DG ‚Dystonia / NBIA / Paroxysmal disorders'
12. May 2020

Joint webinar series

Paroxysmal dyskinesias: update on clinical and genetic features

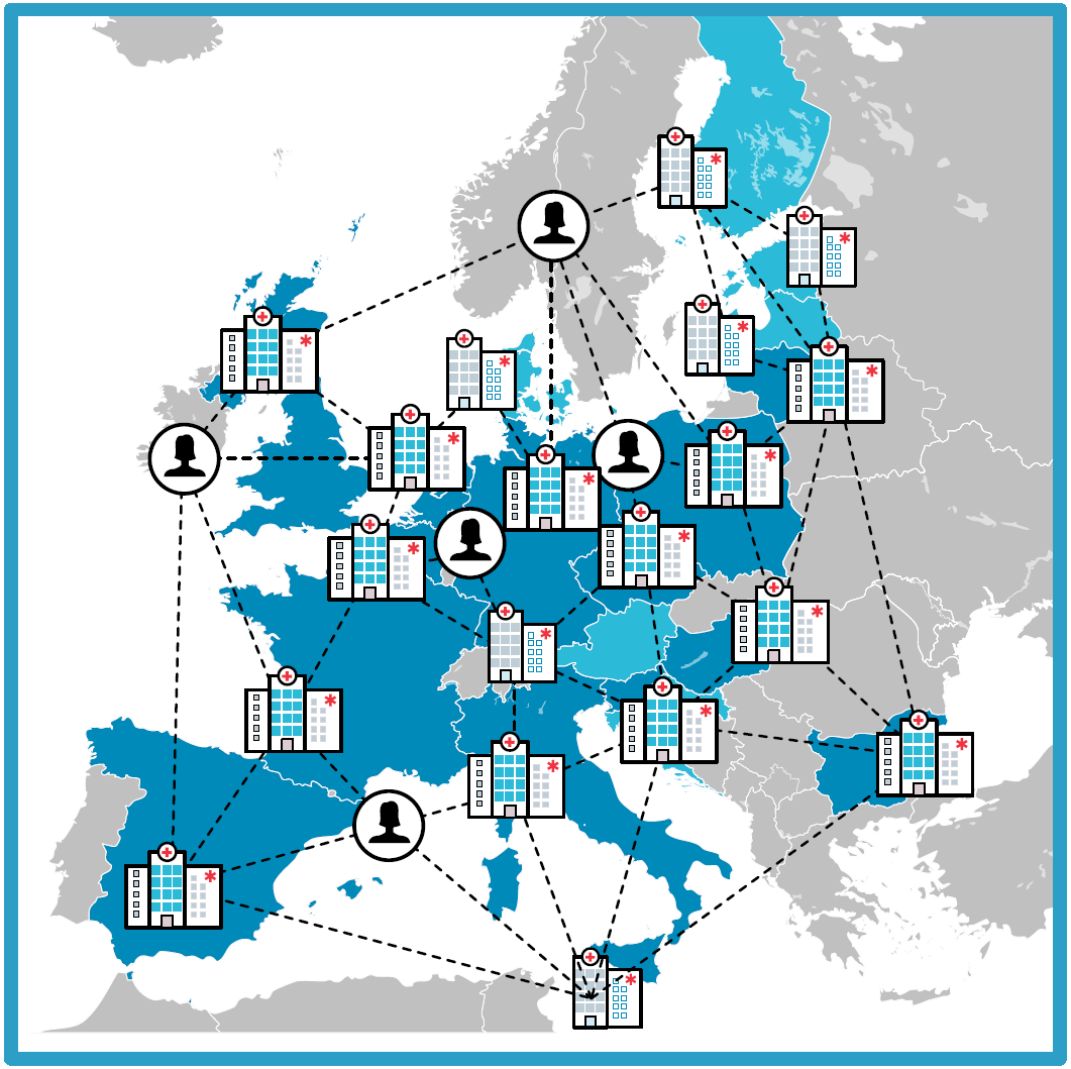
Giovanna Zorzi, IRCCS Besta, Milan Italy

General information about the webinars

- 35-40min presentation
- 15 min Q&A session
- Target audience:
  neurologists, residents, paediatric neurologists, geneticists and other para-medical personnel involved in patient care
- You can find the recorded webinar and presentation at the latest 2 weeks after the webinar on: http://www.ern-rnd.eu/education-training/webinars/
- Further useful information:
  http://www.ern-rnd.eu/disease-knowledge-hub/dystonia/
- Post-webinar survey (2-3min): satisfaction, topic ideas for next webinars

European Reference Network for RARE Neurological Diseases (ERN-RND)

- **Countries with Full Members (31)**
- **Countries with Affiliated Partners (10)**



ERN-RND covers 6 disease groups:

1. Ataxia and HSP
2. Leukodystrophies
3. Dystonias /NBIA/Paroxysmal disorders
4. Chorea and HD
5. FTD
6. Atypical Parkinsonism

