The unravelling of the paroxysmal dyskinesias

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Abstract

Paroxysmal dyskinesias (PxD) refer to a rare group of clinically and genetically heterogeneous disorders presenting with recurrent attacks of abnormal movements, typically dystonia, chorea or a combination thereof, without loss of consciousness. Classically, PxD have been categorized according to their triggers and duration of the attacks, but increasing evidence suggests that there is a certain degree of clinical and genetic overlap and challenges the concept that one phenotype is attributable to one single aetiology. Here we review the increasing spectrum of genetic conditions, as well as of other non-genetic disorders, that might present with PxD, provide criteria for case-definition and propose a diagnostic work-up to reach a definitive diagnosis, upon which treatment is heavily dependent.

1. Introduction

Paroxysmal dyskinesias (PxD) are a group of heterogeneous syndromes that characteristically manifest with recurrent attacks of abnormal movements, typically dystonia, chorea or a combination thereof, without loss of consciousness[1].

Considering the etymology and literal meaning of the words "paroxysmal" and "dyskinesia", one would realize that neither term is specific enough to unequivocally identify the entities that are classically referred to as PxD. The term "paroxysmal", (from Greek paroxusmós - irritation, the severe fit of a disease) refers to sudden attack, recurrence, or intensification of a disease[2]. According to this definition, even waxing-and-waning conditions like tic syndromes or movement disorders that appear or worsen on action (action-myoclonus or action-tremor for instance) would fit into this category. The term dyskinesia (from Greek, dys + kinesis, altered movement) is also used in the medical literature with different meanings. Some medical dictionaries propose that it should be used to indicate an impairment of the ability to execute voluntary movements[3], whereas others emphasize the *hyper*-kinetic nature of the disorder and suggest that dyskinesias are involuntary jerky or slow writhing movements, often of a fixed pattern, including tics, myoclonus, chorea and dystonia[4].

It appears clear that such definitions are too broad and do not match with the meaning that movement disorder experts give to the term "paroxysmal dyskinesias". This calls for the need for a clear definition of what should be intended as PxD, to avoid further ambiguity in the literature.

Moreover, increasing knowledge regarding the possible aetiologies underlying the PxD has challenged the concept they could represent distinct disease entities (i.e., that one

phenotype could be only attributable to one single aetiology)[5–7]. Hence, following a brief overview of the historical aspects and the classification of PxD based on triggers (see below), a further in-depth section will be structured according to the different aetiologies that produce PxD. This section will cover novel genetic disorders that might encompass in their phenotype paroxysmal dystonia and/or chorea, but escape the current classification of PxD.

A final section is meant to provide a diagnostic strategy to deal with PxD. This framework emphasizes that these diagnostic labels represent clinical syndromes (and not disease entities), provides criteria for case-definition, and endorses the approach recently used for dystonia in general[8] (i.e., isolated versus combined PxD, thereby discarding the former criterion requiring normal neurological examination between the attacks). On the basis of different clinical features including, but not limited to, triggers, appropriate investigations are suggested to reach a definite diagnosis, upon which treatment is heavily dependent. It is not in the aims of the current paper to review the pathophysiological mechanisms underpinning this group of disorders and the interested readers are referred elsewhere[9]. The search strategy is detailed in box 1.

BOX 1

Search strategy and selection criteria

References for this Review were identified by searches of PubMed, EMBASE and Google Scholar, between 1940 and January 2018, and references from both relevant articles and book chapters. The search terms "paroxysmal dyskinesias", "paroxysmal dystonia", "PRRT2", "MR-1", "SCL2A1", "GLUT1", "KNCMA1", "ADCY5", "ATP1A3", "PKD", "PNKD", and "PED" were used. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Review.

2. Historical definition and classification of paroxysmal dyskinesias

Between 1940 and 1977, three main forms of episodic movement disorders were recognized[10–12] and classified based on the duration of attacks[12]. Following this earlier classification[12], a subsequent proposal by Demirkiran and Jankovic discarded the duration of attacks as informative and focused on the difference between triggers[13]. They recognized three subtypes, encompassing paroxysmal kinesigenic (PKD), non-kinesigenic (PNKD), and exercise-induced (PED) dyskinesias[13]. The term dyskinesia was privileged over others previously adopted because the specific phenomenology of the attacks (i.e., dystonia vs chorea) could only be presumed based on patients' description. A fourth subtype was also proposed [i.e. paroxysmal hypnogenic dyskinesias (PHD) characterized by attacks occurring during sleep without identifiable trigger][13], but this entity has been subsequently suggested to be a form of autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) in most cases[14].

