Paroxysmal Movement Disorders



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Aspen course
2026

Disclosures

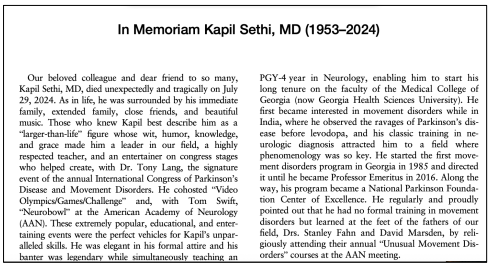
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- Board/leadership positions: Chair of the Lewy Body Dementia Association (LBDA) Industry Advisory Council; LBDA Board of Directors, Member at large; International Consortium for Dementia with Lewy Bodies, Executive Committee member; KeifeRx Scientific Advisory Board; Secretary of the International Parkinson and Movement Disorder Society

- Off-label medication use

Acknowledgment



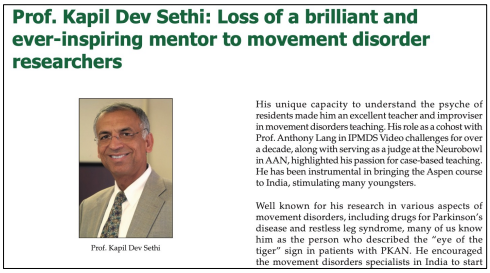
Kapil Sethi, MD



In Memoriam Kapil Sethi, MD (1953–2024)

Our beloved colleague and dear friend to so many, Kapil Sethi, MD, died unexpectedly and tragically on July 29, 2024. As in life, he was surrounded by his immediate family, extended family, close friends, and beautiful music. Those who knew Kapil best describe him as a "larger-than-life" figure whose wit, humor, knowledge, and grace made him a leader in our field, a highly respected teacher, and an entertainer on congress stages who helped create, with Dr. Tony Lang, the signature event of the annual International Congress of Parkinson's Disease and Movement Disorders. He cohosted "Video Olympics/Games/Challenge" and, with Tom Swift, "Neurobowl" at the American Academy of Neurology (AAN). These extremely popular, educational, and entertaining events were the perfect vehicles for Kapil's unparalleled skills. He was elegant in his formal attire and his banter was legendary while simultaneously teaching an PGY-4 year in Neurology, enabling him to start his long tenure on the faculty of the Medical College of Georgia (now Georgia Health Sciences University). He first became interested in movement disorders while in India, where he observed the ravages of Parkinson's disease before levodopa, and his classic training in neurologic diagnosis attracted him to a field where phenomenology was so key. He started the first movement disorders program in Georgia in 1985 and directed it until he became Professor Emeritus in 2016. Along the way, his program became a National Parkinson Foundation Center of Excellence. He regularly and proudly pointed out that he had no formal training in movement disorders but learned at the feet of the fathers of our field, Drs. Stanley Fahn and David Marsden, by religiously attending their annual "Unusual Movement Disorders" courses at the AAN meeting.

Stern MB, Lang A. Movement Disorders 39(10), 2024.



Prof. Kapil Dev Sethi: Loss of a brilliant and ever-inspiring mentor to movement disorder researchers

Prof. Kapil Dev Sethi

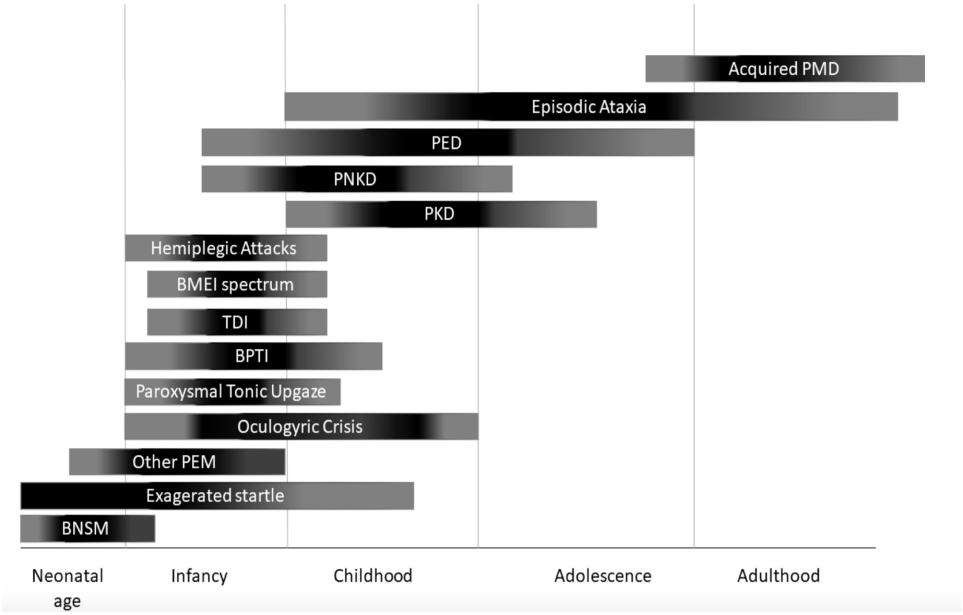
His unique capacity to understand the psyche of residents made him an excellent teacher and improviser in movement disorders teaching. His role as a cohost with Prof. Anthony Lang in IPMDS Video challenges for over a decade, along with serving as a judge at the Neurobowl in AAN, highlighted his passion for case-based teaching. He has been instrumental in bringing the Aspen course to India, stimulating many youngsters.

Well known for his research in various aspects of movement disorders, including drugs for Parkinson's disease and restless leg syndrome, many of us know him as the person who described the "eye of the tiger" sign in patients with PKAN. He encouraged the movement disorders specialists in India to start

Kandadai RM et al. Annals of Movement Disorders 7(2), 2024.

Paroxysmal Movement Disorders

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



What is NOT a paroxysmal dyskinesia?

- Action/Task Specific Dystonia
- Tics - can occur in bursts
- Paroxysmal Exaggeration of Tremor
- Action Myoclonus

Paroxysmal Dyskinesias - themes

Heterogeneous

- Clinically
- Genetically

Characterized by –

- Abrupt onset of abnormal involuntary movements
- Usually out of a background of normal motor behavior

A combination of different movements

- Chorea, ballism, and dystonia

Four main groups of paroxysmal dyskinesias

- PKD, PNKD, PED +/- PHD
- Idiopathic (primary) or secondary
- Familial or sporadic
- Overlap

- Abnormal involuntary movements
- Paroxysmal
- Between episodes, generally normal
- Distinguished by triggers, duration, frequency, and genetics

Paroxysmal kinesigenic dyskinesia (PKD)

Paroxysmal non-kinesigenic dyskinesia (PNKD)

Paroxysmal exercise-induced dyskinesia (PED)

Paroxysmal hypnogenic dyskinesia (PHD)?

History

Paroxysmal choreoathetosis (1940) → Additional families described – including with dystonia → Paroxysmal dystonic choreoathetosis (PDC) → Paroxysmal kinesigenic choreoathetosis (PKC) (1967) → Paroxysmal exercise-induced dyskinesia (PED) (1977) → Proposed PKD and PNKD by Demirkiran and Jankovic (1995)

- 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

- Kertesz described attacks induced by sudden movement
- Different from PDC, very brief attacks, responded well to AEDs

- Lance described "intermediate" type, attack duration > PKC but < PDC

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)



Fig. 2. Hand-made trace of photographs taken of the patient during an attack, from Kure's paper (1892).

