The Paroxysmal Dyskinesias

A heterogeneous and rare group of disorders characterised by recurrent brief episodes of abnormal involuntary movements

(*Interictally the patient is usually normal*)

Movements may be chorea, ballism, dystonia, or a combination

Diagnosis is often missed
Paroxysmal Dyskinesias - Historical Aspects

• Gowers (1885) - called it epilepsy!
• Mount and Reback (1940) - first clear description
  23 yr/male with an AD inherited condition, attacks of choreo-
  athetosis lasting 5 mins to hours, provoked by alcohol, coffee,
  tea, fatigue and smoking
• “Paroxysmal dystonic choreoathetosis” (PDC)
• Other similar families - (Forsmann 1961, Lance 1963, Richard and
Paroxysmal dyskinesias - Historical aspects

• Kertesz (1967) – new term

(Paroxysmal “kinesigenic” choreoathetosis: An entity within the paroxysmal choreo-athetosis syndrome. Description of 10 cases including 1 autopsied)

• Attacks were induced by sudden movement (i.e. kinesigenic) and were very brief

• Response to antiepileptics
Paroxysmal Dyskinesias - Historical Aspects

• Lance 1977 - a new form of paroxysmal dyskinesia in a family
• Affected members had attacks of dystonia lasting 5-30 minutes provoked by prolonged exercise (not sudden movement)
• Paroxysmal exercise-induced dystonia (PED)
Paroxysmal Dyskinesias- Classification

Lance (1977)- “the time factor”

- **PKC**-sudden, brief (secs-5mins), movement induced attacks responding to antiepileptics
- **PED** *(intermediate type)*-attacks (5-30 mins) induced by prolonged exercise
- **PDC**- long duration attacks (upto 6 hrs) induced by coffee, tea, alcohol, fatigue
The Paroxysmal Dyskinesias- Classification

Demekirin & Jankovic (1995), “the phenomenology”

Modified classification

• Dyskinesias instead of choreo athetosis
• Kinesigenic (PKD) or non-kinesigenic (PNKD)
• Short (less than 5 mins) or long
• Idiopathic (usually familial) or secondary
Secondary Paroxysmal Dyskinesias

Variety of Causes

- Multiple sclerosis (tonic spasms, other)
- Stroke
- Metabolic /Endocrine disorders
  - Thyroid/Parathyroid
- Basal ganglia lesions
  - Trauma
  - Infections/ HIV, etc.
- Sandiffer’s syndrome in children
- Psychogenic
The Paroxysmal Dyskinesias

The main types of *idiopathic* paroxysmal dyskinesias

- Paroxysmal kinesigenic dyskinesias (PKC/PKD)
- Paroxysmal exercise-induced dyskinesia (PED)
- Paroxysmal non-kinesigenic dyskinesias (PDC/PNKD)
- Hypnogenic paroxysmal dyskinesia (HPD)

Other (in children often transient)
- Benign Paroxysmal Torticollis of infancy
- Shuddering attacks
- Unclassifiable
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Kailash P. Bhatia
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Paroxysmal kinesigenic choreoathetosis: a report of 26 patients

Received: 9 December 1997
Received in revised form: 16 June 1998
Accepted: 24 June 1998

Abstract Paroxysmal kinesigenic choreoathetosis (PKC) is a neurological condition which results in abnormal involuntary movements that are precipitated by sudden movement. Because of its rarity, large case series of PKC have not been published. We studied 26 patients with PKC, which represents the largest series thus reported. We reviewed our cases with respect to attack characteristics, aetiology, family history, and treatment response. Our population consisted of 23 men and 3 women. Seven patients had a family history of paroxysmal dyskinesia. None of our patients had clear evidence of symptomatic PKC. Two-thirds of our patients had attacks lasting between 30–60 s, and over one-half experienced one to ten attacks per day. Attack distribution varied widely, and most experienced pure dystonia rather than choreodystonic movements. Most patients responded very well to anticonvulsant therapy. We also report the PET results from two of our patients and Bereitschaftspotential abnormalities recorded from two others.

