasses epileptic seizures, primary and functional paroxysmal dyskinesia as well as disorders with exaggerated startle reflexes (e.g. hyperekplexia), is wide. However, as highlighted above patients with functional paroxysmal movement disorders often provide a characteristic list of clinical symptoms and signs that may serve as red flags for suspecting

this particular etiology (Table 10.2). Importantly, patients with functional paroxysmal movement disorders by virtue of their clinical presentation may be referred to either epileptologists, movement disorders clinicians or neuroimmunologists or all three, and this may be associated with delays in reaching conclusive diagnosis (e.g. uncertainty whether a non-epileptic event might be a rare genetic paroxysmal movement disorder or a neuroimmunologic syndrome). Key investigations in cases where some uncertainty remains include EEG video telemetry and video-aided polysomnographic sleep studies (in cases where patients, and often their spouses too, report persistence or emergence of attacks during sleep). Also, in cases with unilateral manifestation of symptoms, brain MRI will be crucial to assess the structural integrity of the nervous system, as lesions in contralateral motor-related brain areas have been associated with secondary paroxysmal dyskinesia [18, 19]. Again, it is important to consider the relatively common issue of functional overlay, where disorders of different etiologies, including functional, co-exist in the same patient.

Upon establishing the diagnosis of a functional paroxysmal movement disorder, the first crucial step is to effectively communicate it to the patient. Indeed, this applies to any medical condition; however, the therapeutic benefit of effective communication between doctor and patient at the time of diagnosis appears to be particularly high for this group of patients. During the delivery of diagnosis, the potential reversibility of the disorder should also be highlighted [3, 5, 20, 21]. Subsequently, a multidisciplinary treatment approach, which may include both psychological and physical rehabilitation interventions, has a clear rationale. In this regard, specific cognitive-behavioural therapies that have been successfully employed in non-epileptic attacks can be particularly helpful [22–25]. Here, focus should be given on enabling awareness of precipitants and triggers of functional paroxysmal episodes, as well as addressing factors related to their persistence, such as abnormal illness beliefs, anxiety and low mood, and provide the appropriate neurocognitive tools to terminate paroxysmal events once they occur [22–24, 26]. Also, physical therapies (e.g. physiotherapy, occupational and speech therapy) that focus on re-establishing normal control of movement during sessions may further

Table 10.2 Red flags for suspecting a functional paroxysmal movement disorder

Adult age of onset
Paroxysmal tremor as predominant clinical feature
High phenomenological variability between episodes
Precipitation of attack or increase in symptom severity during examination
Atypical and variable duration of attacks
Presence of multiple atypical triggers
Altered level of responsiveness
Presence of odd precipitating factors
Presence of unusual relieving manoeuvres
Additional functional physical signs and/or medically unexplained somatic symptoms
Atypical response to medication

Adapted from Ganos et al. [3]. (Elsevier OpenAccess)

augment treatment response [21]. Although pharmacological approaches are generally to be avoided in the treatment of functional paroxysmal movement disorders, medications to aid with comorbid depression or anxiety might be of help. Crucially, follow-up appointments with the neurologist who established the diagnosis during the entire treatment period are particularly important to provide patients with a stable therapeutic environment.

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Chapter 11
Episodic Ataxias

Simone Zittel and Christos Ganos

Introduction

Ataxia in neurology denotes a disruption of coordinated movement and a lack of balance, typically as a result of cerebellar damage [1]. Beyond the common presentation of acute cerebellar ataxia due to structural lesions of the cerebellum, as in stroke, or progressive cerebellar ataxia due to autoimmune or neurodegenerative causes [2], some patients may present with a familial syndrome of episodic or paroxysmal bouts of recurring cerebellar ataxia. In this context, a rare group of disorders termed episodic ataxias (EA) has been delineated to denote autosomal dominant ion channel disorders characterized by recurrent episodes of ataxia, incoordination and vertigo. So far, eight EA subtypes have been described, and five respective causal gene mutations have been identified (EA1, *KCNA1*; EA2, *CACNA1A*; EA5, *CACNB4*; EA6, *SLC1A3*; EA8, *UBR4*). EA1 and EA2 are the most common subtypes of EA with multiple documented families. For the other subtypes, only single families have been reported to date. In the following chapter, clinical characteristics, genetic background and treatment options, especially treatment response to acetazolamide, for the different EA subtypes will be described. Also, a brief overview of the clinico-genetic characteristics of further paroxysmal disorders that may also

Electronic Supplementary Material The online version of this chapter (https://doi.org/10.1007/978-3-030-53721-0_11) contains supplementary material, which is available to authorized users.

