Paroxysmal Movement Disorders

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Paroxysmal Movement Disorders

- Paroxysmal Dyskinesias - Primary and Secondary
- Episodic Ataxias
- Alternating Hemiplegia of Childhood
- Paroxysmal Tremor
- Paroxysmal Torticollis of Infancy
Paroxysmal Dyskinesias

• What is not considered to be a Paroxysmal Dyskinesia?
  • Action/Task Specific Dystonia
  • Tics - can occur in bursts
  • Paroxysmal Exaggeration of Tremor
  • Action Myoclonus

Paroxysmal Dyskinesias

• Heterogeneous – clinically and genetically
• Characterized by the abrupt onset of abnormal involuntary movements usually out of a background of normal motor behavior
• A combination of chorea, ballism, and dystonia
Paroxysmal Dyskinesias

- Four groups
- Idiopathic (primary) or secondary
- Familial or sporadic
- Overlap

- Abnormal involuntary movements
- Paroxysmal
- Between episodes, generally normal

History

- Paroxysmal choreoathetosis (1940)
  - Mount and Reback described a 23-year-old man
  - Episodes of “choreo-dystonia” that could last several hours
  - Autosomal dominance, with > 20 family members affected

- Additional families described – including with dystonia → Paroxysmal dystonic choreoathetosis (PDC)

- Paroxysmal kinesigenic choreoathetosis (PKC) (1967)
  - Kertesz described attacks induced by sudden movement
  - Different from PDC, very brief attacks, responded well to AEDs

- Paroxysmal exercise-induced dyskinesia (PED) (1977)
  - Lance described “intermediate” type, attack duration > PKC but < PDC

- Proposed PKD and PNKD by Demirkiran and Jankovic (1995)
First case

- First reported 1892 by Shuzo Kure, Japanese psychiatrist (1965-1932)
- 23-year old Japanese man
- Symptom onset age 10
- Frequent movement-induced paroxysmal attacks
- Attacks consisted of peculiar, purposeless, irregular involuntary movements, with a very short duration
- Triggered by sudden movement, and initiated from the legs sometimes spreading to the body with right-side dominance
- Preceded by an odd sensation, a kind of sensory aura
- Patient had learned how to inhibit or stunt the attacks, by means of swinging his legs and imaging the next movement in his mind prior to walking and/or standing up
- Never lost consciousness, and abnormal neurological signs were totally absent
- Referred to as atypical Thomsen's disease (Myotonia congenital)

Kato et al., 2006

Paroxysmal kinesigenic dyskinesia (PKD)
Paroxysmal Kinesigenic Dyskinesia

- Most common of paroxysmal movement disorders
- Onset usually in childhood (7-15 years)
- Precipitated by sudden voluntary movement or startle, and sometimes by stress
- Multiple attacks, frequency up to 100 per day
- Attacks are brief, seconds
- Sensory aura (70%) and a refractory period
- Asymmetric dystonia
- Common while others may have chorea, ballism, or a combination
- About 30% experience speech disturbance (dysarthria or anarthria) with face involvement

Bhatia 2011; Gardiner et al., 2015; Harvey et al., 2021

PKD-Proposed Criteria

- Identified kinesigenic trigger for the attacks
- Short duration of attacks (<1 minute)
- No loss of consciousness or pain during attacks
- Exclusion of other organic diseases and normal neurologic examination
- Control of attacks with phenytoin or carbamazepine, if tried
- Age at onset between 1 and 20 years, if no family history of PKD

Bruno et al. 2004
Genetics of PKD
The RICH Area on Chromosome 16

Proline Rich Transmembrane Protein 2 (PRRT2)
Location of 23 mutations in PKD

- > 75% have the same frameshift variant c.649dupC (p.Arg217ProfsTer8) resulting in a premature stop codon and haploinsufficiency
- Missense variants also tend to localize to transmembrane and loop domains of the C-terminal, and for these, are consistent with a loss-of-function mechanism in PRRT2-associated diseases.

Wang et al., Brain 2011; Ebrahimi-Fakhari et al., Brain 2015; Zhao et al., 2020
PRRT2 Function

Valente et al., Enrico Castroflorio, Pia Rossi, ..., Pietro Baldelli, Anna Corradi, Fabio Benfenati

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In Brief
Valente et al. show that PRRT2, a single causative gene for a group of paroxysmal neurological diseases, is a key component of regulated exocytosis. Silencing PRRT2 dramatically impairs neurotransmitter release by markedly reducing release probability. PRRT2 interacts with the fast Ca^{2+} sensors synaptotagmin 1/2 and endows the SNARE complex with Ca^{2+} sensitivity.