Speaker: Giovanna Zorzi

- Degree in Child Neurology in 1999
- 2000-2001 Research contract at the Division of Clinical chemistry and Biochemistry, University Children Hospital, Zurich
- 2002– 2008 Research contract for the project" Childhood movement Disorders: diagnostic and therapeuthical strategies" Dept. Child Neuropsychiatry, Neurological Institute "Carlo Besta" Milan
- 2008-today: Full-time employee as child neurologist at Dept. Child Neuropsychiatry, Neurological Institute Carlo Besta; Milan
- Responsible for the out-clinic patients with movement disorders

Main research focus:
- clinical spectrum and natural history of rare genetic movement disorders
- NBIA, with special interest in PKAN (principal and co-investigator in therapeutic trial)
- Surgical treatment of movement disorder, with special focus on deep brain stimulation for pediatric dystonia

Webinar outline

- Classification of paroxysmal dyskinesias
- Clinical description of the main forms and syndromes
- Genetic
- Differential diagnosis
- Principles of Treatment

Learning objectives

By the end of this webinar you will be able to:

- recognise and classify paroxysmal movement disorder

-define appropriate genetic investigation

-decide therapeutic approach

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Definition

Paroxysmal dyskinesias (or paroxysmal movement disorder) refer to attacks of abnormal movements (chorea, dystonia, ballism, isolated or in combination) lasting from seconds to hours.

History

- ✓ First patient reported in 1892 by Kure et al under the term of "atypical Thomsen disease"
- ✓ Mount and Reback (1940) introduced the term "paroxysmal dystonic choreoathetosis"
- ✓ Kerst and Weber (1967) reported families with "familial kinesigenic choreoathetosis"
- ✓ Lance (1977) classified attacks according to duration, phenomenology and trigger factors
- ✓ Goodenough (1978) noticed familial and acquired dyskinesias
- ✓ Demirkiran and Jankovic in 1995 proposed the current classification and nomenclature

Classification of paroxysmal dyskinesias (PD)

By triggering factor

- ✓ Paroxysmal kinesigenic dyskinesias (PKD)
- ✓ Paroxysmal non kinesigenic dyskinesias (PNKD)
- ✓ Paroxysmal exercise induced dyskinesias (PED)
- ✓ Paroxysmal hypnogenic dyskinesias (PHD)

By etiology

- ✓ Genetic («primary),
- ✓ Secondary (acquired)
- ✓ Psychogenetic

Table 4. Primary vs Secondary dyskinesias.

Primary	Secondary
Early age of onset	Onset in adulthood
Normal interictal examination	Baseline findings on exam (depending on cause)
Positive family history	No family history
Reasonably constant clinical features	Variability in duration and frequency
Reasonably constant trigger	May have mixed triggers

Table 6. Diagnostic clues to psychogenic paroxysmal movement disorders

Adult age of onset
Variability in movement phenomenology, or paroxysmal tremor
Variable and/or prolonged duration of attacks
Odd triggers (i.e. during medical examination)
Unusual relieving maneuvers, including distractibility and entrainment
Additional somatic or medically unexplained symptoms
Multiple, inconsistent triggers
Inconsistent or atypical response to medication

EXPERT REVIEW OF NEUROTHERAPEUTICS
2019, VOL. 19, NO. 9, 807–822

Paroxysmal kinesigenic dyskinesias. Diagnostic criteria

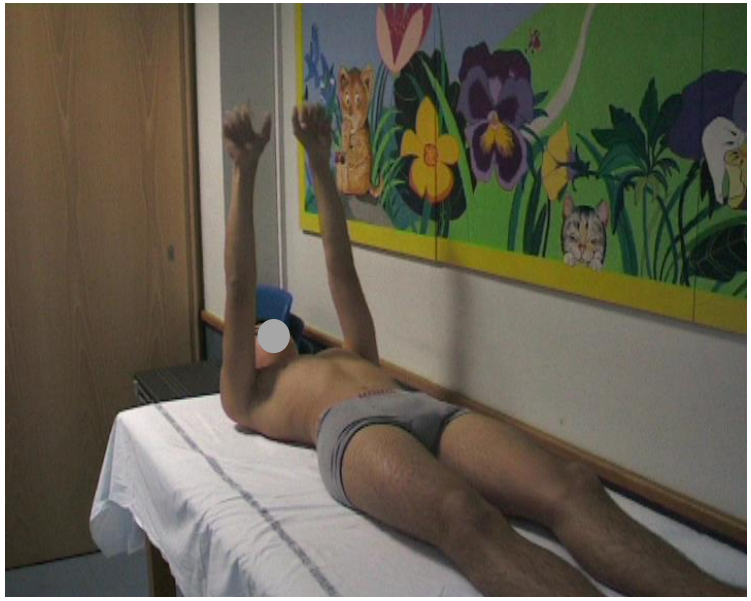
- ✓ Age at onset during infancy or adolescence (1-20 yrs)
- ✓ Kinesigenic trigger for the attacks
- ✓ Short duration >1 min
- ✓ No loss of consciousness or pain
- ✓ Normal interictal neurological examination
- ✓ Lack of an alternative organic or structural explanation
- ✓ Complete response to carbamazepine or phenytoin