Keywords Paroxysmal - Dyskinesia - Choreoathetosis - Movement disorder - Dystonia

J Neurol, 1999
PKC study results (Houser et al, 1999)

- Clear male predilection (23 M: 3 F)
- Young onset [mean age 13.8 yrs (range 1-39)]
- 27% positive family history usually autosomal dominant,

**Attack description**

- Aura in 70%
- 57% mainly dystonic movements
- Attacks unilateral/hemidystonia in 70% of cases
- Attacks rarely could generalise
PKC attacks – duration, frequency and precipitants in 26 patients

<table>
<thead>
<tr>
<th>Duration</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Up to 10 s</td>
<td>5</td>
<td>19.2</td>
</tr>
<tr>
<td>10–30 s</td>
<td>10</td>
<td>38.5</td>
</tr>
<tr>
<td>30–60 s</td>
<td>7</td>
<td>26.9</td>
</tr>
<tr>
<td>60–120 s</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Over 120 s</td>
<td>3</td>
<td>11.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1/week</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>1/week to &lt; 1/day</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>1/day to &lt; 10/day</td>
<td>15</td>
<td>57.7</td>
</tr>
<tr>
<td>10/day to &lt; 20/day</td>
<td>7</td>
<td>26.9</td>
</tr>
<tr>
<td>&gt; 20/day</td>
<td>3</td>
<td>11.5</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Precipitating factors</th>
<th>Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden movement</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td>Startle</td>
<td>2</td>
<td>7.2</td>
</tr>
<tr>
<td>Stress</td>
<td>2</td>
<td>7.2</td>
</tr>
<tr>
<td>Exercise</td>
<td>4</td>
<td>15.3</td>
</tr>
<tr>
<td>At rest</td>
<td>4</td>
<td>15.3</td>
</tr>
<tr>
<td>During sleep</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Intention to move</td>
<td>1</td>
<td>3.8</td>
</tr>
</tbody>
</table>

Houser et al, 1999
PKC study - (Houser et al, 1999)

• All imaging normal
• 7/9 EEG’s normal
• Normal telemetry in 4 cases
• Normal inter-ictal 18FDG PET scans
• 2/2 abnormal pre-movement potential
PKC study - (Houser et al, 1999)

Treatment response:
- 79% responded to carbamazepine
- 6/26 with phenytoin- good response in 3 (50%)
- Other anticonvulsants –poor response

Follow-up:
- Attacks tended to wane with age
  (50% cases attack free 10 years after onset)
PKC/PKD-snapshot

• Sporadic or familial (autosomal dominant)
• Male : F= 5:1
• Provoked (by definition) by sudden movement or startle
• Short lasting (< 5 min) and frequent attacks (10-100/day)
• Attacks decrease with age
• Respond to anticonvulsants- CBZ best
Association of epilepsy with PKC/PKD

- Familial infantile convulsions and choreoathetosis (ICCA) syndrome (Szepetowski et al, 1997, Lee et al, 1998)
- Linkage to pericentromeric region of chromosome 16p
- Benign infantile convulsions
- Later onset of paroxysmal dyskinesia
Paroxysmal exercise-induced dyskinesia/dystonia (PED)

• Rare, *Lance* (1977) - first description,
• Other families (*Plant et al, 1984, Munchau et al, 2000*)
• Initial cases all familial, autosomal dominant
• Sporadic cases: *Demerkirin & Jankovic, 1995 - 5 cases, Bhatia et al, 1997 - 8 cases*
• Precipitants- Prolonged exercise (walking, swimming,) chewing gum, passive movements, vibration (*Plant et al, 1984*), cold exposure (*Wali, 1992*)
Paroxysmal exercise-induced dystonia

