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)

Bhatia 2011
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

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
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

Pierlugi Valente, Enrico Castrovillio, 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

Bhatia et al., 2011; Sethi et al., 2021
Paroxysmal Nonkinesigenic Dyskinesia

- 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
• 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.

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 (PED)
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
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**

<table>
<thead>
<tr>
<th>Epilepsy</th>
<th>Movement disorders</th>
<th>Cognitive/behavioral disturbances</th>
<th>Other neurological symptoms</th>
<th>Non-neurologic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early-onset absence epilepsy (EOAE)</td>
<td>PED, PNKD, PKD</td>
<td>Developmental delay</td>
<td>Spasticity</td>
<td>Hemolytic anaemia</td>
</tr>
<tr>
<td>Childhood-absence epilepsy (CAE)</td>
<td>PED</td>
<td>Cognitive impairment of variable severity</td>
<td>Alternating hemi/quadruplegia</td>
<td>Hepato-splenomegaly</td>
</tr>
<tr>
<td>Epilepsy with myoclonic-atonic seizures (Doose syndrome)</td>
<td>Episodic choreoathetosis and progressive spastic paraparesis</td>
<td>Intellectual disability</td>
<td>Hypotonia</td>
<td>Cataracts</td>
</tr>
<tr>
<td>Focal epilepsy</td>
<td>Intermittent ataxia Chorea</td>
<td>Language delay</td>
<td>Abnormal eye movements</td>
<td>Microcephaly</td>
</tr>
<tr>
<td>Febrile seizures</td>
<td>Intermittent ataxia</td>
<td>Dysphoria</td>
<td>Migraine headaches</td>
<td></td>
</tr>
</tbody>
</table>

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, trihexiphenidyl, acetazolamide, pallidotomy
- Caution/restrict exercise
- GLUT-1 cases, ketogenic diet for PED and epilepsy (Weber et al., 2008)

ECHS1 Mutations and PED

ECHS1 Mutations, Dystonia, 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

Diagnostic approach

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