Bruno et al, 2004

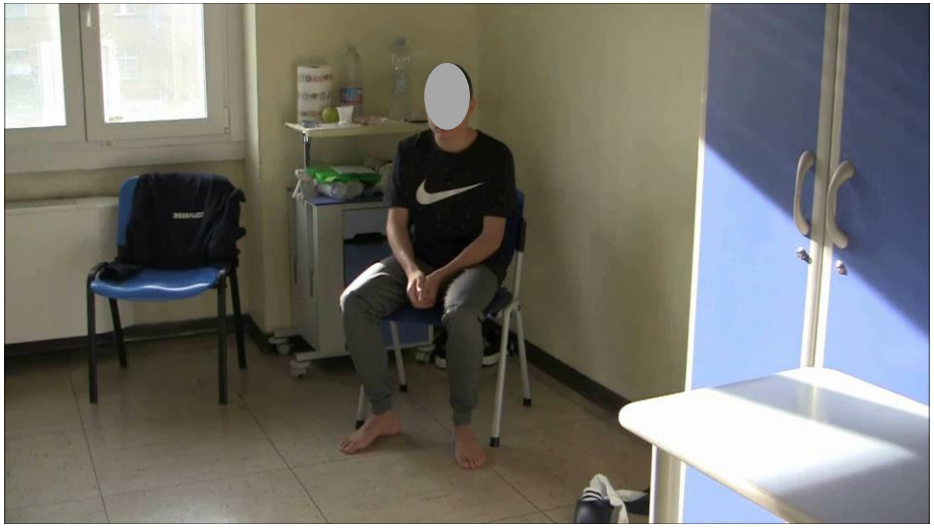
Paroxysmal kinesigenic dyskinesias: clinical aspects

- ✓ Males more affected
- ✓ Generalized, unilateral, involvement of facial muscles
- ✓ Chorea, choreoathetosis, dystonia, ballism isolated or in combination
- ✓ Frequency: occasional to many times a day (>100)
- ✓ Attacks can be preceded by an aura or a premonitoring sensation
- ✓ Attacks can be provoked by the sole intention to move (apparently non kinesigenic)
- ✓ Dyskinesias tend to spontaneously improve over time, some patients have a complete remission in adulthood
- ✓ Patients may have other paroxysmal episodes

Paroxysmal kinesigenic dyskinesias: video cases



Undefined PKD



PRRT2-related PKD

Paroxysmal kinesigenic dyskinesias: video cases

A

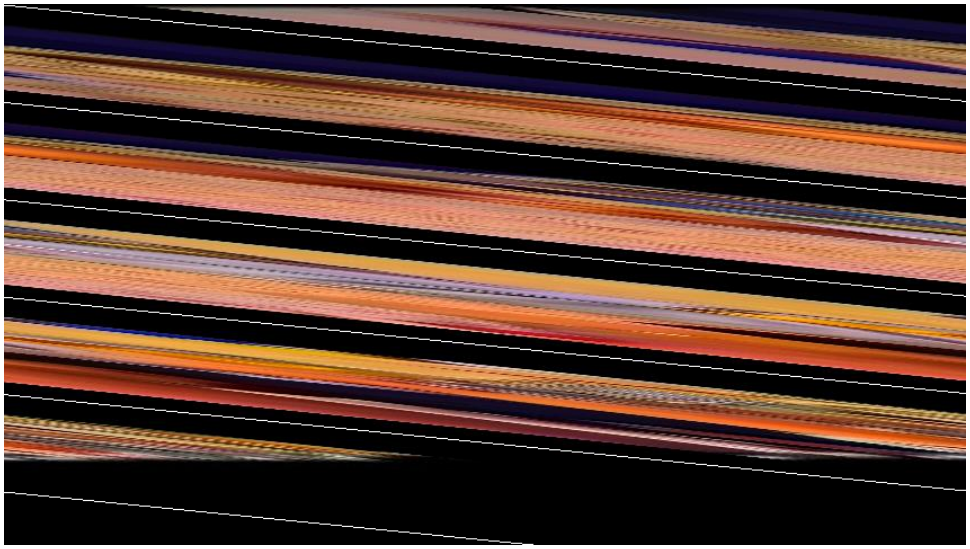
C

B

A-B: PRRT2-related PKD

C. Undefined PKD

Paroxysmal kinesigenic dyskinesias: video cases



Paroxysmal kinesigenic dyskinesias: genetic

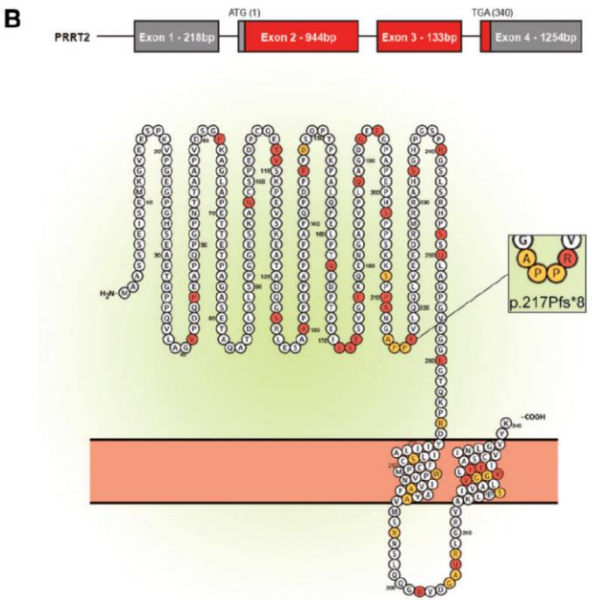
PKD is a genetically heterogeneous condition