Differentiate from

- PKC/PKD
- Action dystonia
- Dopa-responsive dystonia (DRD)
- Rarely young onset PD may present with PED (Bozi and Bhatia 2003)
Total of about 20 cases (5 familial, 15 sporadic)

- **Duration** - 5-30 minutes
- **Distribution** -
  - feet most common (15/20) (2 generalised)
  - hemidystonic next most common
- **Rx response** - no particular drug helps,
  - Antiepileptics - (2/15), Levodopa - (1/5),
  - Acetazolamide - 1, Anticholinergics - 1
Paroxysmal non-kinesigenic dyskinesia (PDC/PNKD)

- Childhood onset,
- Attack frequency diminishes with age
- Males > Females
- Mostly familial - autosomal dominant
- Sporadic cases occur
- Also symptomatic cases (like PKC)
PDC/PNKD attacks

- Aura
- Mixed MD- dystonia, chorea, ballism
- Hemi or generalised
- Speech can be affected
- 1-3/ day, Attack free intervals
- Usually long duration of attacks
- Precipitants- coffee, tea alcohol, fatigue
- Sleep benefit
PDC /PNKD treatment

- No specific drug
- Anticonvulsants help rarely- clonazepam best
- Other drugs
  - Levodopa*  
  - Neuroleptics! 
  - Anticholinergics  
  - Acetazolamide  
- Avoid precipitants
Hypnogenic paroxysmal dyskinesia (HPD)

- Rare
- Brief nocturnal attacks of involuntary movements
- Dystonia/chorea/ballismus
- Several attacks each night
- Sporadic & AD familial cases
- Response to antiepileptics
Hypnogenic paroxysmal dyskinesia

• Initially misdiagnosed as sleep disorder or nocturnal dystonia
• Surface EEG’s often normal
• Mesial frontal epilepsy discharges
• Six families with ADNFLE
• First partial epilepsy disorder due to a single gene inheritance
Fig. 5 Pedigree of Family A. This Australian family was ascertained via the two probands indicated by arrows. Genealogical research later ascertained that they were related and formed part of a large family with 25 affected individuals.
Autosomal dominant nocturnal frontal lobe epilepsy
A distinctive clinical disorder

Ingrid E. Scheffer,1, 2 Kailash P. Bhatia,3 Iscia Lopes-Cendes,4 David R. Fish,5 C. David Marsden,5
Eva Andermann,6 Frederick Andermann,6 Richard Desbiens,7 Daniel Keene,7 Fernando Cendes,6
James I. Manson,3 Jules E. C. Constantinou,4 Anne McIntosh1 and Samuel F. Berkovic1, 2

Brain, 1995
Table 3  Features of autosomal dominant nocturnal frontal lobe epilepsy

<table>
<thead>
<tr>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Childhood onset</td>
</tr>
<tr>
<td>Persistence through adult life</td>
</tr>
<tr>
<td>Clusters of seizures occurring in sleep</td>
</tr>
<tr>
<td>Partial seizures</td>
</tr>
<tr>
<td>Aura nonspecific</td>
</tr>
<tr>
<td>Vocalization at onset</td>
</tr>
<tr>
<td>Prominent motor features: hyperkinetic, tonic</td>
</tr>
<tr>
<td>Awareness retained</td>
</tr>
<tr>
<td>Occasionally secondarily generalized</td>
</tr>
<tr>
<td>Normal intelligence</td>
</tr>
<tr>
<td>Normal neurological examination</td>
</tr>
<tr>
<td>Interictal EEG usually normal</td>
</tr>
<tr>
<td>Ictal EEG bifrontal discharges in some</td>
</tr>
<tr>
<td>CT and MRI of the brain normal</td>
</tr>
<tr>
<td>Often responsive to carbamazepine monotherapy</td>
</tr>
</tbody>
</table>
The pathophysiology of the paroxysmal dyskinesias