Kato et al., 2006

Paroxysmal kinesigenic dyskinesia (PKD)

Paroxysmal Kinesigenic Dyskinesia

- Most common of paroxysmal movement disorders
- Onset usually in childhood (7-15 years, range 6 mos – 33 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
- 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

Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia

New diagnostic criteria

M.K. Bruno, MD; M. Hallett, MD; K. Gwinn-Hardy, MD; B. Sorensen, BA; E. Considine, BSN; S. Tucker, MD; D.R. Lynch, MD, PhD; K.D. Mathews, MD; K.J. Swoboda, MD; J. Harris, PhD; B.-W. Soong, MD, PhD; T. Ashizawa, MD; J. Jankovic, MD; D. Renner, MD; Y.-H. Fu, PhD; and L.J. Ptacek, MD

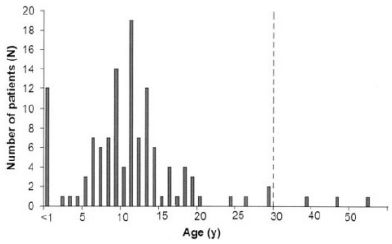
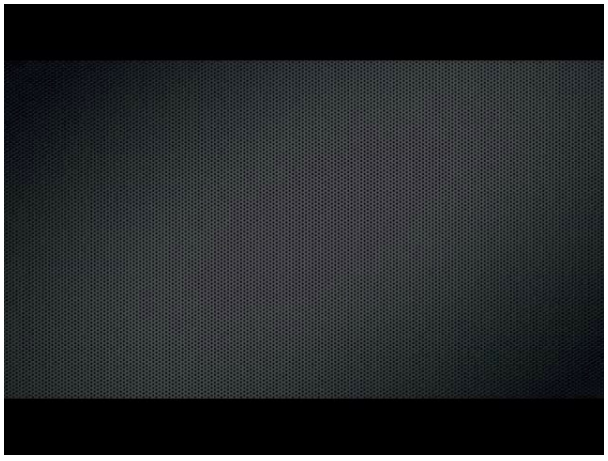


Figure. Histogram for age at attack onset in all probands initially referred as paroxysmal kinesigenic dyskinesia.

Bruno et al 2004

Paroxysmal Kinesigenic Dyskinesia



Courtesy Dr. Kapil Sethi

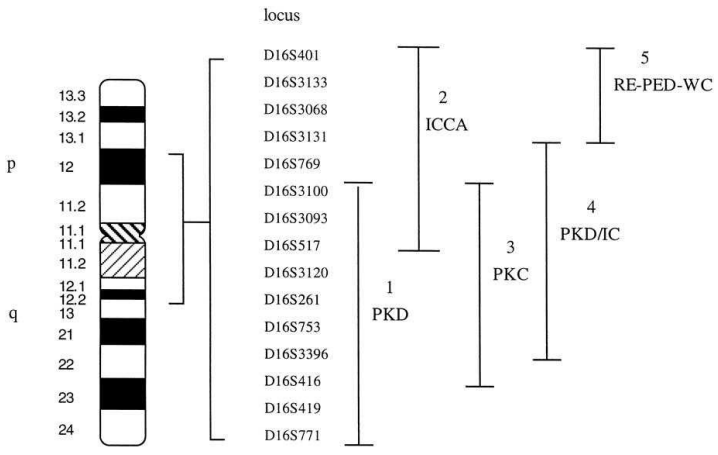
Paroxysmal Kinesigenic Dyskinesia



- Multifocal brachiofacial or generalized dystonic movements and dyskinesias
- Episodes started with a variable aura, triggered by emotional stress or movement initiation
- Brain MRI and EEG were normal
- Treated with carbamazepine, 200 mg daily

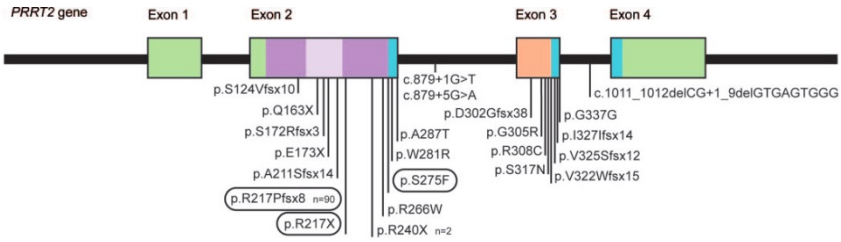
Borchert et al., 2009

Genetics of PKD
The RICH Area on Chromosome 16



- 65-72% have family history of similar disorder with AD inheritance
- Genetic overlap
- CCA, infantile convulsions and paroxysmal choreoathetosis
- RE-PED-WC, rolandic epilepsy, paroxysmal exercise-induced dyskinesia, writer's cramp

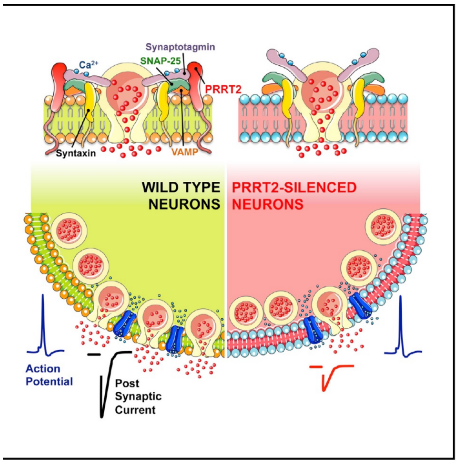
Proline Rich Transmembrane Protein 2 (PRRT2) Location of 23 mutations in PKD



- > 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.
- 150 PKD screened → 8 PRRT2 mutations detected accounting for ~23% of probands (Liu 2022)
- Microdeletion of 16p11.2 may have more severe features

Wang et al., Brain 2011; Ebrahimi-Fakhari et al., Brain 2015; Zhao et al., 2020; Liu et al., 2022

PRRT2 Function



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

Correspondence
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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.

- Vesical fusion and neurotransmitter release
- Modulates Nav1.2/Nav1.6 channels, influencing neuronal excitability
- Elevated cytokine levels and serum TNF-alpha levels (Xu 2022)
- Inflammatory response involved?

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

Phenotypic Heterogeneity in PRRT2 Mutations – a spectrum of symptoms

- Paroxysmal Kinesigenic Dyskinesia
- Benign Familial Infantile Convulsions
- ICCA Syndrome
- Febrile Infantile Convulsions
- Nocturnal Convulsions
- Classic Migraine with PKD
- Hemiplegic Migraine (Riant 2022)
- Episodic Ataxia
- Paroxysmal Nonkinesigenic Dyskinesia
- Paroxysmal Exertional Dyskinesia

Liu et al., J Med Genetics 2011; Gurreni and Mink et al., Neurol 2012; Riant Neurol 2022

Non-Motor Symptoms and Quality of Life in Patients with PRRT2-Related Paroxysmal Kinesigenic Dyskinesia

Asya Ekmen, MD, PhD,[1,2] Mohamed Doulazmi, PhD,[3] Aurélie Méneret, MD, PhD,[1,2] Prasanthi Jegatheesan, PhD,[1,2] Anais Hervé, RN,[1] Philippe Damier, MD, PhD,[4] Domitille Gras, MD, PhD,[1] Agathe Roubertie, MD, PhD,[5] Juliette Piard, MD, PhD,[6,7] Eugenie Mutez, MD, PhD,[8] Clément Tarrano, MD,[1,2] Quentin Welniarz, PhD,[1,2] Marie Vidailhet, MD,[1,2] Yulia Worbe, MD, PhD,[1,2] Cécile Gallea, PhD,[1] and Emmanuel Roze, MD, PhD[1,2,]*

- 21 PKD patients (PRRT2) vs. 21 healthy controls matched for age and sex
- Non-motor symptoms causing ADL impairment reported in 100% of patients and 29% of HCs ($p < 0.001$)
- 52% of patients and 9.5% of HCs reported at least 4 NMS
- NMS: loss of self-confidence due to stigma (100%), sleep disorders (71%) (particularly difficulty to fall asleep), anxiety (48%), fatigue (43%), and depression (29%)
- 62% of the patients were initially misdiagnosed
  - Wrong diagnoses included functional disorder (6 patients), epilepsy (4 patients), panic attack (2 patients), Tourette syndrome (2 patients), and dystonia (1 patient).
- Higher level of stigmatization in patients, positively correlated with a delay in diagnosis and the fear of being judged, but not with the presence of paroxysmal episodes