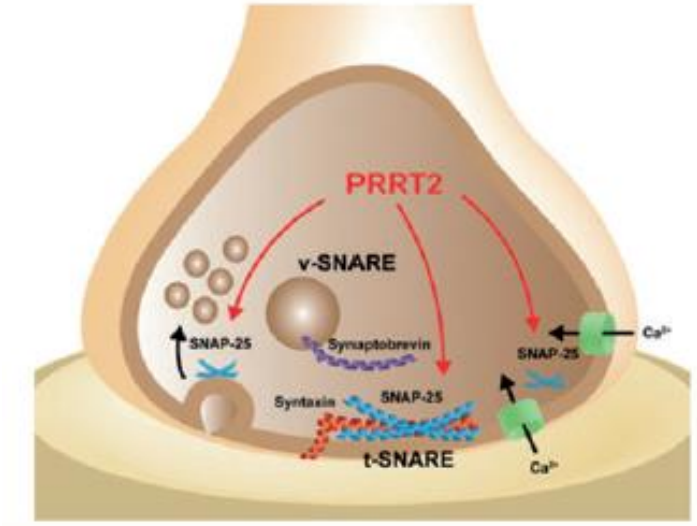
- **PRRT2**
- SLC16A2, KCNA1, ADCY5, SLC2A1, SCN8A, SLC20A2, CLCN1, KCNMA1, DEPDC5, MR-1

PRRT2 gene

PRRT2 (proline-rich transmembrane protein 2) on 16p11.2 is the leading cause for PKD a wide and yet evolving spectrum of paroxysmal diseases.

- ✓ It is expressed in the central nervous system the cortical layers of the cerebral cortex, basal ganglia and cerebellum
- ✓ It is thought to be involved in the modulation of synaptic neurotransmitter release

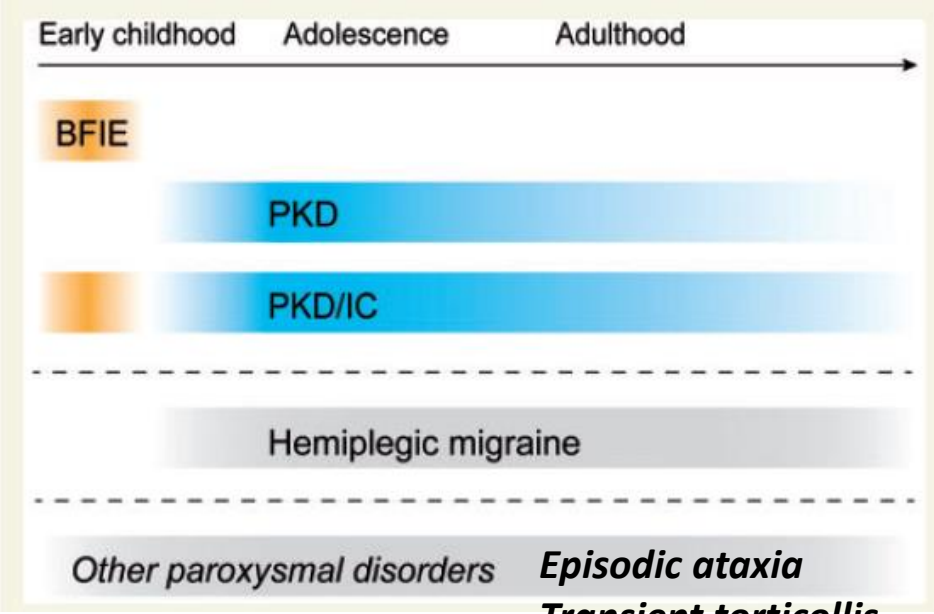




BRAIN 2015: 138; 3476–3495

PRRT2 gene: clinical spectrum

Heterozigous mutations



Episodic ataxia
Transient torticollis
Migraine with aura

BRAIN 2015: 138; 3476–3495

Deletion of the 16p11.2 region

-Intellectual disability
-Developmental problems
-Autism spectrum disorder
-Epilepsy/PD

Biallelic PRRT2 mutations

-intellectual disability
-episodic ataxia
-seizures

PKD: treatment

- Carbamazepine is the drug of choice and low dosages (e.g. 50–200mg/day) are usually sufficient
- Patients with the 4 common PRRT2 mutations (c.649dupC, c.514_517delTCTG, c.972delA, c.649delC) are more likely to achieve remission through treatment with carbamazepine and might even require lower dosages.
- Other anticonvulsive agents may also be effective, including phenytoin, valproate, oxcarbazepine, lamotrigine, levetiracetam or topiramate.
- Some patients respond to levodopa
- Since attack frequency decreases with age, treatment may eventually be tapered or even discontinued in adulthood
- Other paroxysmal episodes (hemiplegic migraine) due to PRRT2 mutations are also respondig to carbamazepine

Paroxysmal non-kinesigenic dyskinesias: diagnostic criteria

- ✓ Hyperkinetic, involuntary dyskinetic attacks usually lasting 10 min-1 hour (up to 4 hours)
- ✓ Attacks not triggered by sudden voluntary movements or physical exertion
- ✓ Normal interictal examination
- ✓ Onset in infancy or early childhood
- ✓ Attacks may be precipitated by caffeine and/or alcohol
- ✓ Family history of movement disorder with the above feaures

