5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 12

EAN/MDS-ES: Hyperkinetic movement disorders (Level 2)

The paroxysm of dyskinesias

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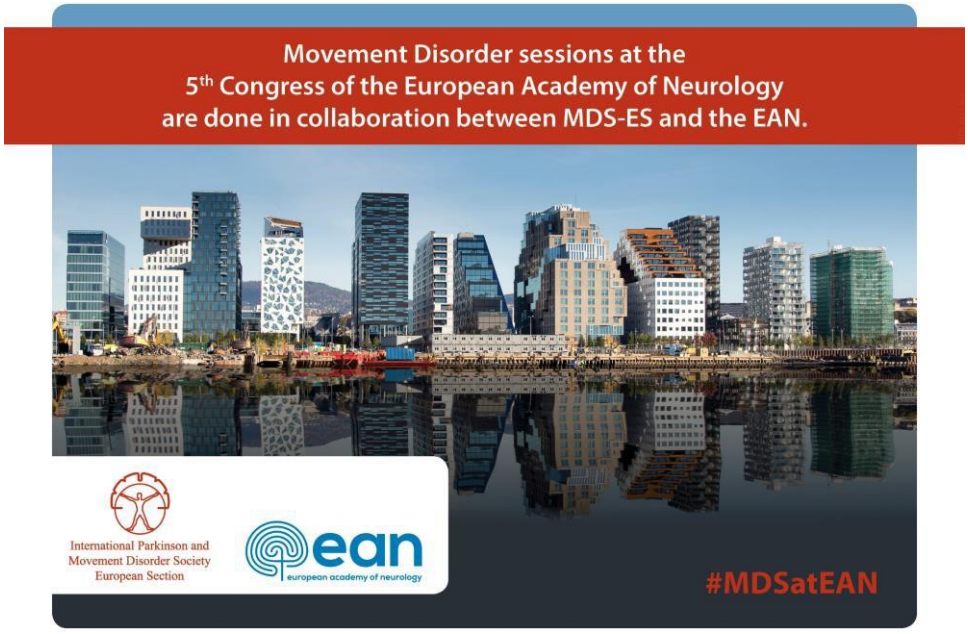

Conflict of Interest

In relation to this presentation and manuscript:

❑ the Author has no conflict of interest in relation to this manuscript.

The paroxysm of dystonia

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Learning objectives

1) **Characterize the various forms of paroxysmal dyskinesia**

2) **Approach the etiology and get some insight into the treatment of paroxysmal dyskinesia**

Paroxysmal dyskinesia

- **Paroxysmal dyskinesias = attacks of dystonic/choreic movements**
  - **no alteration of consciousness, speech can be altered but language is unaffected**

- **A new classification is emerging, based on both clinical and genetic characteristics *(Erro et al, Mov Disord, 2014)***

- **Recent genetic advances are rendering the historical, clinically-based classification obsolete**
  - **a given paroxysmal form of PDys / mutations in various genes**
  - **mutations in a given gene / various forms of PDys**

1. Functional paroxysmal dyskinesias

(Ganos et al., 2014)

- **Is a frequent cause of paroxysmal dyskinesias (ado, youth +++)**
- **Often mixed or complex paroxysmal hyperkinetic movements that are difficult to classify**
- **About 20% of the patients have coexisting organic MDS, usually manifesting in the same or contiguous body parts**
- **Diagnosis should be based on clinical grounds and after careful consideration of genetic and secondary forms**
- **Very important to make the diagnosis because it can lead to therapeutic approaches that are efficient in many patients**

  Very important to communicate this diagnosis to the patient in an appropriate manner because it may be useful therapeutically

Functional paroxysmal dyskinesias: clues

(Ganos et al., 2014)

- **Paroxysmal tremor is part of the phenotype**
- **High within-subject variability between episodes**
- **Precipitation of attacks during examination**
- **Atypical and variable duration of attacks**
- **Presence of multiple and atypical triggers**
- **Presence of odd precipitating/relieving factors**
- **Other unexplained/functional manifestations**
- **Atypical response to medication**