- Unknown
- EEG-normal
- Imaging- normal
- Pathology (autopsy) - 2 cases essentially normal
- Pathology-mutant hamster model- normal
  (Wahnschaffe et al, 1990)
- Basal ganglia disease versus seizure disorder
- Similarities to episodic ataxias
Intermittent neurological disorders due to channelopathies

- Hyperkalemic PP  \(SCNA4\)  17q
  Paramyotonia Congenita
- Hypokalemic periodic paralysis  \(CACNLIA3\)  1q
- Episodic ataxia (EA1)  \(KCNA1\)  12p
- Episodic ataxia (EA2)  \(CACNLIA4\)  19p
- Startle syndrome  \(GLRA-1\)  5q
Ion channels

- Transmembrane proteins
- Determine membrane potential at rest and firing
- Also neurotransmitter release

Classified
- Voltage gated
- Ligand gated

Channelopathies - disorders (genetic or acquired) of ion channels

Permanent ion channel disturbance can cause a paroxysmal neurological disturbance
Figure 1. A schematic diagram of the voltage- and ligand-gated ion channels in the cell membrane
## Central nervous system channelopathies: The episodic ataxias

<table>
<thead>
<tr>
<th></th>
<th><strong>EA-1</strong></th>
<th></th>
<th><strong>EA-2</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td><em>KCNA1</em>, 12p</td>
<td></td>
<td><em>CACLNIA4</em>, 19</td>
</tr>
<tr>
<td>Trigger</td>
<td>startle, exercise</td>
<td></td>
<td>stress, exercise, fatigue</td>
</tr>
<tr>
<td>Duration</td>
<td>secs- minutes</td>
<td></td>
<td>Hours –Days</td>
</tr>
<tr>
<td>Age onset</td>
<td>childhood</td>
<td></td>
<td>Adolescence</td>
</tr>
<tr>
<td>Other features</td>
<td>myokimia, PKC epilepsy</td>
<td>Frequent</td>
<td>Nystagmus, migraine</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>No</td>
<td></td>
<td>cerebellar atrophy</td>
</tr>
<tr>
<td>Treatment</td>
<td>acetazolamide, anticonvulsants</td>
<td>Frequent</td>
<td>acetazolamide</td>
</tr>
</tbody>
</table>
Allelic disorders: 19p13 CACNLA4

- Familial hemiplegic migraine - Missense
- EA2 - Truncation
- Autosomal dominant cerebellar ataxia (SCA6) - CAG triplets
Benign paroxysmal torticollis of infancy

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Abstract

Benign paroxysmal torticollis is an episodic functional disorder of unknown etiology that occurs in the early months of life in healthy individuals. The child’s head tilts to one side for a few hours or days, usually without any associated symptoms. The disorder, which disappears within the first few years of life, is often misinterpreted and the patient pointlessly undergoes numerous tests. We present our series of 22 patients observed at the pediatric neurology outpatients clinic in Padova with a view to refreshing the pediatrician’s memory on this frequent, benign pathology. © 2000 Published by Elsevier Science B.V. All rights reserved.

Keywords: Benign paroxysmal torticollis; Child

• Onset- less than 9 months of age- 95% cases
• Episodes of torticollis with tortipelvis in some
• Duration of attacks – hours to sometimes few days
• 1-2 episodes a day
• Relationship to migraine and kinetosis
Benign paroxysmal torticollis of infancy: four new cases and linkage to CACNA1A mutation.

Giffin NJ, Benton S, Goadsby PJ.