Bruno et al, 2007

Paroxysmal non-kinesigenic dyskinesias: clinical aspects

- ✓ Attacks are predominantly dystonic typically lasting ten minutes to one hour, but potentially up to four hours
- ✓ Unilateral or bilateral involvement
- ✓ Patients may experience pain or exhaustion, attacks can involve respiratory muscles and be life threatening (fatal laryngeal spasms)
- ✓ Usually not more frequent that once a day
- ✓ Precipitation of attacks by menses, caffeine, alcohol, excitement, stress, fatigue.
- ✓ Poor response to pharmacological treatment (compared to PKD)

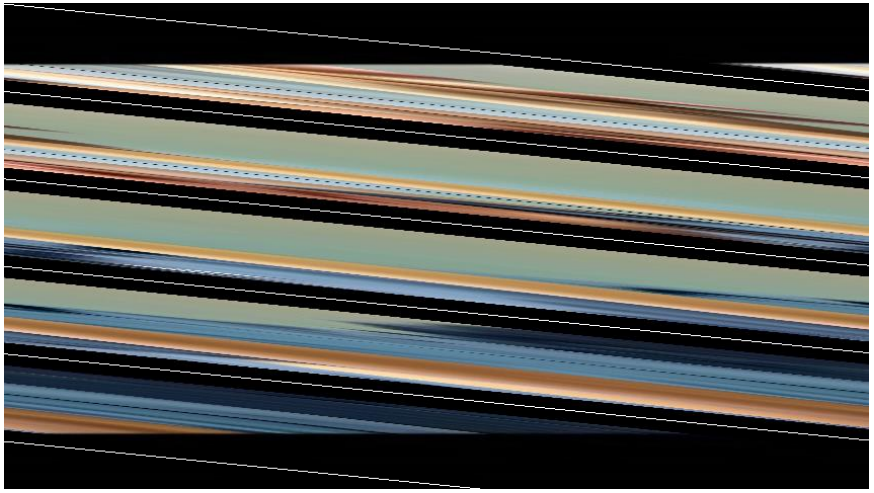
Paroxysmal non-kinesigenic dyskinesias: genetic

PNKD is a genetically heterogeneous condition

- ✓ **Myofibrillogenesis regulator 1 (MR-1) gene** located on chromosome 2q (Familial PNKD) : Three missense mutations: p.A7V p.A9V and p.A33
  Autosomal dominant with reduced penetrance

- ✓ **PRRT2**, **SLC2A1**, KCNMA1, **ADCY5**, **ATP1A3**, ATP1A2, PDGFB, FGF14, BCKDc, GLDC, SLC16A2, SCN8A, PDHA1, PDHX, DLAT, ECHS1, SCN1A, **GNAO1**

Paroxysmal non-kinesigenic dyskinesias: videos



MR-1-related PKND

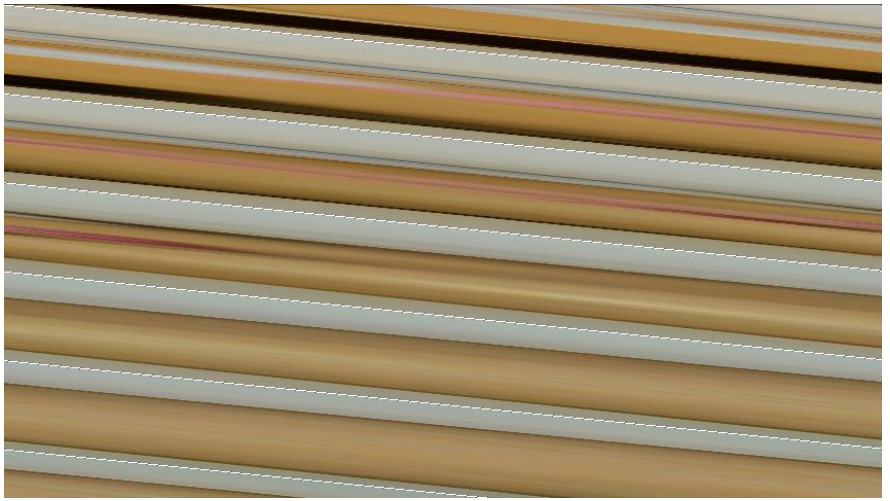
Van Coller et al, Stereotactic Funct Neurosurgery 2014

SLC2A1-related PNKD

Zorzi et al, Neurology 2009

Paroxysmal non-kinesigenic dyskinesias: videos

GNAO1-related PNKD



PNKD of unknown etiology

Paroxysmal non-kinesigenic dyskinesias: treatment

"Genotype –oriented" treatment

MR-1:

- ✓ Avoid triggers (e.g., caffeine, alcohol).
- ✓ Clonazepam or diazepam can be effective in at least 50%
- ✓ Annedoctical cases responding to Carbamazepine, Gabapentin, Levetiracetam, Acetazolamide
- ✓ Few cases responding to DBS