2. Symptomatic paroxysmal dyskinesia

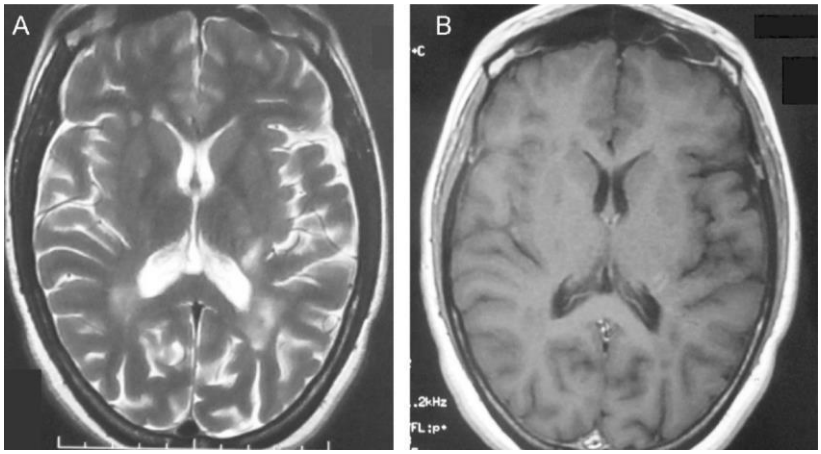
- **First step in the diagnostic process: primary, functional or symptomatic ?**
- **Features suggesting an underlying cause include:**
  - **onset in adulthood (not so frequent in children)**
  - **absence of a family history**
  - **variable duration of attacks and triggering factors**
  - **abnormal interictal clinical status**
  - **abnormal laboratory or MRI findings**

Symptomatic paroxysmal dyskinesia

- **There are numerous causes of symptomatic paroxysmal dyskinesia**
  - **Demyelinating diseases +++**
  - **Vascular disorders (stroke, transient ischemic attack) +**
  - **Autoimmune disorder**
  - **Basal ganglia calcifications**
  - **Hypo-/hyperglycemia**

Paroxysmal dystonia in multiple sclerosis
(El Otmani et al., Rev Neurol, 2014)

Paroxysmal dystonia (tonic spasm) due to multiple sclerosis



New gadolinium enhanced lesion within the posterior limb of the left internal capsule
PD in MS are frequently associated with lesions of the internal capsule
(Fröhlich, J neurol, 2018)

Paroxysmal dystonia / tonic spasm in multiple sclerosis	
Type of movements	Dystonic postures of limbs and/or face
Duration	30 seconds to 2 minutes
frequency	Up to 60/jour
aura	sensitive
Triggering factors	movement, tactile stimulation, noise, hyperventilation
Treatment	Carbamazepine

(Tranchant, Bhatia and Marsden, Mov Disord,1995)

3. Paroxysmal kinesigenic dyskinesia

- **Attacks of dystonia and chorea**
- **Triggered by a brisk movement**
- **Duration is less than one minute**
- **No alteration of consciousness**
- **Good response to antiepileptics**

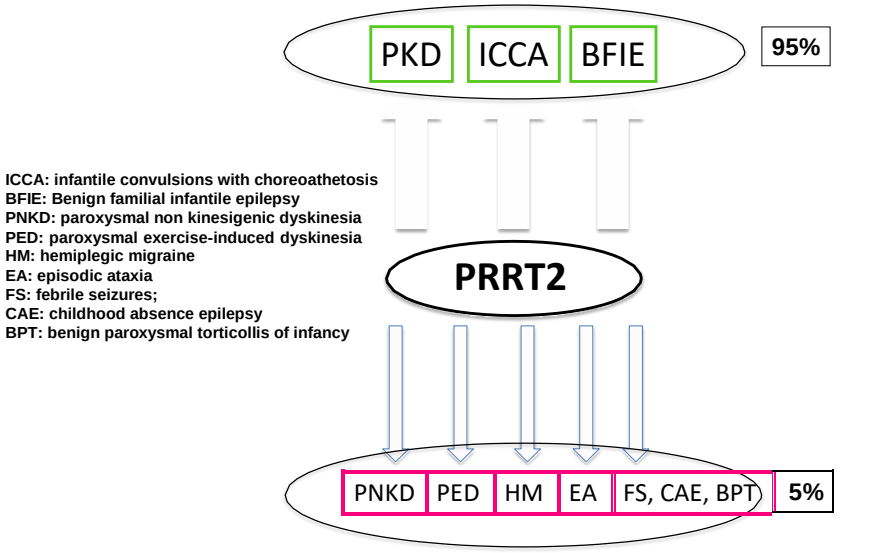
PRRT2 is the main culprit gene for PKD

(Méneret et al, 2012; Méneret et al, 2013; Huang et al, 2015; Ebrahimi-Fakhari 2015)

- **About 50% of PKD patients, autosomal dominant**
- **Probably more than that in the European population and in familial forms**
- **In *PRRT2* patients: onset tend to be at an earlier age**
- **Clinical examination is normal between the episodes**
- **Most patients have a truncating mutation and the prevailing hypothesis is a loss of function resulting in neuronal hyperexcitability within the basal ganglia**

PRRT2 can cause a large variety of paroxysmal disorders

(Méneret et al, 2012; Méneret et al, 2013; Huang et al, 2015; Ebrahimi-Fakhari 2015)



