

Paroxysmal Movement Disorders

Subjects: [Clinical Neurology](#) | [Pediatrics](#) | [Sport Sciences](#)

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Paroxysmal movement disorders (PMDs) are rare neurological diseases typically manifesting with intermittent attacks of abnormal involuntary movements.

hyperkinetic movement disorders

dyskinesia

ataxia

cerebellum

basal ganglia

therapy

acetazolamide

epilepsy

whole exome sequencing

functional movement disorders

1. Introduction

Paroxysmal movement disorders (PMDs) are rare neurological diseases typically manifesting with intermittent attacks of abnormal involuntary movements^[1]. The term “paroxysmal” indicates a well-defined onset and termination of clinical manifestations.

2. Main Categories

Two main categories of PMDs are recognized based on phenomenology: Paroxysmal dyskinesias (PxDs) are characterized by transient episodes hyperkinetic movement disorders, while attacks of cerebellar dysfunction are the hallmark of episodic ataxias (EAs)^[2]. From an etiological point of view, both primary (genetic) and secondary (acquired) causes of PMDs are recognized. Some aspects of clinical history may help to distinguish primary from secondary PMDs: Most primary forms occur as sporadic or familial cases with autosomal dominant inheritance, and most often onset of manifestations is set in childhood or adolescence (Figure 1), and interictal neurological examination is unremarkable; secondary forms occur sporadically, more usually begin after the second decade of life (Figure 1), and clinical examination is frequently abnormal also outside of attacks.

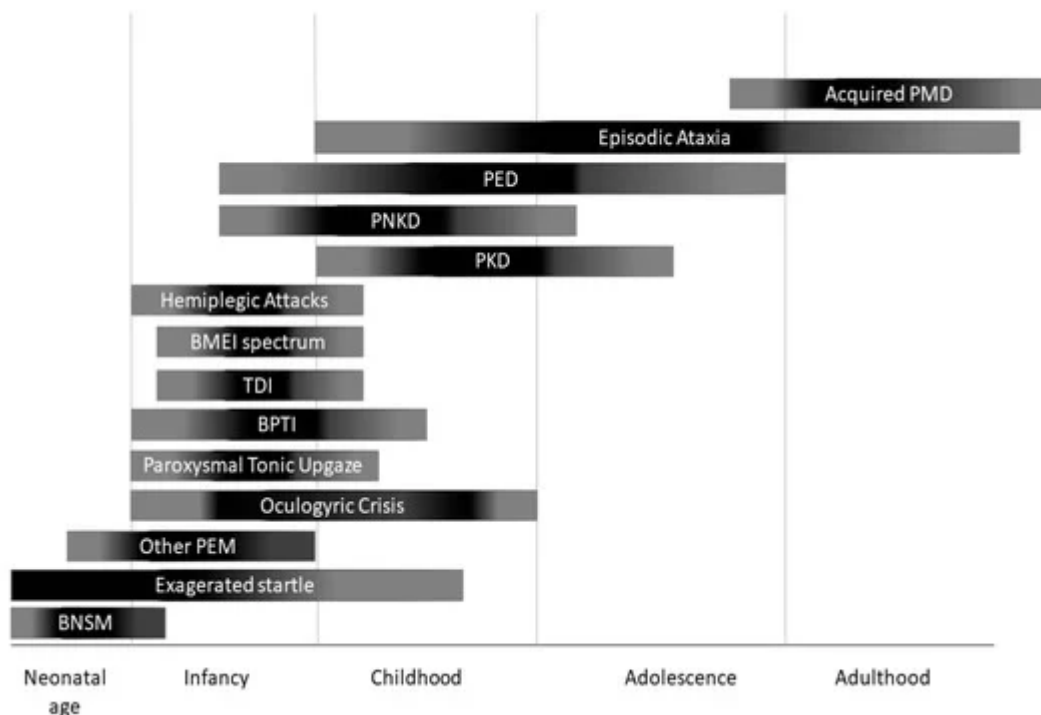


Figure 1. Onset of different paroxysmal movement disorders (PMDs) according with age. BNSM: benign neonatal sleep myoclonus; BMEI: benign myoclonus of early infancy; BPTI: Benign paroxysmal torticollis of infancy; PEM: paroxysmal eye movements; PED: paroxysmal exercise-induced dyskinesia; PKD: paroxysmal kynesigenic dyskinesia; PNKD: paroxysmal non-kynesigenic dyskinesia.