Each of these forms could be further stratified into primary and secondary disorders[13]. However, the term "primary" is increasingly dismissed as it carries the implication that there is absence of detectable abnormalities[15], whereas most *primary* PxD are in fact found to be *secondary* to a genetic defect. Moreover, it was suggested that patients with secondary PxD have inter-ictal signs reflecting the underlying disorder[13], as opposed to cases with primary PxD. However, as anticipated above and discussed in detail below, many patients with "primary" genetic forms of PxD do have inter-ictal findings on examination. One example is represented by *SLC2A1* (GLUT-1) mutations, which can produce isolated PED (previously assigned the DYT18 number)[16], PED with inter-ictal

spasticity (previously assigned the DYT9 number)[17] as well as a number of other different phenotypes.

3. Disorders presenting with paroxysmal dyskinesias

3.1 PRRT2

In 2011 Chen et al. first reported *PRRT2* mutations as the genetic cause of PKD in eight families with PKD[18], opening the way to the identification of *PRRT2* mutation in several clinical syndromes previously associated with PKD such as the so-called ICCA syndrome (i.e., infantile convulsions with choreoathetosis) and BFIS syndrome (i.e., benign familial infantile seizures)[19]. Currently, *PRRT2* is the major gene accounting for PKD, with a frequency ranging from about 40% to over 90%, depending on case ascertainment[14,19,S1,S2]. Onset of paroxysmal dyskinesias is in childhood, very rarely later than 18 years of age. In patients with ICCA, paroxysmal dyskinesias start after the onset of epilepsy (that develops within the first two years of life), usually after age 5, although some patients might exhibit epileptic seizures at a later age[9,14,19].

Virtually all *PRRT2* cases have a clear kinesigenic trigger, although in up to 40-50% of cases anxiety, stress, startle or prolonged exercise can also induce attacks and very rarely (about 1-2% of patients) there are no kinesigenic triggers[14]. The episodes are very brief, usually lasting less than 1 minute, feature both chorea and dystonia, and tend to generalize[14,19,S1,S2]. About half of the patients experience a sensory aura at the initial site of the attacks that patients can use to predict attacks[14]. Often patients have hundreds of episodes per day, although the frequency of attacks usually decreases with advancing age after puberty and the syndrome can completely remit regardless of any treatments[14,19,S1,S2]. Carbamazepine (CBZ) is the first line treatment option, being very effective at low doses (50-600 md/day) [14,19,S1-S4]. A dramatic reduction in attacks is

usually observed and this has been in fact suggested to be typical for patients with *PRRT2* mutation as compared to similar cases of PKD and without such genetic defect[S3,S4].

It is however now clear that *PRRT2* mutations can induce additional phenotypes including episodic ataxia and migraine, often of the hemiplegic subtype[5,19,S5]. As such, these features, whenever present in a single subject or in the family, make the presence of *PRRT2* mutations likely.

Interestingly, *PRRT2* mutations have been recently identified in 2 out of 11 patients (18.2%) with PHD[20], which supports the inclusion of PHD among the PxD. Moreover, *PRRT2* mutations have been further associated with a phenotype reminiscent of benign paroxysmal torticollis of infancy (BTPI)[21] and, in the case of biallelic mutations, with a complex phenotype including neurodevelopmental delay[22]. Complex phenotypes including PKD along with developmental delays, intellectual disability and language abnormalities, minor dysmorphic facial features, and/or autism spectrum disorder should also raise the suspicion of 16p11.2 (micro)deletions[23,S6]. In such rare cases, conventional genetic testing for *PRRT2* mutations might be uninformative and microarray-based comparative genomic hybridization has to be performed[S6]. Table 1 summarizes the clinical features of *PRRT2* mutation as well as of the main genetic conditions producing PxD.