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K. D. Sethi et al. (eds.), *Paroxysmal Movement Disorders*,
https://doi.org/10.1007/978-3-030-53721-0_11

present with suddenly recurring ataxia but do not fall within the EA spectrum will be presented. Table 11.1 displays an overview of the different clinical characteristics for the eight EA subtypes.

EA1

The first reports of EA1 date back to 1975 when episodes of ataxia were reported by VanDyke et al. [4]. EA1 is characterized by brief, abruptly occurring episodes of ataxia lasting seconds to minutes and interictal myokymia or neuromyotonia. Episodes may also include symptoms such as dysarthria, nystagmus, intention tremor, gait incoordination or muscle weakness. Episodes are often precipitated by physical or emotional stress, startle and sudden movements but may also occur spontaneously. Aura-like symptoms, e.g. a vague somatic sensation including a feeling of falling or weakness that may mark the incipient onset of an attack, are typically reported. Frequency of attacks varies from several episodes daily to a few times a year. Symptom onset is typically in early childhood or adolescence. Interestingly, in adult age a decrease of attack frequency is reported.

Although typically considered an episodic ataxic disorder, a case series of 39 EA1 patients showed that cerebellar signs, such as gait and speech impairment as well as ataxia of the extremities, were present interictally in up to 26% of patients [5], particularly in cases with longer disease duration. Moreover, an increased incidence of epilepsy and deafness have been also reported in EA1, further expanding the phenotypic spectrum of the disease [6]. Crucially, perhaps the most characteristic interictal sign of EA1 is myokymia (Video 11.1). Surface or needle electromyography (EMG) of the face or small hand muscles may further support the clinical suspicion, by revealing grouped brief discharges recurring rhythmically with an interval between 100 ms and 10 s at a rate of 20–50 Hz (Fig. 11.1). Brain MRI is typically unremarkable, although cerebellar atrophy might be noted.

Medical treatment is not always necessary because patients often modify their behaviour to avoid attack precipitants. However, in the patients that do require treatment, acetazolamide may be helpful, by reducing both frequency and severity of episodes [5, 7]. Some patients may also benefit from carbamazepine or phenytoin [5, 7].

Mutations in the *KCNA1* gene coding for the α-subunit of Kv1.1 have been identified as causative for EA1. Kv1.1 is widely expressed in the nervous system and plays a key role in neuronal excitability through modulation of membrane repolarization after an action potential. Known pathogenic mutations have been found to impair Kv1.1 function, thereby leading to increased neuronal excitability. Interestingly, most reported mutations cause a loss of protein function leading to a change in neuronal activation thresholds [6]. Investigation of monozygotic twins also revealed a large contribution of non-genetic factors like hormonal influence to phenotypic variability [5, 8].

Table 11.1 Clinical characteristics of episodic ataxias

	EA1	EA2	EA3	EA4	EA5	EA6	EA7	EA8
Gene/chromosomal location	*KCNA1*	*CACNA1A*	Chromosome 1q42	Unknown	*CACNB4*	*SLC1A3*	Chromosome 19q13	*UBR4*
Typical age at onset	Adolescence	Early childhood to adolescence	Variable	Adulthood	Early adulthood	Childhood	Childhood	Childhood
Attack duration	Seconds to minutes	Hours	Minutes	Minutes to days	Hours	Hours to days	Hours to days	Minutes to hours
Nystagmus	No	Downbeat or gaze-evoked	Rare congenital	Gaze-evoked	Downbeat	No	No	No
Myokymia	Y	N	Y	N	N	N	N	(Y)
Acetazolamide response	Variable	Y	Y	N	Y	N	NA	N
Associated features	Epilepsy Myokymia/ Neuromyotonia Deafness	Epilepsy Headache Hemiplegia	Epilepsy Tinnitus Headache	Epilepsy Tinnitus	Epilepsy	Epilepsy Headache Hemiplegia	Headache Weakness	Headache Depression Myokymia

Data from Guterman et al. 2016 [3]