Valente et al., Cell Reports 2016; Liao et al., 2021; Harvey et al., 2021

Phenotypic Heterogeneity in PRRT2 Mutations

- Paroxysmal Kinesigenic Dyskinesia
- Benign Familial Infantile Convulsions
- ICCA Syndrome
- Febrile Infantile Convulsions
- Nocturnal Convulsions
- Classic Migraine with PKD
- Hemiplegic Migraine
- Episodic Ataxia
- Paroxysmal Nonkinesigenic Dyskinesia
- Paroxysmal Exertional Dyskinesia

Liu et al., J Med Genetics 2011; Gurreni and Mink et al., Neurol 2012
Neural mechanisms of PKD

- Disruption of structural and/or functional properties in basal ganglia-thalamo-cortical circuitry and interhemispheric functional connectivity

PKD Treatments

- Attacks usually respond well to anticonvulsants
  - Carbamazepine (86% response, Bruno et al., 2004)
  - Phenytoin
  - Acetazolamide
  - Others – topirimate, barbituates
Paroxysmal non-kinesigenic dyskinesia (PNKD)

- Onset in infancy or childhood
- Precipitating factors - alcohol, fatigue, caffeine, strong emotion
- Duration minutes to hours (e.g., 10 min-1 hour, up to 4 hours)
- Predominant dystonia in some, and some have chorea, or a combination (80%)
- May have premonitory symptoms (40-80%, e.g., sensation of tightness)
- Frequency 3/day to 2/year.
- Inconsistently reported M>F ratio (1-2:1)
- Normal neurological examination between attacks
- Responsive to clonazepam and BZDs

Bruno et al., 2007; Bhatia 2011; Gardiner et al., 2015
Genotype–phenotype correlation of paroxysmal nonkinesigenic dyskinesia

**ABSTRACT** Background: Paroxysmal nonkinesigenic dyskinesia (PNKD) is a rare disorder characterized by episodic hypokinetic movement attacks. We have recently identified mutations in the MR-1 gene causing families’ PNKD. Methods: We reviewed the clinical features of 14 kindreds with familial dyskinesia that was not clearly induced by movement or during sleep. Of these 14 kindreds, 8 had MR-1 mutations and 6 did not. Results: Patients with PNKD with MR-1 mutations had their attack onset in youth (infancy to early childhood). Typical attacks consisted of a mixture of chorea and dystonia in the limbs, face, and trunk, and typical attack duration lasted from 10 minutes to 1 hour. Coffein, alcohol, and emotional stress were prominent precipitants. Attacks had a favorable response to benzodiazepines, such as clonazepam and diazepam. Attacks in families without MR-1 mutations were more variable in their age at onset, precipitants, clinical features, and response to medications. Several were reduced by persistent exercise. Conclusions: Paroxysmal nonkinesigenic dyskinesia (PNKD) should be strictly defined based on age at onset and ability to precipitate attacks with caffeine and alcohol. Patients with this clinical presentation (which is similar to the phenotype initially reported by Mount and Debats) are likely to harbor myofibrillogenesis regulator 1 (MR-1) gene mutations. Other “PNKD-like” families exist, but clinical features suggest that these subjects are clinically distinct from PNKD and do not have MR-1 mutations. Some may represent paroxysmal autonomic dyskinesia. 

**Key Points**
- MR-1 mutations (8/14 kindreds described by Bruno et al.; 98% penetrance)
- PNKD phenotype in MR-1 mutations
- Those without the MR-1 mutations with more variable presentations (e.g. onset age, precipitants, features, response to medications)

**PNKD - Genetics**

- Mutations in the myofibrillogenesis regulator gene (MR-1) on chromosome 2q35
- Substitution of alanine to valine (Lee, 2004)
- MR isoforms
  - MR-1L – exclusively expressed in cell membrane of brain
  - MR-1S – ubiquitously expressed, diffuse cytoplasmic and nuclear localization
- MR-1 gene encodes at least 3 alternatively spliced proteins

Rainier et al., Arch Neurol 2004
MR-1 gene product is homologous to HAGH which detoxifies methylglyoxal present in coffee and alcohol and is an oxidative stress product.

![Diagram](image)

**Figure 6.** The glyoxylase system comprises two enzymes, glyoxylase I (GLO1, lactoylglutathione lyase) and glyoxylase II (GLO2, hydroxyacylglutathione hydrolase, HAGH). Methylglyoxal and glutathione non-enzymatically form a hemithioacetal intermediate and then glyoxylase I catalyzes formation of S-3-hydroxyglutathione. HAGH catalyzes the hydrolysis of S-3-hydroxyglutathione to 3-hydroxyglutathione (GSH).