	PRRT2	*MR-1*	*SLC2A1*	*KNCMA1*	*SCN8A*	*ECHS1*	PDC deficiency (*PDHA1, PDHX, DLAT*)	*ADCY5*	*ATP1A3*	*CACNA1A*	*GCH1*	*SLC16A2*
Inheritance	AD	AD	AD	AD	AD	AR	AR	AD			AD	X-linked
Age at onset	< 18 years	< 18 years	Variable	Infancy	Infancy	Infancy	Infancy	Variable	< 18 months	< 1-2 years	<18y	< 1-2 months

PxD subtype	PKD	PNKD	PED	PNKD	PKD-like	PED	PED/PNKD	PND	PNKD (hemi-dystonic attacks)	BPTI	PED	PKD triggered by passive movements
Attack duration	Very brief (<1min)	Long (>1h)	Intermediate (5-40 min)	Brief	Brief	Variable	Variable	Brief (min)	Variable	Variable (min to days)	Variable	Very brief (sec to min)
Isolated vs combined	I/C	I	I/C	C	C	I/C	I/C	C	C	I/C	I/C	C
Other paroxysmal disorders	Epilepsy, migraine, FHM, ataxia	Migraine (rare)	Ataxia, epilepsy	Epilepsy	Epilepsy	-	-	PNKD	Hemiplegia, Ataxia	EA2, FHM, vomiting, vertigo, paroxysmal tonic upgaze	-	-
Other features	-	-	Anaemia, Hypotonia, Spasticity,	Mental retardation	Mental retardation	Leigh syndrome	Leigh syndrome	Axial hypotonia, non-paroxysmal dystonia and chorea	-	-	parkinsonism	Mental Retardation

Table 1. Characteristics of mutations mainly associated with paroxysmal dyskinesias

AD: Autosomal Dominant; AR: Autosomal Recessive; PKD: Paroxysmal Kinesigenic Dyskinesias;

PNKD: Paroxysmal Non-Kinesigenic Dyskinesias; PED: Paroxysmal Exercise-induced Dyskinesias;

PND: Paroxysmal Nocturnal Dyskinesias; BPTI: Benign Paroxysmal Torticollis of Infancy; EA2:

Episodic Ataxias type 2; FHM: Familial Hemmiplegic Migraine

3.2 MR-1

In 2004, *MR-1* mutations were for the first time discovered in 2 unrelated families with

PNKD[24]. Onset of the attacks is usually in the first decade[5,18,24,S7]. There is always a

dominant family history for similar attacks, no sporadic cases having been reported

thus far[14]. At the phenomenological level, attacks encompass both dystonic and

choreatic features and are generalized in about 50% of the patients[14,24,S7,S8]. Attacks can

be seldom complicated by dysarthria, dysphagia, oculogyric crises, inability to move, and/or pain and might also be fatal[14,S9]. The duration of the attacks is variable but often last for a few hours[5,14,24,S7,S8]. Although several non-kinesigenic triggers (i.e., stress, tiredness, sustained exercise) can be present, in patients with *MR-1* mutations attacks are characteristically brought on by coffee and/or alcohol intake[5,14,24,S7,S8] as compared to patients with PNKD but without mutations in this gene[S7]. *MR-1* carriers do not have associated clinical features, with the exception of migraine in a few cases[5], and the inter-ictal examination is always normal. Clonazepam is the first-line pharmacological option when lifestyle modifications (i.e., avoiding coffee and alcohol) are not efficacious[14]. Regardless of any treatment, there is a tendency for the attacks to reduce or remit in adulthood[5,14,S7]. Rarely, *MR-1* mutations can manifest with very brief attacks trigger by sudden movements, therefore resembling classic PKD[S10].