PRRT2, **SLC2A1**, KCNMA1, **ADCY5**, **ATP1A3**, ATP1A2, PDGFB, FGF14, BCKDc, GLDC, SLC16A2, SCN8A, PDHA1, PDHX, DLAT, ECHS1, SCN1A, **GNAO1**

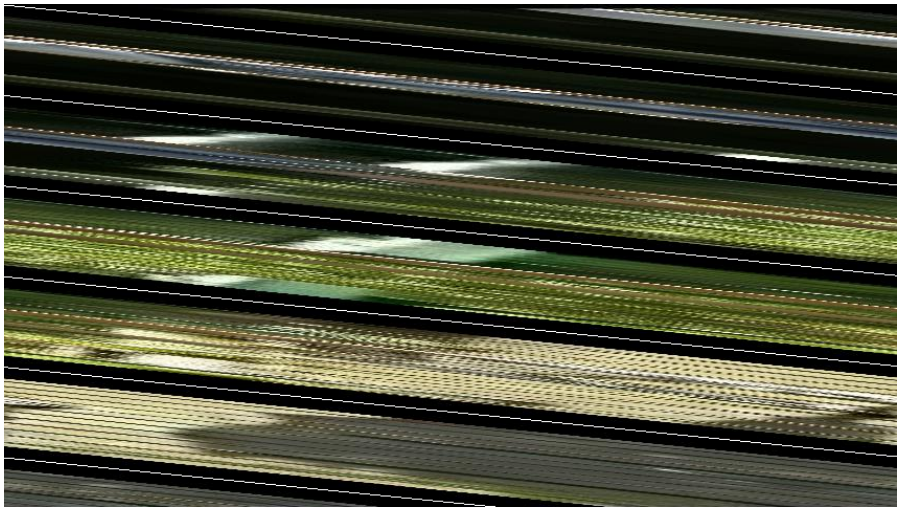
Paroxysmal exercise-induced dyskinesias: diagnostic criteria

- ✓ Hyperkinetic, involuntary dyskinetic attacks occurring after few minutes-1 hour of exercise
- ✓ Duration of attacks is variable, episodes resolve with rest
- ✓ Variable frequency from daily to monthly

Paroxysmal exercise-induced dyskinesias: clinical aspects

- ✓ Attacks are usually dystonic, mainly in the legs
- ✓ Attacks usually arise in the body part most involved in the exercise, but may spread to contiguous body region
- ✓ May be painful, described as muscle cramps
- ✓ Patients may have other paroxysmal symptoms (migraine, epilepsy) or interictal neurological abnormalities
- ✓ Onset ranges from infancy to late adulthood

Paroxysmal exercise-induced dyskinesias: video

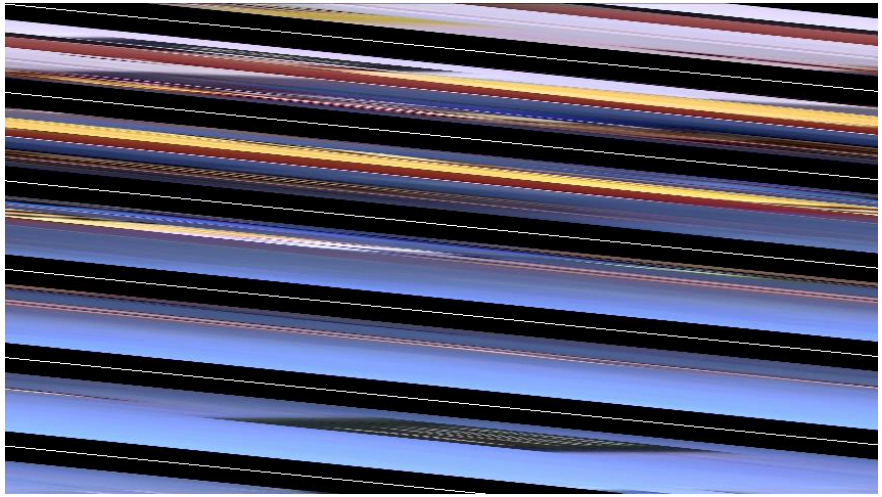


SLC2A1-related PED

Zorzi et a, Neurology 2008

GCH-1 related PED

Paroxysmal exercise-induced dyskinesias: video cases



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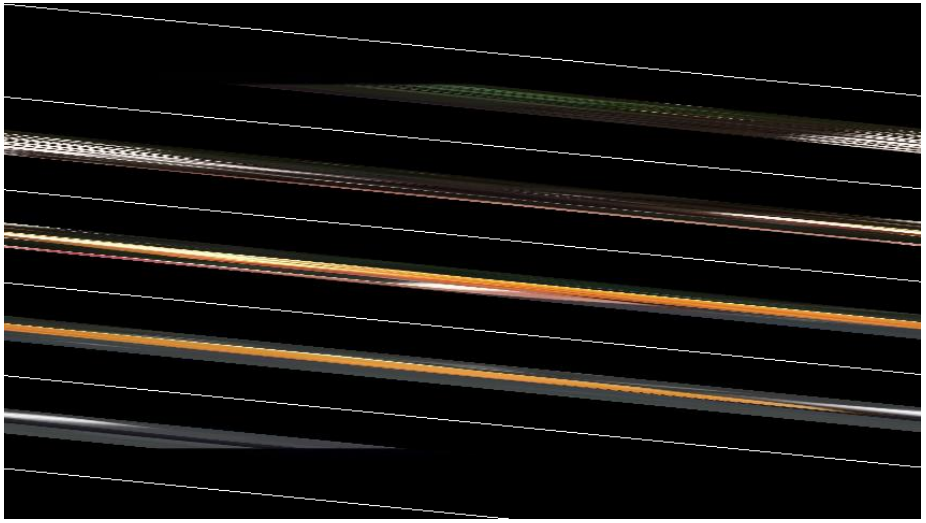


