Paroxysmal Movement Disorders

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

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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.

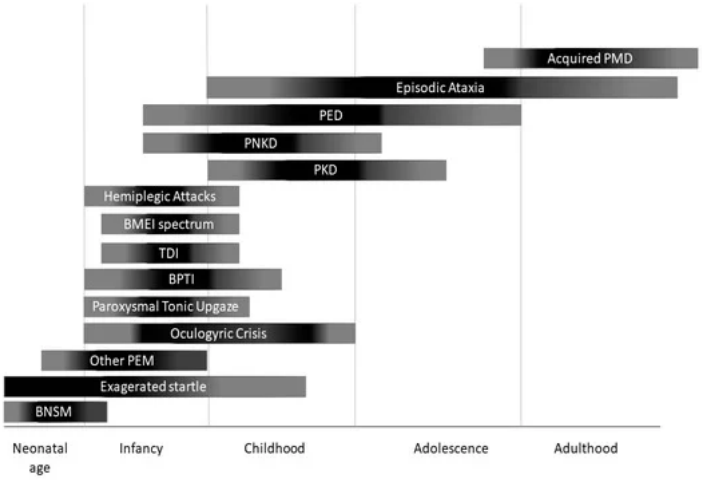

Figure 1. Onset of different paroxysmal movement disorders (PMDs) according with age. BNSM: benign neonatal sleep myoclonus; BMEI: benign myoclonus of early infancy; BPTI: Benign paroxysmal torticollis of infancy; PEM: paroxysmal eye movements; PED: paroxysmal exercise-induced dyskinesia; PKD: paroxysmal 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
PRRT2	**614386**	AD	<18 years	PKD	Very brief (<1 min)	I/C	BFIS, ICCA, FHM, EA
PNKD	**609023**	AD	<18 years	PNKD	Long (>1 hour)	I	Migraine (rare), PKI
SLC2A1 (GLUT-1)	**138140**	AD	Variable	PED, EA, HA, PEM	Intermediate (5–40 min)	I/C	Classic GLUT1-DS HSP,
PDH complex (PDHA1/PDHX /DLAT)	**300502/608769/608770**	AR	Infancy	PED/PNKD	Variable	I/C	Leigh syndrome
ECHS1	**602292**	AR	Infancy	PED	Variable	I/C	
HIBCH	**610690**	AR	Infancy	PED	Variable	I/C	Leigh syndrome

ATP1A3	**182350**	AD	Variable	PNKD ([hemi]dystonic attacks), HA, PEM	Variable	C	EIEE, AHC CAPOS, RECA, RDP
ADCY5	**600293**	AD	Variable	PKD/PNKD/PED/PND	Brief (minutes)	C	PNKD
TBC1D24	**613577**	AR	Childhood	PED	Variable	C	Deafness, DOORS syndrome Rolandic Epilepsy, EIEE16, Myoclonic epilepsy
SLC16A2 (MCT8)	**300095**	X linked	<1–2 months	PKD (triggered by passive movements)	Very brief (seconds to minutes)	C	
SCN8A	**600702**	AD	Infancy	PKD	Brief	C	Epilepsy
KCNMA1	**600150**	AD	Childhood	PNKD	Long (>1 hour)	C	
GCH1	**600225**	AD	<18 years	PED	Variable	I/C	DRD
PDE10A	**610652**	AR/AD	Childhood	PNKD	NR	C	Chorea without paroxysms
KCNA1	**176260**	AD	Childhood (2–15)	EA1	Minutes	I	EIEE, PKD EDE (AR)

CACNA1A	**601011**	AD	Childhood (0–20)	EA2/PTU/BPT	Variable (minutes to days)	I/C	FHM1, SCA6, CA
CACNB4	**601949**	AD	Young-adult onset	EA5	several hours	I	JME, IGE, CND (AR)
SLC1A3 (EAAT1)	**600111**	AD	infancy or childhood (rarely adulthood)	EA6	several hours	I	Adult-onse progressiv ataxia
UBR4	**609890**	AD	around age 2 years	EA8	minutes to hours	I	
FGF14	**601515**	AD	late-childhood to early adulthood	EA9	minutes	I/C	SCA27, C
BCKD Complex	**608348/248611**	AR	Variable	EA/PNKD	Minutes to hours	C	Classic MSUD
KCNA2	**176262**	AD	Infancy or childhood	EA	Seconds to hours	C	EIEE32, SCA, PME
SCN2A	**182390**	AD	infancy or childhood	EA	minutes to days	C	EIEE11, BFIS3

4-APD: 4-amynopiridine; 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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