3.3 SLC2A1

Mutations in *SLC2A1* encoding the glucose transporter type 1 (GLUT1) have been discovered to cause a spectrum of neurological phenotypes, including PED[5,9,14-16]. The latter is characterized by attacks of chorea and dystonia affecting mainly the lower limbs that are typically triggered by sustained exercise[5,9,14-16,25]. There is some phenotype-genotype correlation, with splice site, nonsense, insertions or deletions leading to loss of function *SLC2A1* mutations being associated with younger age at onset and a more severe clinical phenotype of GLUT1 deficiency syndrome, including epilepsy, hypotonia, spasticity, ataxia, and developmental delay [14,25]. This compares with missense *SLC2A1* mutations, which more commonly present with PED in older patients[S11], the age at onset ranging from 1 to 50 years of age. As such, depending on the specific underlying genetic defect, PED can manifest as an isolated syndrome (about one-third of *SLC2A1* cases) or be associated with other neurological

disorders[25,S11]. Most cases with PED are de-novo, whereas only 10% have a positive family history[15,16]. Although autosomal recessive transmission has been described in rare cases of GLUT1 deficiency syndrome[S12], this has not been reported in patients with PED. It is important to remark that while PED is the most common type of PxD reported in *SLC2A1* cases, other non-kinesigenic triggers have also been described[14] and patients can manifest other episodic neurological disorders including episodic ataxia[5,S13].

PxD in the context of *SLC2A1* cases have a positive but partial response to a ketogenic diet[26], which should be pursued to treat the underlying neuroglycopenia.

3.4 KNCMA1

Mutations in *KNCMA1*, which encodes for a subunit of a calcium-activated potassium channel, have been reported in 2005 to cause a syndrome of PNKD and epilepsy[27]. Clinically, the PxD borne resemblance with the non-kinesigenic variant and alcohol was noted as a possible (but not constant) trigger[27]. Two additional PNKD patients with *KCNMA1* mutations have been subsequently reported to lack epilepsy, but they presented with neurodevelopmental delay[S14]. As such, at variance from *MR-1* patients, *KCNMA1* mutations cause PNKD associated with either epilepsy or neurodevelopmental delay. PNKD in *KNCMA1* carriers variably respond to antiepileptic drugs[27,S14].

3.5 ECHS1

ECHS1 encodes for the short-chain enoyl-CoA hydratase protein, mutations of which have been reported as a cause of early-onset Leigh syndrome (or a Leigh-like syndrome with atypical, often milder form with later onset)[S15]. *ECHS1* mutations have been further associated with PxD, which can be either isolated or combined with a number of features suggestive of a mitochondrial disease[28–30,S15]. Thus, *ECHS1* mutations have

been associated with intermittent episodes of long-duration (30-50 min) opisthotonus with no identifiable trigger[S15], but also with episodes of dystonia clearly induced by sustained exercise[29,30]. Although a previous report has labelled the latter episodes as "kinesigenic" [28], a careful analysis of the original case description reveals that the attacks were actually triggered by "physical strain"[28]. Two more recent reports have confirmed that PxD due to *ECHS1* mutations are more likely to be in the form of PED, with or without normal inter-ictal neurological examination[29,30].

It is worthy of note that all patients described so far have pallidal hyperintensity on T2-MRI sequences (despite being very mild in one patient with isolated PED[29]), suggesting this might be a clue to suspect *ECHS1* mutations. A possible benefit with ketogenic diet or a mitochondrial cocktail including thiamine, riboflavin, carnitine, coenzyme Q-10, vitamin B6 and vitamin C has been reported in PxD[28,30].

3.6 Pyruvate dehydrogenase deficiency: *PDHA1, PDHX* and *DLAT*

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)[S16]. Deficits in either subunit have been reported to cause PxD usually, but not always, embedded in complex neurologic pictures[31,32,S17,S18].

Mutations in the *PDHA1* gene are typically associated with a wide range of clinical presentations[S16,S17]. Most patients have severe, often lethal early encephalopathy with lactic acidosis. Some cases have more chronic or subacute neurodegenerative disorders ranging from Leigh syndrome, episodes of ataxia or recurrent acute flaccid paralysis [S16,S17]. Interestingly, a subset of patients manifest paroxysmal dystonia, which can be

either isolated or combined with the aforementioned phenotypes or other clinical signs/symptoms including hypotonia, epilepsy and neurodevelopmental delay[S16,S17]. The paroxysmal dystonia might be brought on by prolonged exercise, thus meeting the criteria for PED, or without any clear trigger, thus falling into the PNKD category[31,32,S17,S18]. Attacks are sometimes reported to be hemi-dystonic. Similar attacks have been reported in patients with *PDHX* and *DLAT* mutations[32,S16,S18] acknowledging that the latter two conditions are far less common than *PDHA1* mutations.