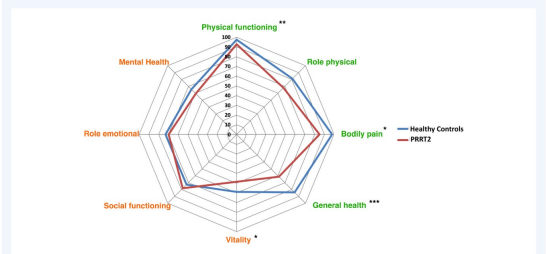


Figure 1. Radar chart with the eight domains of the Quality of life (Short Form-36) for PRRT2 patients and Healthy Controls (red line: *PRRT2* patients, blue line: Healthy Controls). Each spoke on the radar chart represents an SF-36 domain on a scale of 0–100, with higher scores representing better health-related quality of life. The four green domains (Physical functioning, Role physical, Bodily pain and General health) contribute to the scoring of physical component summary (PCS) measure. The four orange domains (Vitality, Social functioning, Role emotional and Mental Health) contribute to the scoring of Mental Component Summary (MCS) measure. ***$P < 0.001$, **$P < 0.01$, *$P<0.05$, using Student's *t*-test or the Mann–Whitney's test as appropriate.

Ekmen et al., 2023

Neural mechanisms of PKD

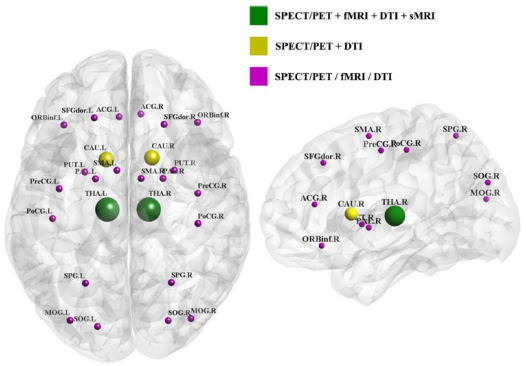


Fig 1. Summary map showing the abnormal brain regions involved in PKD from published neuroimaging studies, including the thalamus, the basal ganglia, and the frontoparietal cortex. The large green spots represent the abnormal brain regions identified by all of multimodal neuroimaging methods including SPECT/PET, fMRI, DTI, and sMRI. The mid-sized yellow spots represent the abnormal brain regions identified by two-modal neuroimaging methods including SPECT/PET and DTI. The small purple spots represent the abnormal brain regions identified by single-modal neuroimaging methods such as SPECT/PET, fMRI, or DTI.

- Disruption of structural and/or functional properties in basal ganglia-thalamo-cortical circuitry and interhemispheric functional connectivity
- PRRT2 PKD with decreased gray matter volume in cerebellar lobules and medial prefrontal cortex and altered WM tracts connecting cerebellum – striatum – cortical motor areas
- Cortico-striato-thalamo-cortical loop abnormalities with significant thinning of the left S1, pronounced reduction in volume of bilateral putamen and significantly increased covariant connections between the left putamen and the left globus pallidus in PKD patients (Wang et al., 2024)

Liu et al., J Neuroimaging 2021; Ekmen et al., 2022; Wang et al., 2024

REVIEW

The Pathogenesis of Paroxysmal Kinesigenic Dyskinesia: Current Concepts

Zi-yi Li, MB,[1] Wo-tu Tian, MD,[1] Xiao-jun Huang, MD,[2*] and Li Cao, MD, PhD[1*]

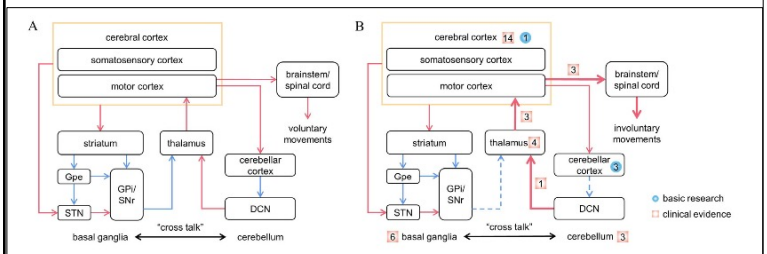


FIG. 1. Two main neural circuits involved in paroxysmal kinesigenic dyskinesia (PKD). **(A)** The basal ganglia-thalamo-cortical circuit and cerebellum-thalamo-cortical circuit achieve fine control of movement under physiological conditions (*red arrow*: excitation; *blue arrow*: inhibition). **(B)** The pathogenesis of PKD mainly includes two neural circuits: (i) impairment of the basal ganglia or thalamus causes an excessive activation in the cerebral cortex; and (ii) insufficient suppression from the cerebellar cortex toward the DCN leads to an abnormal overexcitation of the thalamocortical pathway (*bold line*: increased; *dotted line*: reduced). *Blue circles and red squares represent the number of basic or clinical studies suggesting that the abnormality in this part is related to the pathogenesis of PKD. Detailed information about the clinical studies of PKD is summarized in Supporting Information Table S1. DCN, deep cerebellar nuclei; Gpe, globus pallidus externa; Gpi, globus pallidus interna; SNr, substantia nigra; STN, subthalamic nucleus. [Color figure can be viewed at wileyonlinelibrary.com]

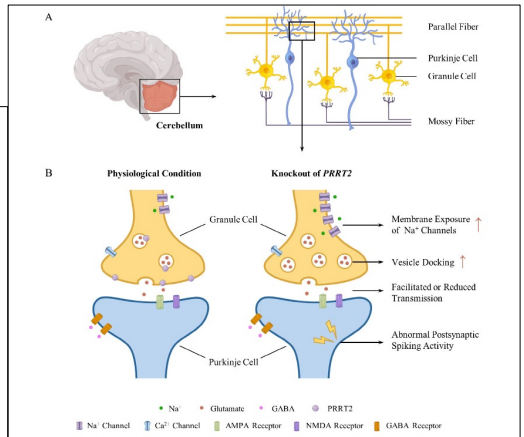


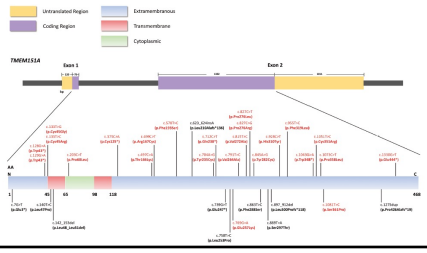
FIG. 2. The pathogenesis in the cerebellum in paroxysmal kinesigenic dyskinesia (PKD) (by Figdraw). **(A)** Current studies highlight the cerebellum's role in PKD. Cerebellar granule cells (GCs) receive information input from the cortex and brainstem via mossy fibers (MFs), subsequently transmitting excitatory projections to Purkinje cells (PCs) through parallel fibers (PFs). **(B,** left*)* *PRRT2* is highly expressed in the cerebellum, especially in the GCs, and is enriched at the presynaptic membrane and small vesicles in the molecular layer. **(B,** right*)* In *PRRT2* knockout mice, the expression of Na^+ channel was increased, and the synaptic vesicle docking in the molecular layer was increased. However, the experiments demonstrated different results regarding the PF-PC synaptic transmission and the electrophysiological activity of PCs. Loss of *PRRT2* results in abnormal neurotransmitter transmission and excitability of PCs, which ultimately influence the output nuclei of the cerebellum. [Color figure can be viewed at wileyonlinelibrary.com]

- Disturbance of basal ganglia-thalamo-cortical circuit
- Impairment of the BG gating function → aberrant output toward the thalamus → excessive activation of cerebral cortex
- Role of the cerebellum with insufficient suppression from cerebellar cortex to deep cerebellar nuclei → overexcitation of the thalamocortical pathway