A further category that may manifest as PMDs are functional (psychogenic) movement disorders (FMDs). Patients with FMDs may show tremor, dystonia, myoclonus, parkinsonism, speech and gait disturbances, or other movement disorders whose patterns are usually incongruent with that observed in organic diseases, although sometimes diagnosis may be challenging. Diagnosis of FMDs is based on positive clinical features (e.g., variability, inconsistency, suggestibility, distractibility, and suppressibility) during physical examination and should be considered in presence of some clues such as intra-individual variability of phenomenology, duration and frequency of attacks, and/or precipitation of the disorder by physical or emotional life events. Other supporting information can be helpful (i.e., neurophysiologic and imaging studies)^[3].

3. Recognition and Diagnosis

Recognition and diagnosis of PMDs are based on personal and familial medical history, physical examination, detailed reconstruction of ictal phenomenology (possibly including video-recording of at least one attack), brain magnetic resonance imaging (MRI), and genetic analysis. Neurophysiological (i.e., standard electroencephalogram or long-term monitoring) or laboratory tests are reserved for cases in which an epileptic origin of the attack cannot be excluded, or brain MRI reveals alterations that are compatible with genetic-metabolic or secondary causes. Genetic knowledge of PMDs has been largely incremented by the advent of next generation sequencing (NGS) methodologies, which allowed to increase both molecular diagnosis and identification of ultra-rare or new genes.

The wide number of genes involved in the pathogenesis of PMDs (Table 1) reflects a high complexity of molecular bases of neurotransmission in cerebellar and basal ganglia circuits (Figures 2–4). This comprehensive review is focused on clinical and genetic features of PMDs according to current nosology (Table 2). As this review is mainly targeted on genetic causes of PMDs, functional PMDs will not be discussed further.

Table 1. Main genetic causes of paroxysmal movement disorders. A question mark follows treatment options that have been proposed basing on pathophysiological assumptions, are under investigation or have been shown to be beneficial only in single-case reports.

Gene	OMIM	Inheritance	Age at onset	PMDs subtype	Attack duration	Isolated versus combined	Allelic disorders	Other possible features	MRI	Treatment
PRRT2	614386	AD	<18 years	PKD	Very brief (<1 min)	I/C	BFIS, ICCA, FHM, EA		Normal	CBZ (PKD) ACZM (EA)
PNKD	609023	AD	<18 years	PNKD	Long (>1 hour)	I	Migraine (rare), PKD			BDZ (Attacks relief)
SLC2A1 (GLUT-1)	138140	AD	Variable	PED, EA, HA, PEM	Intermediate (5–40 min)	I/C	Classic GLUT1-DS, HSP,	Anaemia, hypotonia, spasticity, seizures, Developmental delay/ID, dystonia, ataxia		Ketogenic diet, triheptanoin
PDH complex (PDHA1/PDHX /DLAT)	300502/608769/608770	AR	Infancy	PED/PNKD	Variable	I/C	Leigh syndrome	Developmental delay/ID, Seizures, progressive dystonia	Pallidal hyperintensities, Callosal agenesis	Ketogenic diet
ECHS1	602292	AR	Infancy	PED	Variable	I/C		Leigh syndrome	From Pallidal hyperintensities	Valine-restricted

										to Leigh-like abnormalities	diet? detoxifying drugs?
HIBCH	610690	AR	Infancy	PED	Variable	I/C	Leigh syndrome	ID, Seizures, progressive dystonia		From Pallidal hyperintensities to Leigh-like abnormalities	Valine-restricted diet? detoxifying drugs?
ATP1A3	182350	AD	Variable	PNKD ([hem]dystonic attacks), HA, PEM	Variable	C	EIEE, AHC, CAPOS, RECA, RDP	Seizures, dysautonomic paroxysms, nonparoxysmal dystonia, ataxia, parkinsonism			Flunarizine (HA prophylaxis), BDZ (HA relief)
ADCY5	600293	AD	Variable	PKD/PNKD/PED/PND	Brief (minutes)	C	PNKD	Axial hypotonia, nonparoxysmal dystonia and chorea			Caffeine?
TBC1D24	613577	AR	Childhood	PED	Variable	C	Deafness, DOORS syndrome, Rolandic Epilepsy, EIEE16, Myoclonic epilepsy	Sizures, Developmental delay/ID, myoclonus, ataxia, extraneurological abnormalities			