TBC1D24-related PED

Luthy et al, Brain 2109

Paroxysmal exercise-induced dyskinesias: genetic

PED is a genetically heterogeneous condition

SCL2A1 encodes for the glucose transporter type 1 (Glut1), the most important energy carrier of the brain across the blood–brain barrier

CGH-1 (DRD**), Park-2** (Parkin)

PDHA1, PDHX, DLAT, ECHS1

CACNA1A, PRRT2, PNKD, ATP1A3, ADCY5, ALDH5A, TBC124

Paroxysmal exercise-induced dyskinesias: treatment

Genotype-oriented treatment

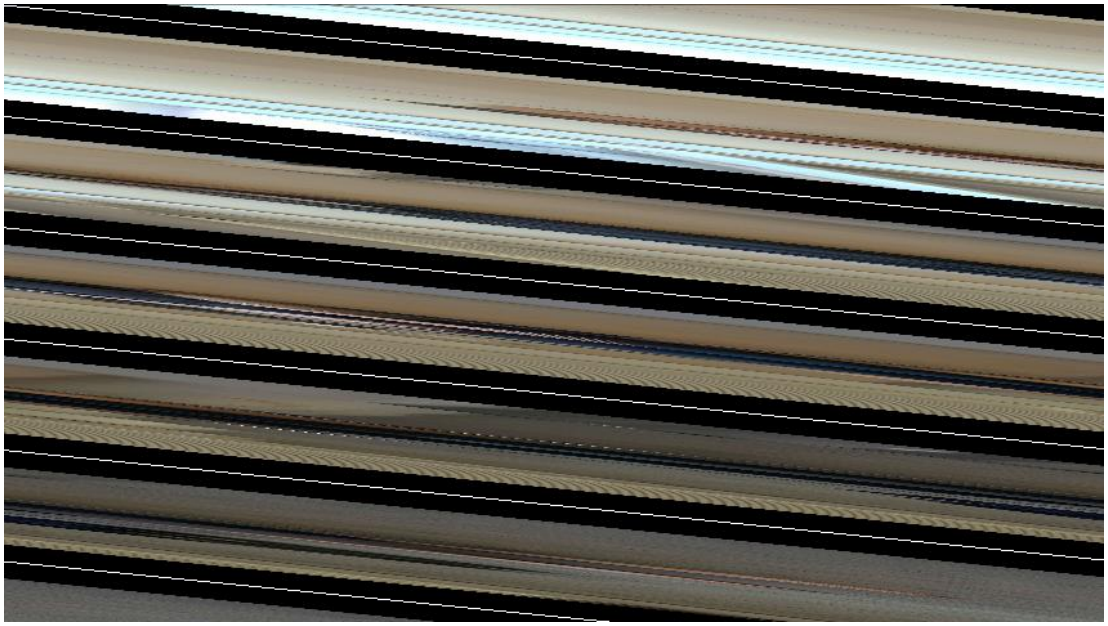
- **SCL2A1:**
  - ✓ The ketogenic diet is the goal standard treatment
  - ✓ Triheptanoin appears useful in decreasing the frequency of attacks
- **CGH-1** (DRD**), Park-2** (Parkin) : L-Dopa\Carbidopa
- **Piruvate dehidrogenate complex (PDHA1, PDHX, DLAT):** thiamine
- **ECHS1** : , valine restricted diet and N-acetylcysteine supplementation
- **CACNA1A, PRRT2, PNKD, ATP1A3, ADCY5, ALDH5A, TBC124**

Paroxysmal hypnogenic dyskinesias: clinical and genetic

- ✓ First described in 1981 (Lugaresi et al): brief dyskinetic attacks arising in NON-REM sleep, responding to CBZ (ADNFLE)