Li et al., Mov Disord 2023

TMEM151A gene

- Causative gene for PKD in PRRT2-negative cohort
  - 24 heterozygous variants detected in 29 patients (from 25 families)
  - Frequency ~4.8%
- TMEM151A – 24 variants identified
  - Decreased protein expression, potential loss of function
  - Levels peaked postnatal, declined in adulthood (mice)
  - Role in intracellular Ca dynamics, homeostasis, and remodeling



- Clinical features
  - Mean age onset 12.9 +/- 3.2 years
  - May have spontaneous remission or decreased attacks with age
  - Premonitory sensation
  - Precipitants: sudden movement, speed change, stress, fatigue
  - Transient involuntary movements/postures – dystonia, chorea, +/- ballism; < 30 sec; face involved
  - **Differentiation from PPRT2+:** More dystonia, shorter duration, h/o of benign infantile epilepsy, residual attacks/aura when treated with AEDs
- Treatment - carbamazepine, oxcarbazepine

Tian et al., 2021; Wirth et al., 2022; Ma et al., 2022; Chen et al., 2022; Mounir Alaoui et al., 2023; Kurahashi et al., 2025 – new cases in Japan

PKD with TMEM151A mutations





Mounir Alaoui et al., Park Rel Dis 2023

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 non-kinesigenic dyskinesia (PNKD)

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

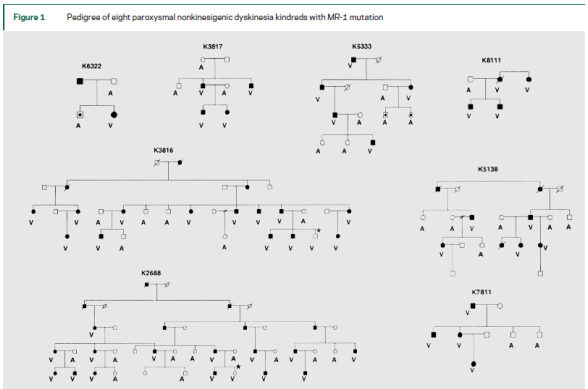
- Most common phenotype with MFR-1 mutation

Bruno et al., 2007; Bhatia 2011; Gardiner et al., 2015

Genotype–phenotype correlation of paroxysmal nonkinesigenic dyskinesia

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A. Friedman, MD
J.E. Nielsen, MD, PhD
A.E. Lang, MD
E. Bertini, MD
P. Van Bogaert, MD
Y. Averyanov, MD
M. Hallett, MD
K. Gwinn-Hardy, MD
B. Sorenson
M. Pandolfo
H. Kwiecinski, MD
S. Servidei, MD
Y.-H. Fu, PhD
L. Ptáček, MD

ABSTRACT Background: Paroxysmal nonkinesigenic dyskinesia (PNKD) is a rare disorder characterized by episodic hyperkinetic movement attacks. We have recently identified mutations in the *MR-1* gene causing familial 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 and 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. Caffeine, 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 induced 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 Reback) are likely to harbor myofibrillogenesis regulator 1 (*MR-1*) gene mutations. Other "PNKD-like" families exist, but atypical features suggests that these subjects are clinically distinct from PNKD and do not have *MR-1* mutations. Some may represent paroxysmal exertional dyskinesia. **NEUROLOGY 2007;68:1782-1789**



- 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)

Bruno et al., 2007

Paroxysmal Nonkinesigenic Dyskinesia



Courtesy Dr. Kapil Sethi

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

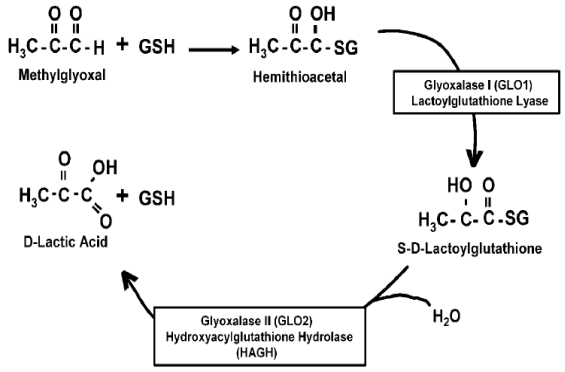


Figure 6. The glyoxylase system comprises two enzymes, glyoxylase I (GLO1, lactoylglutathione lyase) and glyoxylase II (GLOII, hydroxyacylglutathione hydrolase, HAGH). Methylglyoxal and glutathione non-enzymatically form a hemithioacetal intermediate and then glyoxylase I catalyzes formation of *S*-D-lactoylglutathione.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



PNKD – Genetics and mechanism

- 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)

- Mouse model of PNKD (Nelson 2022)
  - Loss of striatal indirect pathway (iMSN) neurons firing during dyskinesia
  - Aberrant endocannabinoid-mediated suppression of glutamatergic inputs

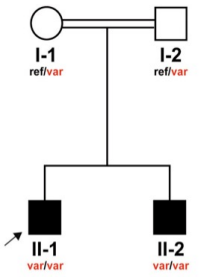
Liao et al., 2021; Nelson et al., 2022

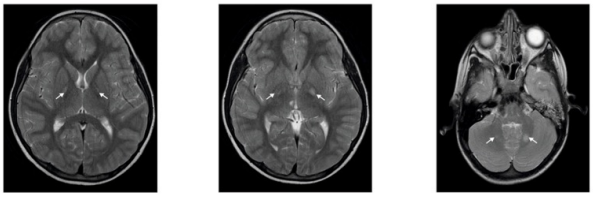
Isolated Paroxysmal Non-kinesigenic Dystonia Associated with Homozygous *PDHB* Variant in an Indian Family

- Pyruvate dehydrogenase gene
- PDHB, gene coding for the E1β subunit of the PDH complex

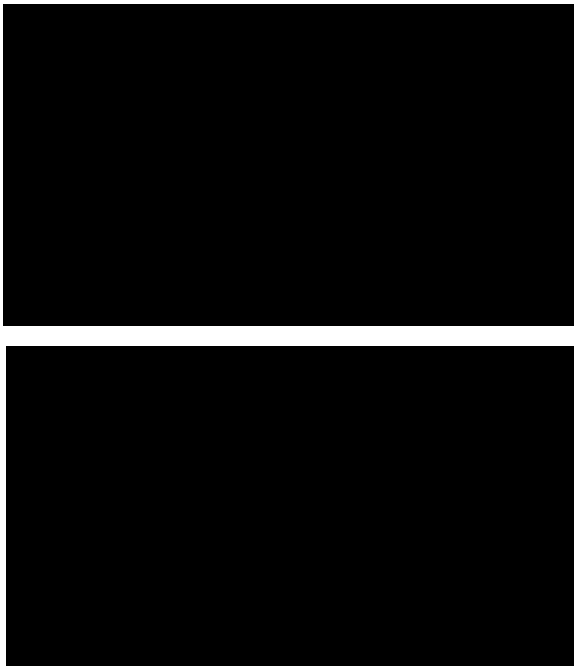
- Dystonia
- Episodes 1-2 hours
- CBZ responsive, also consider thiamine

- Pallidal and dentate nucleus hyperintensities





II-1 II-1 II-2



Agarwal et al., Mov Disord 2022.