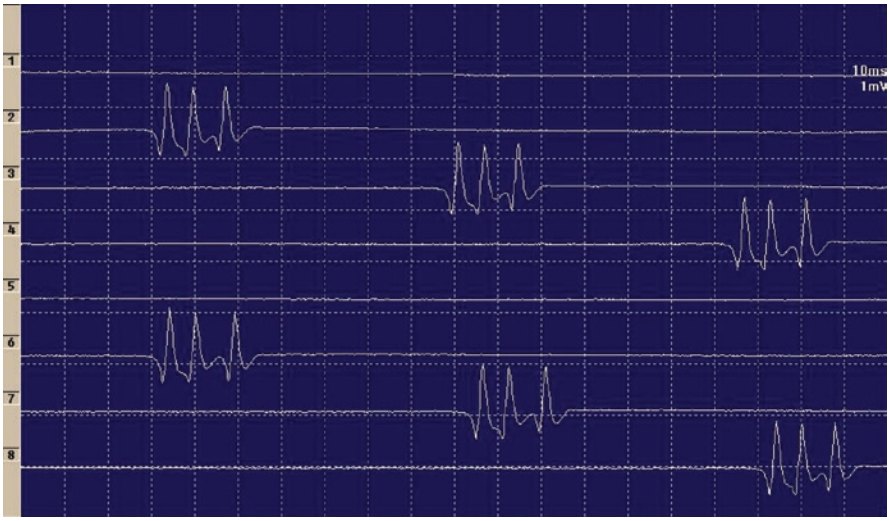

Fig. 11.1 EMG of the platysma muscle is shown with rhythmical grouped discharges (also see Video 11.1)

EA2

EA2 is by far the most common episodic ataxia syndrome. Contrasted to EA1, episodes of ataxic symptoms in EA2 are typically longer with durations of hours to days. Beyond balance difficulties and lack of coordinated movement, patients may also commonly experience further cerebellar/brainstem symptoms such as vertigo and nausea or vomiting. Further associated signs include migraine (in up to 50% of cases), generalized or hemiplegic weakness, seizures and some degree of dystonia [3, 9]. Interestingly, in some patients learning disabilities have also been reported [9]. Moreover, paroxysmal head tremor has also been reported in a patient with EA2 gene mutation (also see below) [10]. Beyond ataxia episodes, EA2 patients characteristically develop a slowly progressive cerebellar syndrome, often accompanied by gaze-evoked (downbeat) nystagmus.

Symptom onset typically occurs in early childhood or adolescence. Episode triggers include physical exertion, emotional stress, alcohol and caffeine. Brain MRI typically shows cerebellar atrophy, notably of the anterior vermis [11], particularly in cases with a long disease duration.

EA2 typically responds well to pharmacological treatment, particularly acetazolamide in 50–75% of the patients with recommended dosages between 250 and 1000 mg per day [9]. Alternatively, treatment with 4-aminopyridine 5 mg three times daily or levetiracetam 750 mg daily may also be helpful [12, 13].

CACNA1A is the disease-causing gene for EA2 coding for Cav2.1, the α1-subunit of the P/Q-type voltage-gated Ca^{2+} channel. The channel is widely expressed in Purkinje and granule cells of the cerebellum. It mediates Ca^{2+} entry into the cell and

regulates the precision of pacemaking. Missense mutations lead to decreased Ca^{2+} entry and irregular firing of Purkinje cells. The vast majority of mutations cause a premature stop leading to a loss of function [14].

EA2 is allelic with familial hemiplegic migraine type 1 (FHM1) and spinocerebellar ataxia type 6 (SCA6), a late-onset pure cerebellar ataxia syndrome. Typically, loss-of-function mutations cause EA2 and missense mutations FHM1. Glutamine-encoding CAG-repeat extensions in CACNA1A gene are causative for SCA6. The distinction of the clinical phenotype is not always clear though based on the underlying gene mutation since a broad clinical variability has been reported in families with the same mutation [8, 15]. Of particular interest is the fact that the same point mutations in the CACNA1A gene that may cause EA2 have also been found to cause a pure isolated and late-onset cerebellar ataxia syndrome. The exact interplay between genetic, epigenetic and environmental factors in the pathophysiology of the disease is still unclear [8].

EA3–EA8

EA3 is clinically characterized by episodes of ataxia, vertigo and tinnitus in the majority of cases [16]. Patients may also report visual disturbances, e.g. blurred vision or diplopia, during an attack [17]. Duration of episodes is several minutes. Symptoms can be improved by acetazolamide. Linkage of EA3 to chromosome 1q42 has been demonstrated [16]. So far, 51 affected patients in two families have been reported [16, 17].

EA4 has also been termed vestibulocerebellar ataxia and has been reported in several families in North Carolina ($n = 36$ affected individuals) [18–20]. Symptoms typically begin between the age of 30 and 60 years and are characterized by attacks of vertigo, cerebellar ataxia and diplopia [18]. Tinnitus has also been reported in some of these patients during an attack and may be a helpful diagnostic clue. Duration of attacks ranges between minutes and days, and triggers include sudden movement or fatigue [19]. Similar to EA2, ataxia attacks in EA4 are also accompanied by a slowly progressive cerebellar syndrome including gaze evoked nystagmus and impaired smooth pursuit [18, 20]. In contrast to EA2, response to acetazolamide is generally poor [19].

EA5 is caused by mutations in the *CACNB4* gene. It has so far been reported in only one family with episodic ataxia and another family with generalized epilepsy [21].