Raised (serum or CSF) lactate and/or pyruvate levels along with pallidal hyperintensity suggesting striatal necrosis are important clues to suspect PDC deficiency mutations[S16-S18], 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, as it is a treatable condition that responds to thiamine supplementation[S19]. In other cases, beneficial outcomes have been also reported with a ketogenic diet[S17], which supports energy failure as the main pathophysiological mechanism for the PxD occurring in the context of PDC deficiency.

3.7 *GCH1*

GCH1 codes 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 dystonias. A few patients with *GCH1* mutations have been described with a phenotype consistent with PED. In 2010, Dale and colleagues described a family with two affected members with isolated PED[33]. Attack duration was about 5 minutes and they never occurred at rest or during movement initiation[33]. Moreover, Erro et al. found 2 *GCH1* carriers in a series of 16 patients with PED (12.5%)[34]. The phenomenology

was that of dystonia and attacks were localized to the lower limbs[34]. As expected, patients had a dramatic benefit upon levodopa supplementation[34].

3.8 SCN8A

Recently mutations in *SCN8A*, which encodes for sodium voltage-gated channel alpha subunit 8, have been suggested to be an alternative cause of the ICCA syndrome (i.e., PKD and infantile convulsions) in one recent report[35]. However, this proposal has been subsequently questioned[S20] based on the evidence that, in one affected case, a "PKD" spell was recorded by video-EEG and a cortical signal was documented, suggesting that such attacks might in fact be epileptic in nature. Therefore, it is unclear whether mutations in this gene truly cause PKD or not. However, it has to be acknowledged that in other reports *SCN8A* mutations have been associated with episodic dystonia, although the term paroxysmal dyskinesia was not explicitly used[36]. As such, it is worth considering this condition in the differential diagnosis of PxD, especially when associated with epileptic seizures, particularly those refractory to antiepileptic therapy, and/or with neurodevelopmental delay[36].

3.9 ADCY5

Mutations in *ADCY5*, which encodes for the adenylate cyclase 5, have been reported to cause a spectrum of (non-paroxysmal) movement disorders ranging from dystonia to chorea, sometimes associated with axial hypotonia and PxD[37-39]. PxD do not always fit clearly within previously identified PxD categories and might be painful, a point of difference from PxD due to other genetic causes of PxD[37,39]. Moreover, *ADCY5*-PxD may manifest, even within the same patient, as multiple sub-types, including PKD and PNKD[37,39]. Of note, also at variance with other genetic disorders that can produce PxD, *ADCY5* carriers characteristically develop PxD during sleep[39]. Night-time dyskinesias (along with non-paroxysmal movement disorders) are therefore a clue to suspect

ADCY5 mutations. Interestingly, Westenberger and colleagues have recently reported two unrelated *ADCY5* patients with attacks reminiscent of Alternating Hemiplegia of Childhood (AHC; see below) in the context of a more complex neurological picture including dysarthria, hypotonia and non-paroxysmal choreo-dystonia[40]. Partial benefit has been reported with both tetrabenazine[S21] and deep brain stimulation (DBS)[S22].

3.10 *ATP1A3*

ATP1A3 mutations cause different clinical syndromes including AHC, Rapid-onset Dystonia Parkinsonism and Cerebellar Ataxia with Pes cavus and Optic neuropathy, although there is increasing evidence of overlapping phenotypes[41,42,S23,S24]. In the context of this review, we will only cover AHC. It is a largely sporadic disorder with onset within the first 18 months, by definition[41,42]. Despite its name, the highly distinguish feature of AHC is occurrence of frequent episodes of either hemi-dystonia or hemiplegia, which can manifest together with other paroxysmal neurological signs including nystagmus, anarthria, dysphagia, and seizures[41,42,S24]. Duration of attacks ranges from a few minutes to several days, and episodes occur from repeatedly within a day to several times a month[41,42,S24]. Attacks are almost invariably induced by emotional stressors, such as excitement or less frequently by physical stressors, including hypo- or hyperthermia, respiratory tract infections, and bright light[41,42,S24]. Characteristically, there is a rostrocaudal gradient in the hemiplegic/hemi-dystonic episodes (face/neck>arm>leg)[41,42,S24], which can aid the differentiation from other types of hemi-dystonic attacks. Hemiplegic and hemi-dystonic episodes typically shift from one side of the body to the other and typically disappear falling asleep[41,42,S24]. Almost invariably the hemi-dystonic attacks are combined with other (inter-ictal) features such as developmental impairment, walking difficulties/ataxia, muscular hypotonia, dysarthria and choreoathetosis. The mainstay of treatment is flunarizine (10-

20 mg/day) as a prophylactic drug along with avoiding trigger situations[41,42,S24]. Patients should be encouraged to sleep when attacks begin, using fast-acting benzodiazepines if necessary.