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
  - For some, muscle vibration, electric nerve stimulation, cold exposure
- 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

Paroxysmal Exercise-Induced Dyskinesia

Courtesy Dr. Kapil Sethi

A few caveats - Paroxysmal Exercise Dyskinesias

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

Maria Bozi, MD, and Kailash P. Bhatia, FRCP*

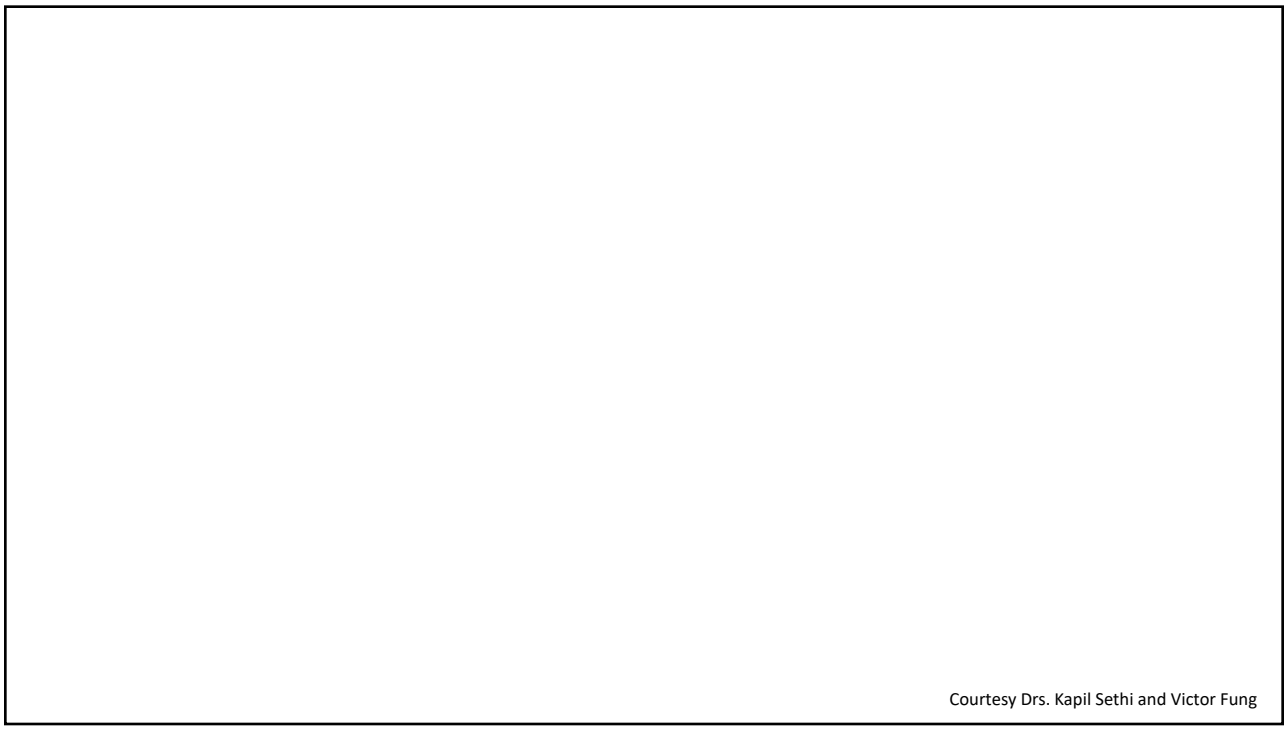
Sobell Department of Movement Neuroscience and Movement Disorders, Institute of Neurology, University College London, London, United Kingdom

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

- 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

Bozi and Bhatia 2003; Dale et al., 2010; Erro et al., 2014



Courtesy Drs. Kapil Sethi and Victor Fung

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)
    - Realignment with DYT 18 (GLUT1-DS due to SLC2A1 mutations)

GLUT 1 deficiency syndrome

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 anemia
	PNKD	Cognitive impairment of variable severity	Alternating hemi/quadriplegia	Hepato-splenomegaly
	PKD		Hypotonia	Cataracts
Childhood-absence epilepsy (CAE)	Episodic choreoathetosis and progressive spastic paraparesis	Intellectual disability	Abnormal eye movements	Microcephaly
Epilepsy with myoclonic-atonic seizures (Doose syndrome)	Intermittent ataxia	Language delay	Migraine headaches	
	Chorea	Dysphoria	Cyclical vomiting	
Focal epilepsy	Dystonia	Inconsolable crying	Sleep disturbance	
Febrile seizures	Parkinsonism		Encephalopathy	
	Myoclonus			
	Oculogyric crises			

Liao et al., 2021; Anurat et al., 2022



Courtesy Dr. Kapil Sethi and Katya Koschet

PED - Genetics

- Mutations in the SLC2A1 gene
- Encodes GLUT1 mutations (glucose transporter type), located 1p35-p31.3
- Glucose transporter into erythrocytes and across BBB
  - CSF glucose levels – low or lower limit normal
  - Role for quantification in RBCs with flow cytometry? (Soliani 2022)
- Mutations – de novo, AD, but AR also reported
- Missense mutations – milder symptoms
- However, SLC2A1 mutations only < 30% of PED

Genetic and clinical features of *SLC2A1*-related paroxysmal exercise-induced dyskinesia

Jiao-Jiao Xu [1] · Yu-Lan Chen [1] · Hao Yu [1] · Dian-Fu Chen [1] · Hong-Fu Li [1] · Zhi-Ying Wu [1,2]

- Two Chinese PED families with involuntary movements after prolonged exercise
- Whole-exome sequencing identified 2 missense mutations in SLC2A1, including a known disease-causing mutation, c.997C>T (p.R333W), and a novel mutation, c.823G>C (p.A275P)
- Familial PED had a later onset and a higher cerebrospinal fluid/blood glucose ratio
- Patients with missense mutations had later onset than those with truncated mutations.

Weber et al., J Clin Invest 2008; Harvey et al., 2021; Liao et al., 2021; Soliani et al, 2022; Xu et al., 2025

GLUT1-DS Italian registry: past, present, and future: a useful tool for rare disorders

Costanza Varesio[1,2], Valentina De Giorgis[1,2*], Pierangelo Veggiotti[3,4], Nardo Nardocci[5], Tiziana Granata[5], Francesca Ragona[5], Ludovica Pasca[1,2], Martina Maria Mensi[1], Renato Borgatti[1,2], Sara Olivotto[3], Roberto Previtali[4], Antonella Riva[6,7], Maria Margherita Mancardi[8], Pasquale Striano[6,7], Mara Cavallin[9], Renzo Guerrini[9], Francesca Felicia Operto[10], Alice Pizzolato[11], Ruggero Di Maulo[11], Fabiola Martino[12], Andrea Lodi[12] and Carla Marini[13]

Table 2 Summary of clinical data of collected patients

Age distribution of pts	gender: F/M	Age at symptoms onset	Age at GLUT1DS diagnosis	Symptoms at onset	ketogenic diet
< 8 years 12 pts (17.9%)	40 females (59.7%)	1st year: 40 patients (60%)	Infancy: 34 pts (51%)	paroxysmal symptoms (63 pts): 56% seizure + paroxysmal ocular movement disorder (20%)	53 patients (79%): KD
8–17 years: 28 pts (41.8%)	27 males (40.3%)	1–5 year: 22 patients (33%)	8–14 years: 16 pts (24%)	mixed paroxysmal and fixed symptoms (35 pts): psychomotor delay (70%)	4 patients (6%): Triheptanoin
> 18 years: 27 pts (40.3%)		> 5 yrs five patients (7%)	15–17 years in 2 pts (3%)		10 patients (15%) not treated
			Adulthood: 15 pts (22%)		



Fig. 2 shows geographical distribution of patients participating to the Italian GLUT1-DS Registry