Headache Group, Institute of Neurology, London, UK. n.giffin@ion.ucl.ac.uk

Benign paroxysmal torticollis of infancy (BPTI) is a disorder characterized by recurrent episodes of head tilt secondary to cervical dystonia. Attacks are often accompanied by vomiting, pallor, and ataxia, settling spontaneously within hours or days. Episodes begin within the first 12 months of life and resolve by 5 years. We report four patients with BPTI. Symptoms started from 3 months of age, with head tilting lasting between 10 minutes and 2 months; the shorter episodes were followed by vomiting, apathy, and unsteadiness. Head tilt became less prominent after infancy, replaced by vertigo and eventually by migraine headaches. Two patients came from a kindred with familial hemiplegic migraine linked to CACNA1A mutation. BPTI may be regarded as a migraine aura equivalent. The syndrome poses interesting questions regarding varying phenotypic expression of calcium channelopathies at different stages of development.
Episodic Movement Disorders as Channelopathies

*Kailash P. Bhatia, MD, MRCP, †Robert C. Griggs, MD, and ‡Louis J. Ptacek, MD

Episodic Neurological Disorders

- Episodic Movement Disorders
- Episodic Ataxias
- Epilepsy
- Migraine

Mov Disord 2001
The genetics of the paroxysmal movement disorders
Familial Infantile Convulsions and Paroxysmal Choreoathetosis: A New Neurological Syndrome Linked to the Pericentromeric Region of Human Chromosome 16

Pierre Szepetowski, Jacques Rochette, Patrick Berquin, Charles Piussan, G. Mark Lathrop, and Anthony P. Monaco

1The Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, 2Pédiatrie 1 and Centre de Génétique Clinique, CHU d'Aмиens, and Laboratoire de Génétique Moléculaire Médicale, Faculté de Médecine, Université Jules Verne, Amiens, France

“The ICCA syndrome”
Indian family with PKC - courtesy Dr Wali
PKC/PKD – links to chromosome 16p

- Japanese PKC families mapped to chromosome 16p11.2-q12.1 (Tomita et al, 1999)
- African-American family (Bennett et al, 2000)
- 9 families of different ancestry with ICCA phenotype linked to 16 p (Swobodo et al, 2001) but 1/11 families did not suggesting genetic heterogeneity
- Indian family with typical PKC and epilepsy linked to 16p (Valente et al, 2000), but distinct from ICCA site suggesting second locus
Valente et al, *Brain*, 2000
A second paroxysmal kinesigenic choreoathetosis locus (EKD2) mapping on 16q13-q22.1 indicates a family of genes which give rise to paroxysmal disorders on human chromosome 16

E. M. Valente,1,2,* S. D. Spacey,1,3,* G. M. Wali,4 K. P. Bhatia,1 P. H. Dixon,1 N. W. Wood1 and M. B. Davis1
PKC/PKD genetics

PKC/PKD is genetically heterogeneous

- At least two (or more) loci on chromosome 16
- Some families with PKC don’t link to these sites on chromosome 16 suggesting yet another gene locus (EKD3) (Spacey et al, 2002)
PDC/PNKD genetics

• Fouad et al. *A gene for familial dyskinesia (FPD1) maps to chromosome 2q.* (Am J Hum Genet, 1996)

• Fink et al. *PDC- tight linkage to chromosome 2q.* (Am J Hum Genet, 1996)

• Linkage close to a cluster of sodium/other channel genes - could be a novel channel disorder

• Candidate genes - SLC4A3, 5-HT2B, delta subunit of nicotinic acetycholine receptor all ruled out
Mapping PDC to chromosome 2

- D2S128
- D2S164
- D2S126
- D2S159

Fouad et al

10 cM

Fink et al

15 cM

PDC locus

6 cM
PDC/PNKD is genetically homogenous

All families with “typical” PDC /PNKD link to chromosome 2q
- Fouad et al, 1996
- Fink et al, 1996
- Jarman et al, 1997
- Hofele et al, 1997
- Raskind et al, 1998
- Matsuo et al, 1999

However, the gene is still to be found!!
PDC with spasticity (PNKD-plus syndrome)

- One family with PDC associated with spasticity

- Other features included perioral paresthesia, diplopia, generalised myoclonic jerks and seizures

- Linked to chromosome 1p (CSE1) close to potassium channel gene (Auburger et al., 1996)