3.11 *CACNA1A*

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 as well as familial hemiplegic migraine[S25]. In a minority of cases, *CACNA1A* mutations have been suggested to account for some cases of paroxysmal benign torticollis of infancy (BPTI)[43,44]. It is characterized by episodes of head tilt with onset within the first 18 months of life that usually resolve by age 5[43,44]. The attack duration ranges from 10 minutes to several days and are frequently accompanied vomiting, pallor, and ataxia[43,44]. BPTI usually resolves after infancy, but can be replaced by paroxysmal vertigo and/or migraine[43,44]. The co-occurrence of episodic ataxia, hemiplegic migraine and paroxysmal tonic upgaze in a single subject or in the family make mutations in this gene more likely[45]. This condition is self-limiting and usually no treatment is required.

3.12 *SLC16A2*

SLC16A2 encodes for the monocarboxylate transporter type 8 (MCT8), which is required for trans-membrane uptake of free triiodothyronine (fT3) from blood into neurons. MCT8 deficiency results in a complex, X-linked disorder (also known as Allan-Herndon-Dudley syndrome) characterized by proximal hypotonia with poor head control, generalized muscular hypotrophy, microcephaly and marked developmental delay[46].

The disorder is progressive and spasticity, ataxia, and severe dysarthria complicate the clinical phenotype. In a subset of patients, a specific sort of PKD is observed[46,47].

Attacks are in fact classically triggered by passive movements such as changing of their clothes or nappies or by lifting the children from one place to another[46,47]. However, attacks can also be triggered by excitement, happiness or crying[46,47]. Attacks are brief, lasting seconds to few minutes, and are dystonic in nature[46,47]. The hallmark of MCT8 deficiency is raised serum concentration of fT3[46].

3.13 Other causes of paroxysmal dyskinesias

Table 2 lists the conditions that have been associated with PxD or similar episodes of choreo-dystonia[13,48,S26-S55]. These include a variety of acquired, immunological and neurodegenerative causes that were formerly ascribed to secondary PxD[13,48]. For this reason, we have also included here brain calcification, by virtue of the fact that a lesional mechanism is assumed in such cases[S35,S36]. However, two PxD families have been recently reported on, in whom genetic analysis revealed novel mutations in *SLC20A2* and *PDGFB* genes, respectively[S48,S49]. The fact that all affected members shared the phenotype of isolated PxD with normal inter-ictal examination [S48,S49]might support the idea that PxD are intrinsically associated with these mutations rather than being merely secondary to basal ganglia calcification, as assumed in earlier reports of the pre-genetic era[S49]. This, however, remains speculative, but it further exemplifies the ambiguity regarding the concept of primary and secondary PxD.

In general, PxD due to acquired, immunological or neurodegenerative causes, present usually at a later age compared to the main genetic forms reviewed above and manifest with additional signs or symptoms that will easily drive the diagnostic work-up and lead to the correct diagnosis and appropriate management in most cases.

Recently, *DEPDC5*[S10] and *CHRNA4*[49] mutations have been associated with the syndrome of PKD plus epilepsy in single families. However, these two genes are also a cause of ADNFLE[50] and it remains to be seen whether these episodes of paroxysmal

dystonia are epileptic in nature or not. Moreover, these results require replication before screening of these genes might be recommended in clinical practice.