Varesio et al., Orphanet J Rare Dis. 2023

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

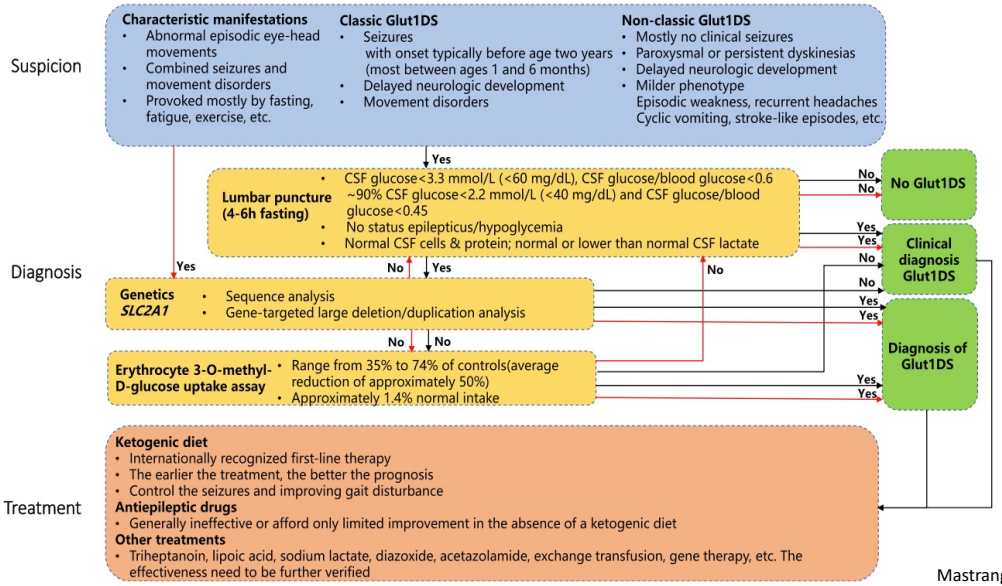
Bhatia et al., 2011; Margari et al., 2000

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)

Bhatia et al., 2011

A practical approach to GLUT1DS



CSF Systematic Review

•CSF blood/glucose ratio may predict better than CSF glucose the dx in children with early onset absences

• CSF blood/glucose ratio may predict better than CSF glucose the dx in children presenting with PED and intellectual disability.

• CSF glucose may predict better than CSF blood/glucose and lactate the response to ketogenic diet and antiseizure medications

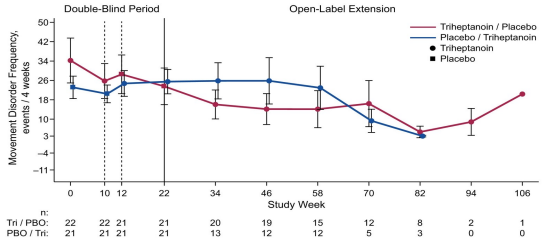
Mastrangelo et al., 2024; Zhang et al., 2025

RESEARCH ARTICLE

Triheptanoin Did Not Show Benefit versus Placebo for the Treatment of Paroxysmal Movement Disorders in Glut1 Deficiency Syndrome: Results of a Randomized Phase 3 Study

Valentina De Giorgis, MD, PhD,[1*] Kailash P. Bhatia, FRCP,[2] Odile Boespflug-Tanguy, MD,[3] Domitille Gras, MD,[3] Adela Della Marina, MD,[4] Archana Desurkar, MD,[5] Manuel Toledo, MD,[6] Ian Miller, MD,[7] Michael Rotstein, MD,[8] Susanne A. Schneider, MD,[9] Daniel C. Tarquinio, DO,[10] Yvonne Weber, MD,[11,12] Melanie Brandabur, MD,[13] Jill Mayhew, PT,[13] Tony Koutsoukos, PhD,[13] and Darryl C. De Vivo, MD[14]

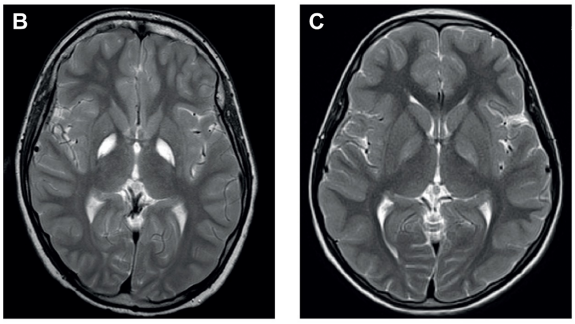
- Ultragenyx Pharmaceutical Inc.
- UX007G-CL301 (Triheptanoin)
  - Odd medium C7 chain triglyceride that is metabolized into acetyl-CoA and propionyl-CoA - key entries of the tricarboxylic acid cycle
- RCT, DB PC, Phase 3 crossover study
- 10-12 weeks titration, 8 weeks maintainence, and OLE for up to 3 years
- Primary endpoint: frequency of disabling paroxysmal movement disorder events per 4 weeks (recorded by diary during maintenance)
- 43 patients (63% adults)
- No difference between drug and placebo in mean # of disabling paroxysmal movement disorder events
- Treatment AE – mild/mod, GI, HA
- Early termination of study in OLE due to lack of effectiveness



De Giorgis et al., 2024

ECHS1 Mutations and PED

ECHS1 MUTATIONS, DYSTONIA, AND PED



- ECHS1 encodes a mitochondrial enzyme involved in degradation of essential amino acids and fatty acids
- ECHS1 mutations → Leigh or Leigh-like syndromes, isolated paroxysmal dyskinesia (including paroxysmal exercise-induced dystonia), or neonatal presentations
- Role for cysteamine and N-acetylcysteine in tx?





Olgiati et al., Mov Dis 2016; François-Heude et al., 2022

Paroxysmal hypnogenic dyskinesia (PHD)

? Paroxysmal Hypnogenic Dyskinesia

- 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 night-time attacks

Meierkord et al., 1992; Provini et al., 200; Friedman et al., 2016; Liu et al., 2016

PHD example





Almeida and Dure 2014

An Update on the Phenotype, Genotype and Neurobiology of ADCY5-Related Disease

Arianna Ferrini, PhD,[1] Dora Steel, MRCPCH,[1,2] Katy Barwick, PhD,[1] and Manju A. Kurian, PhD[1*]

- ADCY5 mutations – range of complex movement disorders and neurodevelopmental phenotypes
- Adenylyl cyclases – involved in conversion of ATP to cAMP
- ADCY5 – 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

Movement Disorders
CLINICAL PRACTICE
REVIEW

Scoping Review on ADCY5-Related Movement Disorders

Poornima Jayadev Menon, MB BCh BAO, MRCPI,[1,2] Christelle Nilles, MD,[3] Laura Silveira-Moriyama, MD, PhD,[4] Ruiyi Yuan, MSc,[1] Claudio M. de Gusmao, MD,[4,5] Alexander Münchau, MD,[6] Miryam Carecchio, MD, PhD,[7] Steve Grossman, BA,[8] Gay Grossman, BA,[8] Aurélie Méneret, MD, PhD,[1] Emmanuel Roze, MD, PhD,[1] and Tamara Pringsheim, MD, FRCPC[3]*

ABSTRACT: Background: Adenylyl cyclase 5 (ADCY5)-related movement disorder (ADCY5-RMD) is a rare, childhood-onset disease resulting from pathogenic variants in the *ADCY5* gene. The clinical features, diagnostic options, natural history, and treatments for this disease are poorly characterized and have never been established through a structured approach.
Objective: This scoping review attempts to summarize all available clinical literature on ADCY5-RMD.
Methods: Eighty-seven articles were selected for inclusion in this scoping review. The majority of articles identified were case reports or case series.
Results: These articles demonstrate that patients with ADCY5-RMD suffer from permanent and/ or paroxysmal hyperkinetic movements. The paroxysmal episodes can be worsened by environmental triggers, in particular the sleep–wake transition phase in the early morning. Occurrence of nocturnal paroxysmal dyskinesias and perioral twitches are highly suggestive of the diagnosis when present. In the majority of patients intellectual capacity is preserved. ADCY5-RMD is considered a non-progressive disorder, with inter-individual variations in evolution with aging. Somatic mosaicism, mode of inheritance and the location of the mutation within the protein can influence phenotype.
Conclusions: The current evidence for therapeutic options for ADCY5-RMD is limited: caffeine, benzodiazepines and deep brain stimulation have been consistently reported to be useful in case reports and case series.