Mutations in the *SLC1A3* gene encoding the glutamate transporter EAAT1 cause EA6 which may be associated with variable symptoms of different severity. The first patient with a reported pathogenic *SLCA1A3* mutation suffered from childhood-onset episodic ataxia, seizures, hemiplegia and migraine [22]. Three further patients with a different mutation at the same gene were subsequently described. Their clinical presentation was characterized by childhood-onset (<14y) syndrome consisting of EA, albeit without hemiplegia or seizures [23]. Recently, a case with late-onset

episodic ataxia beginning in the sixth decade has been reported further expanding the phenotypic spectrum of EA6 [24]. Presumably mutations are associated with toxic gain of protein function [25], and severity of symptoms appears to be related to the extent of glutamate transporter dysfunction.

EA7 has been described in only one family with linkage to chromosome 19q13 [26]. Episodes are characterized by ataxia, dysarthria and weakness typically lasting for hours but rarely also for days. Interictal examination showed normal result. Episodes can be triggered by physical exercise or emotional excitement, and advancing age was associated with reduced attack frequency. Patients may additionally experience migrainous headaches.

EA8 has been reported to cause ataxia episodes with onset in early childhood [27]. During episodes patients experience cerebellar symptoms including speech impairment and generalized weakness. Episodes can be triggered by physical or emotional stress. As in EA7, attack frequency typically decreases with increasing age. Treatment response to acetazolamide is poor, but clonazepam may be of some benefit. On interictal examination, cerebellar dysarthria, intention tremor and impaired tandem gait can be observed. One single patient with interictal myokymia has also been reported. Exome sequencing revealed a variant in the *UBR4* gene which may be associated with this type of episodic ataxia [27].

Other Paroxysmal or Episodic Disorders Presenting with Ataxia

Beyond the EA spectrum, three further gene mutations should be considered in the context of episodic – or paroxysmal – ataxia, particularly if other neurological signs are also present. Mutations in the ATP1A3 gene are typically associated with a spectrum of different disorders including rapid-onset dystonia parkinsonism, alternating hemiplegia of childhood and a complex neurologic syndrome characterized by cerebellar ataxia, areflexia, pes cavus, optic atrophy and sensorineural hearing loss (CAPOS) [28, 29]. Characteristically, in all different disorders, neurologic deterioration typically occurs paroxysmally or episodic, and it is often triggered by precipitants such as fever or as a result of physical trauma and may be as severe as to include alterations of consciousness (encephalopathic episodes). Both the plethora of associated neurologic features and signs beyond the presence of ataxia and the typically only partial symptom remission between episodes are helpful clues to distinguish syndromes related to *ATP1A3* mutations from the classic group of EA. Moreover, the onset age for CAPOS, the prototypical *ATP1A3* disorder with episodes of ataxia, is in most reported cases the first months of life. However, as the phenotypic spectrum of *ATP1A3* continues to expand, potentially more overlapping features with EA could come to the fore [30, 31].

Further, mutations in the proline-rich transmembrane protein (*PRRT2*) have also been associated with the manifestation of episodic ataxia. The classic phenotype of *PRRT2* mutations (cfr. Chap. 3) includes autosomal dominant paroxysmal kinesigenic dyskinesia (PKD), benign familial infantile convulsions and infantile convulsions with choreoathetosis (ICCA syndrome) [32]. PKD is characterized by episodes

of choreic, ballistic and/or dystonic movements lasting for seconds to minutes. Episodes are typically induced by sudden movements or stressful events. Interestingly, among a cohort of 182 patients with episodic ataxia, genetic screening for *PRRT2* mutations identified 1 patient with episodic ataxia and hemiplegic migraine [33]. The patient experienced sudden bouts of ataxia since the age of 18 years. Attacks occurred on a daily basis and were also accompanied by unilateral headaches and recurring hemiplegia [33]. Therefore, although rarely, the differential diagnosis of episodic ataxia, particularly in cases with atypical age of onset and associated neurological features as the ones reported in this case, should also consider the genetic aetiology of *PRRT2* gene mutations. Moreover, *SLC2A1* mutations, which are associated with a wide spectrum of clinical manifestations related to GLUT1 deficiency syndrome including paroxysmal exercise-induce dyskinesia (PED; cfr. Chap. 5), can rarely produce a phenotype of isolated or combined EA. In most of the reported cases, onset was in infancy before 10 years of age, associated features, namely prior history of epilepsy, were present in about one-third of patients, there was a beneficial response to acetozolamide (thus "mimicking" the classical EA) in up to 37% of patients, and a tendency to develop chronic ataxia over the years was observed in about half of the cases [34]. Future clinico-genetic studies in large cohorts may further help to distinguish classical EA subtypes from other genetic causes of episodic ataxia syndromes.

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