Immune-mediated disorders	Multiple sclerosis[48,S26]
	Acute disseminated encephalomyelitis[S27]
	VGKC complex protein antibody encephalitis[S28]
	Anti-Caspr2 syndrome[S29]
	Hashimoto encephalopathy[S30]
	Antiphospholipid syndrome[S31]
	Parry-Romberg syndrome[S32]
	Cryopyrin-associated periodic syndrome[S33]
Vascular	Stroke[48,S34,S35]
	Moyamoya[S35,S36]
	Cerebral palsy[S37]
Metabolic causes	Hypo/hyperglycaemia[S35,S38,S39]
	Hypocalcemia/ Hypoparathyroidism/ Pseudohypoparathyroidism[S35,S40-S42]
	Thyrotoxicosis/Hypothyroidism[S43,S44]
	Wilson's disease[S45]
	Maple syrup urine disease[S54]
	Lesch–Nyhan disease[S55]
Trauma	Central and peripheral[48,S35]
Other	Basal ganglia calcifications[S46-S48]
	Central pontine myelinolysis[S35,S50]
	Kernicterus[48,S35]
	Encephalitis/postinfectious[48,S35,S51]
	Brain neoplasm[S35,S52]

Table 2. Different aetiologies associated with episodic movement disorders resembling paroxysmal dyskinesias

4. Proposed criteria for case-definition and diagnostic strategy

Paroxysmal dyskinesias represent clinical syndromes where the disorder of movement is intermittent in nature (and thus does not encompass exacerbation of existing abnormalities). The intermittent character of the disorder means it is not continuous or steady, but should not be used to refer to disorders that wax-and-wane over a period of time such as tics.

As to the phenomenology, the clinical spectrum ranges from dystonia to chorea, with ballism being possible but does not encompass tremor or myoclonus. Such a clarification automatically excludes stimulus-sensitive myoclonus or startle syndromes from this category. Moreover, excluded from this definition are those phenomena that are clearly drug-induced (i.e., acute dystonic reaction or levodopa-induced dyskinesias in the context of PD, for instance).

Using this definition, the first step for the differential diagnosis is to decide whether the clinical abnormality is in fact a PxD or not. Epilepsy, tonic spasms, tetany, neuromyotonia, periodic paralyses, and episodic ataxias, all of which can produce intermittent disordered movements, need to be excluded clinically and/or by ancillary investigations whenever appropriate. Moreover, psychogenic/functional causes have to be ruled out. While some authors have suggested that the diagnosis of psychogenic/functional paroxysmal movement disorders is fundamentally one of exclusion, we would rather support alternative claims that the diagnosis should be

based on the presence of positive signs: These include profound within-subject phenomenological variability with marked increases in attack frequency and severity during examination, highly variable attack duration, presence of several and non-specific triggers, frequent alteration of responsiveness during attacks, medically unexplained somatic or neurological symptoms and, finally, atypical response to medications[51,52]. These clues will make a *positive* diagnosis of psychogenic/functional movement disorders likely, without the need for additional investigations in most, if not all, cases.

Once the clinical syndrome of PxD is established, the second step is to fully characterize the attacks in terms of trigger and duration, further exploring the presence of family history and additional clinical features (by history or on examination) and to set the identified clinical syndrome in the context of age at onset. A clinical syndrome with onset in childhood, which is characterized by attacks with specific triggers and duration, is most likely to be genetic in nature. The definition of the trigger(s), duration, and body distribution of the attacks, as well as the presence of suggestive associated clinical features and the pattern of inheritance should help the clinician to drive the genetic analysis (figure 1). Most of these disorders account for those forms that were formerly considered *primary* PxD and include PKD, PNKD and PED. While supporting the trigger-based approach as very useful, we further suggest some modifications and clarifications.

For instance, the term non-kinesigenic does not carry any useful information rather than specifying that the trigger is not kinesigenic. It reflects the absence, rather than the presence, of a clinical feature with the obvious implication that, with one notable exception, the majority of non-kinesigenic triggers are non-specific and are shared across different PxD subtypes, being therefore not predictive of the underlying genetic

defect. The exception is represented by alcohol/caffeine in the case of *MR-1* mutations. The presence of this trigger is highly specific of *MR-1* mutations, being present in about 95% of carriers. We therefore advocate considering alcohol/caffeine-sensitivity as a distinctive trigger for PxD rather than relegating it within the (unspecific) subgroup of non-kinesigenic triggers (figure 1). The vagueness of the non-kinesigenic category further justifies the fact that, in some instances, other clinical features such as the body distribution of the attacks might prevail in the definition of the paroxysmal movement disorders. This is the case of dystonic and hemiplegic attacks alternating from one body side to the other (AHC) or episodic attacks of neck dystonia (BPTI).