Menon et al., 2023; Kozon et al., 2024

Mosaic and clinical variants

ADCY5-Mosaic Variants: A Diagnosis Not to Be Missed

Alice Innocenti, MD,[1] Emmanuel Roze, MD, PhD,[2,3,*] Florence Riant, PharmD,[4] Marie-Céline François-Heude, MD,[5] Bérénice Lecardonnel, MSc,[5] Giacomo Garone, MD, PhD,[1] Maxime Colmard, MD,[5] Eline Chauvet-Piat, MD,[5] Anne-Cécile Chaux, MD,[6] Marie-Aude Spitz, MD,[7] Beatrice Desnous, MD, PhD,[8] Catherine Sarret, MD, PhD,[9] Philippe Damier, MD, PhD,[10] Thomas Wirth, MD, PhD,[11,12,13] Mathieu Anheim, MD, PhD,[11,12,13] Emilie Retailleau, MD,[1] Estelle Conabady, PhD,[3] Caroline Dubacq, PhD,[3] Oriane Trouillard, PhD,[3,14] Aurélie Méneret, MD, PhD,[2,3] and Agathe Roubertie, MD, PhD[5,15]

- 19 cases of mosaicism
- Less-severe phenotype than non-mosaic ADCY5 patients
  - Fewer baseline hyperkinetic movements (63% vs. 90%)
  - Milder manifestations compared to non-mosaic offspring
- Early-onset isolated paroxysmal dyskinesias +/- developmental delay, were the initial motor sxs in 70% of mosaic patients
- In 1 family, the father with mosaicism had a more severe phenotype than his non-mosaic son → perhaps paternal striatal neurons carry the pathogenic variant despite the observed mosaicism in blood cells?
- 68% of cases had c.1252C>T/p.R418W variant (position 418 of the gene is a mutational hot spot in non-mosaic patients)
- ADCY5-mosaic patients represented 43% (7/16) of de novo cases

Atypical ADCY5–related movement disorders: Highlighting adolescent/adult–onset cervical dystonia

Floriane Quazza [1], Florence Riant [2], Martina Patera [3], Antonio Suppa [4], Sara Satolli [5], Lydie Burglen [6], Michael Zech [7], Sylvia Boesch [8], Elisabetta Indelicato [8], Elodie Hainque [9], Emmanuelle Apartis [10], Diana Rodriguez [1], Diane Doummar [1], Aurélie Méneret [9], Claudia Ravelli [11]

- 13 patients from 8 families
- Adolescent/adult-onset phenotype with cervical dystonia related to ADCY5
- Possible spontaneous remission of pediatric-onset ADCY5- PxD
- Novel mutations in atypical cases of ADCY5: p. Arg726Val, p. Arg727Gly, p. Arg1208Cys
- Poor effect of caffeine in static ADCY5-related cervical dystonia
- Efficacy of botulinum toxin therapy in static ADCY5-related cervical dystonia

Innocenti et al., 2025; Quazza et al., 2025

Caffeine?

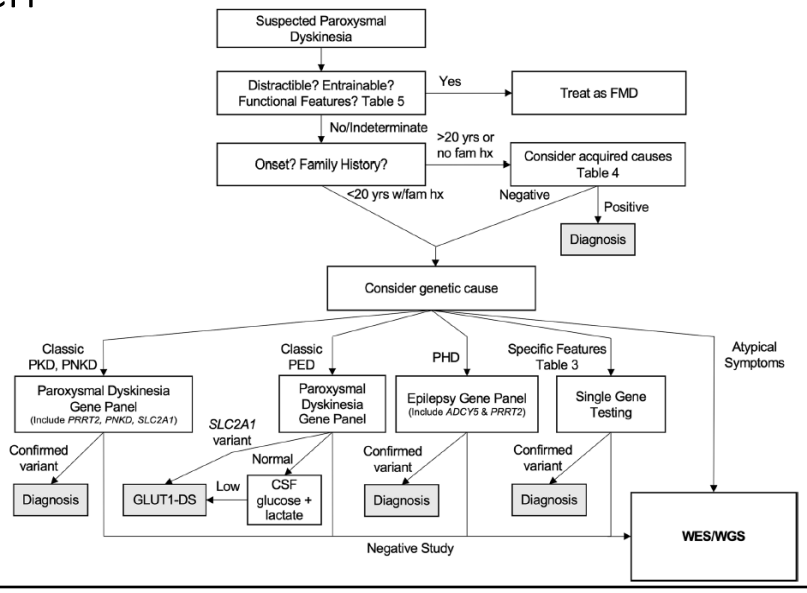
- Real-life retrospective study
- 30 patients (>8 years old), ADCY5 mutation, currently or previously tried caffeine
- Responders – improvement in movements >40%
- 26/30 (87%) = responders
- Decreased episode frequency
- Other benefits: improved gait, pain, dysarthria, attention, sleep and QoL
- Doses 60-800 mg/day
- Good tolerance, mild side effects (GI, sleep, cardiovascular)

Efficacy of Caffeine in ADCY5-Related Dyskinesia: A Retrospective Study

Aurélie Méneret, MD, PhD,[1*] Shekeeb S. Mohammad, PhD,[2] Laura Cif, MD, PhD,[3] Diane Doummar, MD,[4] Claudio DeGusmao, MD,[5] Mathieu Anheim, MD, PhD,[6,7,8] Magalie Barth, MD,[9] Philippe Damier, MD, PhD,[10] Nathalie Demonceau, MD,[11] Jennifer Friedman, MD,[12,13,14] Cécile Gallea, PhD,[15] Domitille Gras, MD,[16] Juliana Gurgel-Giannetti, MD, PhD,[17] Emily A. Innes, MB/BS,[2,18] Ján Necpál, MD,[19] Florence Riant, PharmD,[20] Sandrine Sagnes, MS,[21] Catherine Sarret, MD,[22] Yury Seliverstov, MD, PhD,[23,24] Vijayashankar Paramanandam, MD,[25] Kuldeep Shetty, MD,[26] Christine Tranchant, MD, PhD,[6,7,8] Mohamed Doulazmi,[27] Marie Vidailhet, MD,[1] Tamara Pringsheim, MD,[28] and Emmanuel Roze, MD, PhD[1]