### PNKD - Genetics

- Later onset PNKD like patients may not have the MR-1 gene mutation
- Some reported PNKD families lack this mutation (Spacey, 2006)
- Another locus for PNKD and generalized epilepsy on chromosome 10q22 – a calcium sensitive K channelopathy (Nature Genetics, 2005)
PNKD Treatments

• Attacks – limited response to anticonvulsants (contrast to PKD)
• Avoid triggers, e.g., caffeine, alcohol, or stress
• Clonazepam
  • 49 MR-1 carriers, 97% favorable response to BZD
• Other agents tried
  • Haloperidol, gabapentin, acetazolamide, levodopa
• Attack frequency may decrease with age

Bhatia et al., 2011; Bruno et al., 2007
Paroxysmal Exercise-Induced Dyskinesia

- Usually dominant, though sporadic cases reported
- Overlap between PNKD and PED, or “intermediate” form
- Onset in childhood (5 years, range 2-30 years)
- Precipitated by prolonged or sustained exercise
- Most common presentation is dystonia (e.g., feet, hemidystonia)
- Attacks last between 2-5 min (up to 2 hours), stop within 10 min after stopping exercise
- Frequency varies
- M:F or 2:3

A few caveats - Paroxysmal Exercise Dyskinesias

- Dopa-responsive dystonia
- May have PED
- Report of family with PED
- Autosomal dominant
- Childhood onset
- Some family members also with RLS or parkinsonism
- Mutation in GTP-cyclohydrolase 1 (GCH-1) gene, nonsense mutation in exon 1
- Low CSF neurotransmitters
- PED and RLS improved with levodopa

Paroxysmal Exercise-Induced Dystonia as a Presenting Feature of Young-Onset Parkinson’s Disease

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Abstract: Paroxysmal exercise-induced dystonia (PED) is a rare, typically idiopathic familial condition, although sporadic and secondary cases have been reported. We present 2 cases where PED was the presenting feature of young-onset idiopathic Parkinson’s disease (PD), preceding the onset of parkinsonian symptoms by 1.5 and 5 years, respectively. Initially, the dystonic symptoms occurred after prolonged exercise and were unilateral, affecting the foot in both patients. Over time, symptoms occurred with minimal exercise. We conclude that PED can rarely be the first and only feature of PD. © 2003 Movement Disorder Society

Bozi and Bhatia 2003; Dale et al., 2010; Erro et al., 2014
GLUT 1 deficiency syndrome

• Expanding phenotype
  • Classical (De Vivo 1991) - majority of cases, usually de novo
    • Developmental delay, seizures, acquired microcephaly, variable ataxia/spasticity/dystonia
  • New phenotypes emerging - milder, adult onset, often familial
    • Infancy onset MD without seizures
    • Familial PED and epilepsy (+/- haemolytic anaemia), sporadic PED
    • Carbohydrate responsive phenotypes
    • PED, Writer’s cramp, migraine and absence seizures
    • Absence seizures

• DYT 9 – paroxysmal choreoathetosis/spasticity, with episodic ataxia (Auburger et al., 1996) + these twins
  • Realignment with DYT 18 (GLUT1-DS due to SLC2A1 mutations)

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Table 2  Clinical spectrum of GLUT1 deficiency syndrome

| Epilepsy | Movement disorders | Cognitive/behavioral disturbances | Other neurological symptoms | Non-neurologic features |
|----------|--------------------|----------------------------------|-----------------------------|-------------------------|
| Early-onset absence epilepsy (EOAE) | PED | Developmental delay | Spasticity | Hemolytic anaemia |
| | PNKD | Cognitive impairment of variable severity | Alternating hemi/quadriplegia | Hepato-splenomegaly |
| Childhood-absence epilepsy (CAE) | PKD | Intellectual disability | Hypotonia | Cataracts |
| | | | Abnormal eye movements | Microcephaly |
| Epilepsy with myoclonic-atonic seizures (Doose syndrome) | Intermittent ataxia | Language delay | Migraine headaches |
| Focal epilepsy | Chorea | Dysphoria | Cyclic vomiting |
| Febrile seizures | Dystonia | Inconsolable crying | Sleep disturbance |
| | Parkinsonism | | |
| | Myoclonus | | |
| | Oculogyric crises | | |

Liao et al., 2021
PED - Genetics

- SLC2A1 gene, GLUT1 mutations (glucose transporter type), located 1p35-p31.3
- Encodes glucose transporter into erythrocytes and across BBB
  - CSF glucose levels – low or lower limit normal
- Mutations – de novo, AD, but AR also reported
- Missense mutations – milder symptoms
- However, SLC2A1 mutations only < 30% of PED

Pathophysiology - PED

- EEG recordings typical normal
- Neurophysiological studies – suggestive of hyperexcitability at muscular and brain membrane levels
- Cortical excitability and inhibitory neuronal mechanisms normal (inter-ictal)
- SPECT during motor attacks
  - Reduced perfusion of frontal cortex and basal ganglia
  - Increased perfusion of cerebellum