Moreover, we support the concept of PxD occurring during sleep as a further trigger-based subtype. Although sleep is not strictly a trigger, it can be considered equivalent to other triggers since they all give an answer to the question of *when* PxD occur (i.e., after sudden movements, after alcohol/caffeine ingestion, during sleep, etc.).

At variance with former classifications of PxD, we discard the criterion of normal inter-ictal examination. As such, all the aforementioned trigger-based subtypes can be isolated or combined with additional features. This reiterates a previous suggestion proposing the stratification of PxD into "pure" and "complicated" forms[53], based on the absence or presence of additional inter-ictal neurological signs, respectively. We also advocate this approach for two main reasons. Firstly, there is evidence of clinical heterogeneity for single gene mutations. For instance, *PRRT2* and *SLC2A1* mutations can produce either isolated or combined PxD. Secondly, we believe the syndromic approach will facilitate the differential diagnosis (figure 1). For instance, the presence of epilepsy in a patient with "classic" PNKD will make the presence of *MR-1* mutations very unlikely. Such a syndromic approach would also prioritize some investigations over others. This might be the case for PED in which CSF examination for glucose,

pterin pathway components, pyruvate and lactate would provide more information than imaging.

Whenever the attacks lack specific and consistent triggers, have variable duration, and when the onset is in adulthood, "symptomatic" causes (table 2) need to be excluded, especially in the absence of family history. Given the huge variability of symptomatic PxD forms in their clinical presentation, even within the single subject, it is hard identify any phenotypic patterns suggestive of the underlying aetiology. In general, certain findings including painful attacks, fluctuating levels of consciousness, and dysautonomic crises that are not classically seen in the genetic conditions reviewed here, should prompt the clinician to rule out acquired causes. In such cases, an initial diagnostic work up including metabolic and electrolyte panels, investigation for autoimmune disorders, and brain imaging will allow a definitive diagnosis to be determined in most cases.

5. Conclusions

In recent years, great advances have led to a better understanding of the broad spectrum of genetic conditions underlying the PxD. This has increasingly challenged the former phenomenological classification as well as the idea that any specific phenotypes were associated to single gene mutations. Such an argument reiterates previous proposals[14] that classification of PxD should follow a two-pronged method, according to which both the clinical phenotype and the specific genetic mutation should be stated (*PRRT2-*PKD for example).

It is worth specifying that our proposal does not represent a classification scheme, but reflects an algorithmic approach to help clinicians in the differential diagnosis. First, it gives clarity to the definition of PxD. Second, it has the merit of encompassing an

increasing number of recently identified conditions with PxD as a feature that would escape the current classification. On the other hand, the phenotypic and genetic heterogeneity of PxD highlighted here might render the test of candidate genes, based on a specific clinical syndrome, unsuccessful. In this context, it might be argued that next-generation sequencing approaches would better apply to the need of a rapid comprehensive genetic screening[54]. This would further reduce costs in comparison to single gene testing[55].

Of course there will be cases where no definitive cause for PxD can be found and treatment is to be pursued empirically. These can be labelled as idiopathic forms while awaiting for further elucidation of genetic or other causes. In turn, our proposal will require updating as soon as novel evidence is available.

Figure caption

Figure 1. Suggested genetic mutations that should be tested for according to clinical presentations

^ = Mimics include epilepsy, tonic spasms, tetany, neuromyotonia, periodic paralyses, and episodic ataxias; #= these might include stress, anxiety, fatigue, fasting, startle and sleep deprivation; § = by history or on examination; - = none/negative; + = present; AD = Autosomal Dominant; E=Epilepsy; M=Migraine; EA= Episodic Ataxia; MR= Mental Retardation; HP=Hemiplegia; A=Ataxia; Au=Autonomic dysfunction; S=Spasticity; MD= non-paroxysmal movement disorders; *including 16p11.2 deletion; $\cong$ = might have a kinesigenic trigger; **should include glucose, lactate, pterins, and dopamine metabolites.

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