- Gene to be discovered
ADNFLE caused by a ligand gated ion channel gene defect

A missense mutation in the neuronal nicotinic acetylcholine receptor α4 subunit is associated with autosomal dominant nocturnal frontal lobe epilepsy

Ortrud K. Steinlein¹, John C. Mulley², Peter Propping¹, Robyn H. Wallace²,³, Hilary A. Phillips³, Grant R. Sutherland²,³, Ingrid E. Scheffer⁴ & Samuel F. Berkovic⁴

Autosomal Dominant Nocturnal Frontal-Lobe Epilepsy: Genetic Heterogeneity and Evidence for a Second Locus at 15q24


Am J Hum Genet, 1998
The loci/genes for paroxysmal dyskinesias

- **PKC/PKD** 16p not known
  (ICCA syndrome) 16p not known
- **PED** - not known
  (RE-WC-PED) 16p not known
- **PDC/PNKD** 2q known
  (PDC-spasticity) 1p not known
- **ADNFLE** 20q *CHRNA4*
  15q *CHRNA3*
  1q *CHRN2*
- **Benign P torticollis** 19p Ca channel
What will the discovery of the genes lead to?

• Explain pathophysiological mechanisms

• Possible to do functional studies

• Animal models

• Treatments and prevention
Paroxysmal Dystonic Choreoathetosis: Clinical Features and Investigation of Pathophysiology in a Large Family

*Paul R. Jarman, PhD, *Kailash P. Bhatia, MRCP, †Charles Davie, MD, ‡Simon J. R. Heales, MD, §Nora Turjanski, MRCP, §§Simon D. Taylor-Robinson, MD, *C. David Marsden, FRS, and *Nicholas W. Wood, PhD

Departments of *Clinical Neurology, †NMR Research Group, ‡Department of Neurochemistry, Institute of Neurology, London, U.K.; and §Magnetic Resonance Unit, Hammersmith Hospital, Imperial College of Science, Technology and Medicine, London, U.K.

Summary: Paroxysmal dystonic choreoathetosis (PDC) is an unusual hyperkinetic movement disorder characterized by attacks of chorea, dystonia, and ballism with onset in childhood. We report a large British family with dominantly inherited PDC linked to chromosome 2q and describe the clinical features in 20 affected family members. Attacks were precipitated by a variety of factors, including caffeine, alcohol, or emotion, and could be relieved by short periods of sleep in most subjects. The clinical features in the family are compared with those of 11 other PDC families in the literature and a core phenotype for PDC suggested. CSF monoamine metabolites measured at baseline and during an attack in one subject were found to increase during the attack. Magnetic resonance spectroscopy of brain and basal ganglia performed both during and between attacks was normal. Positron emission tomography using the D2 receptor ligand, 11C-raclopride, showed no abnormalities.

Key Words: PDC—Dystonia—Genetics—Pathophysiology—PET—MRS—Dopamine.
Table 1: Results of CSF monoamine metabolites at baseline and during an attack in individual V-9

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Attack</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>HVA (nmol/L)</td>
<td>165</td>
<td>537</td>
<td>71 - 565</td>
</tr>
<tr>
<td>HIAA (nmol/L)</td>
<td>88</td>
<td>221</td>
<td>58 - 220</td>
</tr>
</tbody>
</table>
Functional investigation of mutants

Plasmid DNA → Site-directed mutagenesis → In vitro transcription

Blood sample → cRNA → Injection into Xenopus oocytes

Genomic DNA → PCR

Subcloning

Physiology
EA1 subunits reduce hKv1.1 current

Zubeiri et al, 1999
Approach to a patient

- Decide which category best fits (PKD, PNKD, PED or nocturnal)
- Attention to age of onset, family history and duration of episodes
- Onset of PKC/PNKD below 8 years or above 30 years could suggest a secondary cause
- Episodes of PKC > 2-3 minutes, or PNKD less than 5 minutes is suspicious of secondary cause
- Associated inter-ictal features suggests secondary cause