SLC16A2 (MCT8)	300095	X linked	<1–2 months	PKD (triggered by passive movements)	Very brief (seconds to minutes)	C			Mental retardation		TRIAC?
SCN8A	600702	AD	Infancy	PKD	Brief	C	Epilepsy		Mental retardation		CBZ, oxcarbazepine
KCNMA1	600150	AD	Childhood	PNKD	Long (>1 hour)	C			epilepsy, developmental delay, progressive HSP, ataxia		
GCH1	600225	AD	<18 years	PED	Variable	I/C	DRD		Non paroxysmal dystonia and parkinsonism		L-DOPA
PDE10A	610652	AR/AD	Childhood	PNKD	NR	C	Chorea without paroxysms		Dystonia, Parkinsonism, marked fluctuations	Striatal hyperintensities (in AD cases)	
KCNA1	176260	AD	Childhood (2–15)	EA1	Minutes	I	EIEE, PKD, EDE (AR)		interictal Myokymia; progressive ataxia (20%), epilepsy (10%)	Normal ore cerebellar atrophy (10%)	CBZ, PHT, ACZM
CACNA1A	601011	AD	Childhood (0–20)	EA2/PTU/BPT	Variable (minutes to days)	I/C	FHM1, SCA6, CA		progressive ataxia, Developmental delay	Normal or cerebellar atrophy	ACZM, 4-APD, LEV

CACNB4	601949	AD	Young-adult onset	EA5	several hours	I	JME, IGE, CND (AR)	Epilepsy, permanent ataxia	Normal	ACZM
SLC1A3 (EAAT1)	600111	AD	infancy or childhood (rarely adulthood)	EA6	several hours	I	Adult-onset progressive ataxia	Seizures (rare) HA	Normal; rarely cerebellar atrophy	ACZM
UBR4	609890	AD	around age 2 years	EA8	minutes to hours	I		nystagmus, myokymia, tremor		Clonazepam
FGF14	601515	AD	late-childhood to early adulthood	EA9	minutes	I/C	SCA27, CA	progressive ataxia, nystagmus, postural upper limb tremor, ID		
BCKD Complex	608348/248611	AR	Variable	EA/PNKD	Minutes to hours	C	Classic MSUD	developmental delay, progressive psychomotor retardation, seizures, ataxia,	T2 hypersignal in in the brainstem, globus pallidus, thalami, and dentate nuclei	BCAA restricted diet
KCNA2	176262	AD	Infancy or childhood	EA	Seconds to hours	C	EIEE32, SCA, PME	Epilepsy		ACZM (variable)
SCN2A	182390	AD	infancy or childhood	EA	minutes to days	C	EIEE11, BFIS3	Seizures +/- encephalopathy, developmental delay/ID	Normal or cerebellar atrophy	ACZM (variable)

4-APD: 4-aminopyridine; ACZM: acetazolamide; AHC: alternating hemiplegia of childhood; AR: autosomic recessive; AD autosomic dominant; BDZ: benzodiazepines; BFIS: benign familial infantile seizures; BPTI: Benign paroxysmal torticollis of infancy; C. Combined; CA: congenital ataxia; CAPOS: cerebellar ataxia, pes cavus, optic atrophy, sensorineural hearing loss; CBZ: carbamazepine; CND: complex neurodevelopmental disorder; DOORS: deafness, onychodystrophy, osteodystrophy, mental retardation, and seizures; DRD: Dopa-Responsive Dystonia EA: episodic ataxia; EDE: epileptic dyskinetic encephalopathy; EIEE: early infantile epileptic encephalopathy; FHM: familiar hemiplegic migraine; HA: hemiplegic attacks; I: Isolated; ID: Intellectual disability; JME: juvenile myoclonic epilepsy; LEV: levetiracetam; MSUD: maple syrup urine disease; PED: paroxysmal exercise-induced dyskinesia; PEM: paroxysmal eye movements; PHT: phenytoin; PKD: paroxysmal kynesigenic dyskinesia; PNKD: paroxysmal non-kynesigenic dyskinesia; PME: progressive myoclonic epilepsy; PTU: paroxysmal tonic upgaze, RECA: recurrent encephalopathy with cerebellar ataxia; RDP: rapid onset dystonia-parkinsonism; SCA: spinocerebellar ataxia; VPA: Valproic Acid.

References

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