- ✓ Dyskinetic attacks arising during sleep:
  ADCY5, PRRT2

Paroxysmal hypnogenic dyskinesias: video case



ADCY5-related PHD

Chan et al, Mov Disord 2016

Secondary paroxysmal dyskinesias

Cause	Phenomenology	Clinical clues*
Demyelinating disease	PKD, PNKD, EA, 'tonic spasms'	Abnormal brain or spine MRI; OCBs in the CSF
Cerebrovascular disease (e.g. TIA, Stroke, Moya Moya)	PKD, PNKD, EA	Contralateral to disease area, most often BG, subcortical WM or brainstem, headaches or seizures (Moya Moya), abnormal vessel imaging
CNS trauma	PKD, PNKD	Other neurological deficits from trauma
PNS Trauma	PKD, PNKD	Controversial; may have previous hx of neurological disease; most often delayed presentation of dystonic posturing in the myotomal distribution, paresthesias
Hypoxic-ischemic injury	PKD, PNKD	May have delay between injury and presentation
Kernicterus	PNKD	May have delay between injury and presentation
Infections (syphilis, CMV, HIV, H1N1)	PKD, PNKD	Laboratory abnormalities; MRI brain may be normal or with WM changes
Migraine	PNKD	Usually as an aural symptom, followed by migraine. Responds to migraine treatment.
Autoimmune conditions (SLE, APLS, Behçet's, anti-VGKC, Hashimoto's, paraneoplastic limbic encephalitis, Celiac disease	PKD, PNKD, EA	Systemic involvement, seizures, encephalopathy, Autoantibodies, MRI changes in WM or BG, mesial temporal areas in limbic encephalitides
Metabolic disorders (hypo or hyperglycemia, hypo/hyperparathyroidism, hypocalcemia, thyrotoxicosis)	PKD, PNKD	Presence of diabetes, thyroid or parathyroid disease, laboratory abnormalities in basic chemistry and/or hormonal levels
Basal ganglia calcifications (with or without hypocalcemia)	PKD, PNKD	Calcifications on brain CT, hypointense on T2 and hyperintense on T1 brain MRI; occasionally laboratory abnormalities in Ca, P and PTH levels
Other structural lesions in the CNS (e.g. tumor, meningioma, Chiari with syringomyelia, etc.)	PKD, PNKD	Baseline deficits or abnormal imaging in neuroanatomically congruent area
Methylphenidate treatment	PKD	Onset shortly after treatment initiation
Parkinsonism (Parkinson's disease, PSP, vascular Parkinsonism)	PKD, PED	Late onset, clinical examination and imaging
Neuroacanthocytosis	PKD	Acanthocytes on blood smear

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Clinical case 1

Age 12 yrs
No family history
Normal psychomotor development
Brief, stereotyped episodes mostly occurring after a sudden movement: eye deviation and abnormal hand posturing
No loss of consciousness

What is the most probable diagnosis

A: paroxysmal kinesigenic dyskinesias
B: focal seizure
C: tic
D : psychogenic paroxysmal dyskinesias

Clinical case 2

Age 5 yrs
No family history
Normal psychomotor development
At age 4.5 abnormal movement of one leg occurring only when walking, with progressive disability (she needs support for walking)

What is the most probable diagnosis

A:Paroxysmal exercise induced dyskinesia
B: Action dystonia (walking dystonia)
C: Paroxysmal kinesigenic dyskinesia

Differential diagnosis (functional MD excluded)

PKD:

- ✓ tics
- ✓ Action induced movement disorder
- ✓ Chronic movement disorder (autoimmune chorea)
- ✓ Focal seizures

PNKD

- ✓ stereotypes
- ✓ Tics

PED

- ✓ Action induced movement disorder
- ✓ Stereotypes
- ✓ Tics

PHD

- ✓ Focal seizures
- ✓ Sleep-related non-epileptic paroxysmal motor phenomena (parasomnia)

Key Points /Conclusions

Paroxysmal dyskinesias
(exclusion of mimics^ and psychogenic cause)

→ Exclusion of acquired/neurodegenerative causes (usually later onset; table 2)

Trigger	Sudden movement		Alcohol or caffeine	Other non-kinesigenic triggers# / none				Prolonged exercise		During sleep	
	Active	*Passive*									
Duration	Sec to min	Sec to min	Hours	Variable				Min to hours		Sec to min	
Typical distribution	Limbs	Limbs	Limbs	Limbs	Limbs	Rostro-caudal	Neck	Limbs/Axial	Limbs	Limbs	
Additional clinical features§	-/E/M/EA	MR	-/M	E/MR	-	HP/A/E/Au	-/M/EA	-/ Leigh syndrome	-/A/S/E/MR	-/E	MD/ hypotonia
Family History	-/+ (AD)	X-linked	+ (AD)	-/+ (AD)	+ (AD)	-/+ (AD)	-/+ (AD)	Variable	-/+ (AD)	-/+ (AD)	+ (AD)
Investigations	-	Raised serum fT3	-	-	Brain calcification	-	-	Pallidal hyper-intensity/CSF**	CSF**	-	-
Most common mutations (onset)	*PRRT2** (<18y)	*SLC16A2* (<2m)	*MR-1* (<18y)	*KNCMA1* (<18y)	*SLC20A2*= *PDGFB* (<18y)	*ATP1A3* (<18m)	*CACNA1A* (<1y)	*ECHS1* (<18y) *PDHA1*(<2y)	*SLC2A1* (variable, usually <18y)	*PRRT2* (<18y)	*ADCY5* (<18y)
Least common mutations (onset)	*MR-1* (<18y) *SCN8A* (<18y)					*ADCY5* (<18y)	*PRRT2* (<18y)	*PDHX* (<1y) *DLAT* (<1y)	*GCH1* (<18y)		

Roberto Erro, and Kailash P Bhatia J Neurol Neurosurg Psychiatry 2019;90:227-234

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European Reference Network Neurological Diseases (ERN-RND)

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Joint webinar series

THANK YOU

Next Webinar: ‘Primary progressive aphasia subtyping in clinical practice‘

26. May 2020, 15-16h CET