Weber et al., J Clin Invest 2008; Harvey et al., 2021; Liao et al., 2021
Bhatia et al., 2011; Margari et al., 2000
PED Treatments

• Attacks – limited response to anticonvulsants (contrast to PKD)
  • Gabapentin – may reduce frequency and severity of attacks
• Other agents tried (? Benefit)
  • Levodopa, trihexiphendyl, acetazolamide, pallidotomy

• Caution/restrict exercise

• GLUT-1 cases, ketogenic diet for PED and epilepsy (Weber et al., 2008)

ECHS1 Mutations and PED

Olgiati et al., Mov Dis 2016
Paroxysmal hypnogenic dyskinesia (PHD)

- First description by Joynt and Green in a patient with multiple sclerosis
- Attacks occur during Non-REM sleep
- Dystonic posturing, ballistic or choreic movements, without ictal EEG abnormalities
- Many attacks < 1 min, can be indistinguishable from frontal lobe epilepsy
  - Epilepsy vs. movement disorder?
- However, ADCY5 and PRRT2 can present with PHD
- ADCY5 mutation carriers may have predominantly night time attacks and some individuals with mixed PKD and PNKD may have nighttime attacks

Meierkord et al., 1992; Provini et al., 200; Friedman et al., 2016; Liu et al., 2016
• ADCYS mutations – range of complex movement disorders and neurodevelopmental phenotypes
• Adenylyl cyclases – involved in conversion of ATP to cAMP
• ADCYS – highly expressed in brain and myocardium
  • Brain – striatum, nucleus accumbens, and olfactory tubercle

• Clinical manifestations
  • Early childhood
  • Dystonia, chorea, and/or myoclonus.
  • Paroxysmal, but may progress to more continuous movements
  • Exacerbations last min to hours/days
  • Triggers – anxiety, excitement, illness, caffeine
  • Nocturnal dyskinesia. Stage 2 and REM sleep. Sleep associated movements (and in wake periods), lower sleep efficiencies on PSG

• Treatment - challenging
  • Reports - clonazepam, clobazam, methylphenidate, istradefylline, DBS

Ferrini et al., 2021; Liao et al., 2021; Meneret et al., 2019; Miyamoto et al., 2020; Pringsheim et al., 2021

Diagnostic approach

Liao et al., 2021
Secondary Paroxysmal Dyskinesias

- Multiple sclerosis
- Cerebral Palsy
- Hypoparathyroidism and pseudohypoparathyroidism
- Hypoglycemia
- Head trauma
- Cerebrovascular disease
- Neuroacanthocytosis
- Functional (psychogenic)
Miscellaneous causes of secondary paroxysmal dyskinesia

- Cytomegalovirus Encephalitis
- Neurosarcoidosis
- Migraine
- Cervical Cord lesions
- Primary CNS Lymphoma
- Kernicterus
- Hypoglycemia
- Urea Cycle defects and aminoacidurias

Secondary paroxysmal dyskinesia - Multiple Sclerosis

- Known as tonic seizures
- Presenting feature in some
- Unilateral, bilateral attacks described more in the Japanese
- Hyperventilation precipitates the attack
- Painful

Courtesy Dr. Kapil Sethi
Secondary Paroxysmal Dyskinesia - Vascular

- Paroxysmal dyskinesia as a manifestation of TIA’s
- Limb shaking TIA well described in the literature
- These attacks may herald a major infarction
- A variant is orthostatic paroxysmal dystonia in severe bilateral large vessel disease

Metabolic Disorders

- PNKD in hypoparathyroidism
- PNKD and PKD in pseudohypoparathyroidism (Dure, 1998)
- May respond to Vitamin D and Calcium
Faciobrachial dystonic seizures (FBDS)

- Late-onset, frequent and brief (often<5 secs)
- Involve upper limb, face and are dystonic in nature
- VGKC-complex antibodies and/or LGI1-antibody
- Hyponatremia (SIADH)
- Skin rash with anticonvulsants
- May respond to immunotherapy

Sandifer syndrome

- Paroxysmal spasms of head, neck, and back arching, spares limbs
- Associated with GERD in children
  - Also reported in adults
- Due to the abnormal posturing, parents may describe the dystonic episodes as possible seizures
- Often seen by multiple specialists prior to diagnosis
- Ddx for nonepileptic paroxysmal dystonic events
- Treat GERD

Patel and Tas 2021; Somjit et al., 2004
Summary

• Paroxysmal dyskinesias
• Heterogeneous group of disorders
• Idiopathic/primary vs. secondary
• PKD, PNKD, PED, and PHD
• Multiple other causes
• High index of suspicion, careful history, genetics

Thank you for your attention!

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