Paroxysmal movement disorders: diagnostic approach



Liao et al., 2021

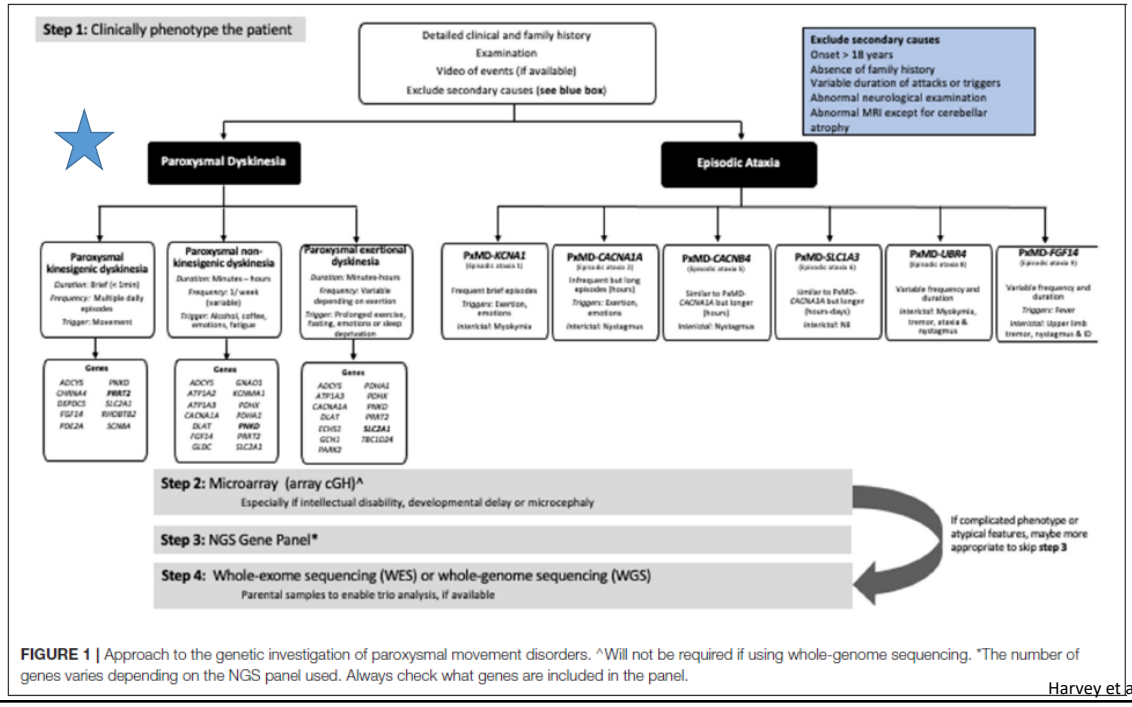


FIGURE 1 | Approach to the genetic investigation of paroxysmal movement disorders. ^Will not be required if using whole-genome sequencing. *The number of genes varies depending on the NGS panel used. Always check what genes are included in the panel.

Harvey et al., 2021

REVIEW





Paroxysmal movement disorders: an update on genetics, mechanisms, and emerging therapeutic strategies

Maria Makrygianni[a], *Roberto Erro*[b,c] *and Maria Stamelou*[a]

Purpose of review
This review will discuss the latest genetic and pathophysiological spectrum of paroxysmal movement disorders and emerging therapeutic strategies.

Recent findings
Paroxysmal movement disorders comprise a heterogenous group of rare movement disorders characterized by intermittent episodes of spontaneous or triggered attacks of hyperkinetic movement disorders. Genetic spectrum has evolved offering new insights in the pathophysiological mechanisms of known genes as *PRRT2* and new ones as *TMEM151A*. Also, SCA27B-related adult-onset cerebellar ataxia has emerged as a new treatable cause of episodic ataxia.

Summary
Exploring new pathophysiological associations can offer diagnostic precision and development of new therapeutic directions.

Keywords
episodic ataxia, parosymal kinesigenic dyskinesia, paroxysmal exercise-induced dyskinesia, paroxysmal nonkinesigenic dyskinesia

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

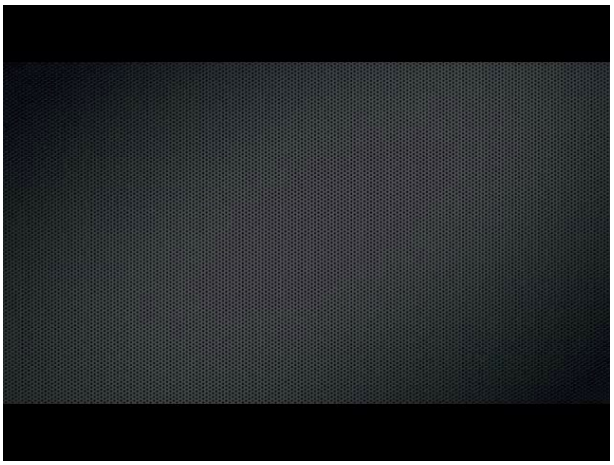
Secondary paroxysmal dyskinesia - Multiple Sclerosis

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

- Poulidou et al., Multiple Sclerosis-Related Paroxysmal Kinesigenic Dyskinesia: Long Term, Favorable Response to Lacosamide. J Mov Disord. 2022

Courtesy Dr. Kapil Sethi

Post-traumatic PKD

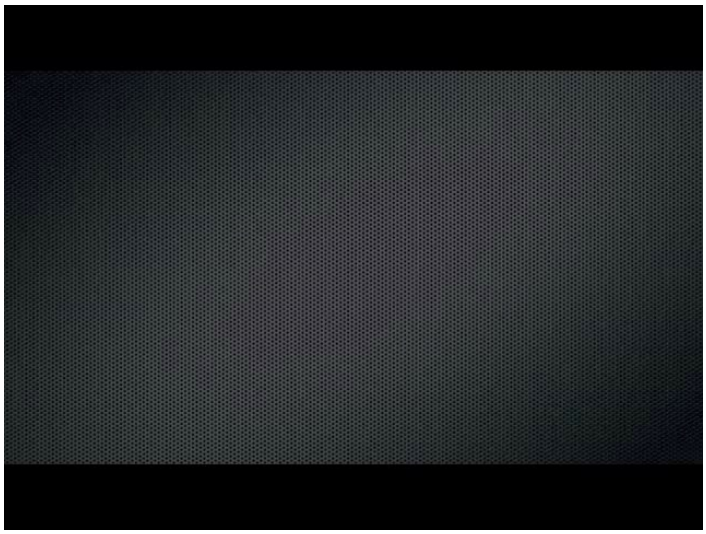


Courtesy Dr. Kapil Sethi

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

Vascular paroxysmal dyskinesia



Courtesy Dr. Kapil Sethi

Movement Disorders
CLINICAL PRACTICE

PHENOMENOLOGY VIDEO

HOT OFF THE PRESS!

Paroxysmal Dystonia: An Etiology Not to Be Missed in an Older Adult Patient

Valentin Mira, MD,[1,*] Jan Patrick Stellman, MD, PhD,[2] and Stephan Grimaldi, MD, PhD[1,2]

Question

A 57-year-old man with a history of hypertension, managed with Ramipril, exhibited paroxysmal and painful contractures on the right-side hemibody for 10 days. The contractures initially involved his right hand and subsequently affected the whole hemibody (Video 1). Episodes were triggered by sudden movements, lasted less than a minute, and recurred every 5 minutes. He reported no similar episode in the past. One month prior, he experienced a brief and transient right-sided weakness; he did not seek medical attention at that time. Neurological examination conducted between episodes was unremarkable. Brain tomography, electroencephalogram, and laboratory tests revealed no abnormalities.

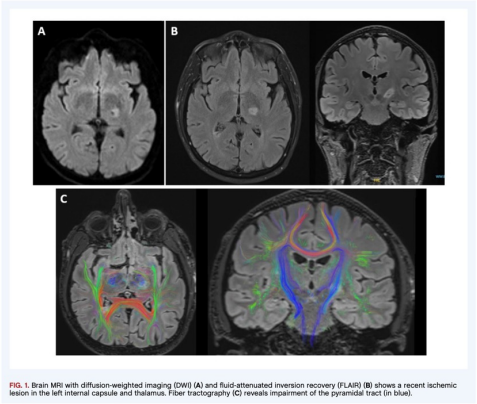


FIG. 1. Brain MRI with diffusion-weighted imaging (DWI) (A) and fluid-attenuated inversion recovery (FLAIR) (B) shows a recent ischemic lesion in the left internal capsule and thalamus. Fiber tractography (C) reveals impairment of the pyramidal tract (in blue).

Mira et al., 2025

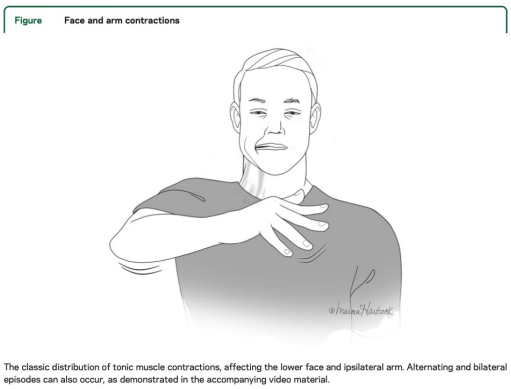
Metabolic Disorders

- 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



Schmerler et al., 2016

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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