ICCA: infantile convulsions with choreoathetosis
BFIE: Benign familial infantile epilepsy
PNKD: paroxysmal non kinesigenic dyskinesia
PED: paroxysmal exercise-induced dyskinesia
HM: hemiplegic migraine
EA: episodic ataxia
FS: febrile seizures;
CAE: childhood absence epilepsy
BPT: benign paroxysmal torticollis of infancy

Méneret et al., Eur J Neurol, 2013

4. Paroxysmal exercise-induced dyskinesia

- **Attacks of dystonia and chorea**
- **Triggered by prolonged exercise**
- **Duration from a few minutes to a few hours**
- **No alteration of consciousness**
- **No response to antiepileptics**

GLUT1 deficiency due to mutations in *SLC2A1*

(Pons et al., 2010; Leen et al., 2012; Gras et al., 2014)

- **Glucose transporter type 1 deficiency syndrome is due to a dysfunction of the glucose transporter GLUT1 that limits brain glucose availability, thereby resulting in cerebral energy deficiency**

- **Clinical severity varies**
  - **from mild and/or intermittent motor problems**
  - **to severe neurological disability.**

- **Phenotype = variable combination of**
  - **acquired microcephaly**
  - **mental retardation**
  - **complex motor disorders (cerebellar, spasticity and mixed MDS)**
  - **paroxysmal manifestations (seizures, non epileptic)**

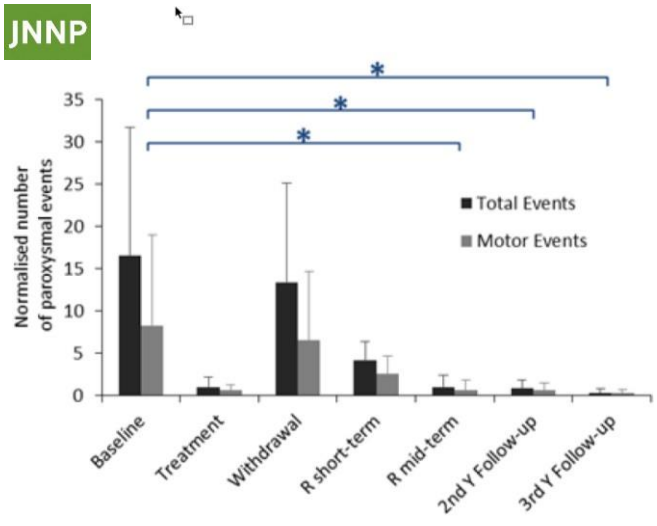
GLUT1 deficiency

(Leen et al., 2012; Gras et al., 2014)

- **Paroxysmal disorders other than seizures including paroxysmal dystonia are frequently observed and can be the sole or main manifestation of the disease** *(Schneider et al., 2009)*
- **Triggering of paroxysmal episodes by prolonged exercise or fasting is suggestive of this diagnosis**
- **The association of a wide range of paroxysmal manifestations is a good clue to the diagnosis**
- **Make an early diagnosis because the treatment, ketogenic diet, is effective**

Effect of triheptanoin on paroxysmal motor events GLUT1-def patients

Mochel et al., J Neurol Neurosurg Psychiatry, 2016; Hainque et al., J Neurol Neurosurg Psychiatry, 2019



(Mongin et al., Tremor and Other Hyperkinet Mov, 2016)
PED due to GLUT1 deficiency

(Castiglioni et al., Europ J Paed Neurol, 2015)
PED due to pyruvate dehydrogenase deficiency

Dopa-responsive dystonia: clinical clues

(Clot et al., 2009; Trender-Gerhardt et al., 2009)

- **Onset usually before age 10y**
- **Presenting symptom = (lower) limb dystonia, then generalization**
- **Possible associated features:**
  - **Parkinsonism tremor**
  - **Oculogyric crises**
  - **Axial hypotonia**
- **Marked diurnal fluctuation is a key feature when present**
- **Dramatic response to levodopa**
- **Mutation in the *GCH1* gene +++**

(Dale et al., DMCN, 2010)
PED due to dopa-responsive dystonia

5. Paroxysmal non kinesigenic dyskinesia

- **Attacks of dystonia and chorea**
- **No clear triggering factor but alcohol, coffee and stress could be precipitating factors**
- **Duration from a few minutes to a few hours**
- **No alteration of consciousness**
- **No response to antiepileptics apart from benzodiazepines**

Courtesy of Dr Sophie Drapier (Rennes)

PNKD due to mutations in *PNKD*

(Erro et al., 2014)

- **Onset in childhood or adolescence**
- **Typically : attacks of dystonia and chorea**
- **Triggering factors: alcohol, stress, coffee**
- **Minutes to hours**
- **No additional manifestations**
- **Good response to benzodiazepine**

PNKD due to *ATP1A3* mutations

(Roubergue 2012; Rosewitch 2012; Ozelius 2012; Heinzen 2012; Dard 2014; Sweney 2015)

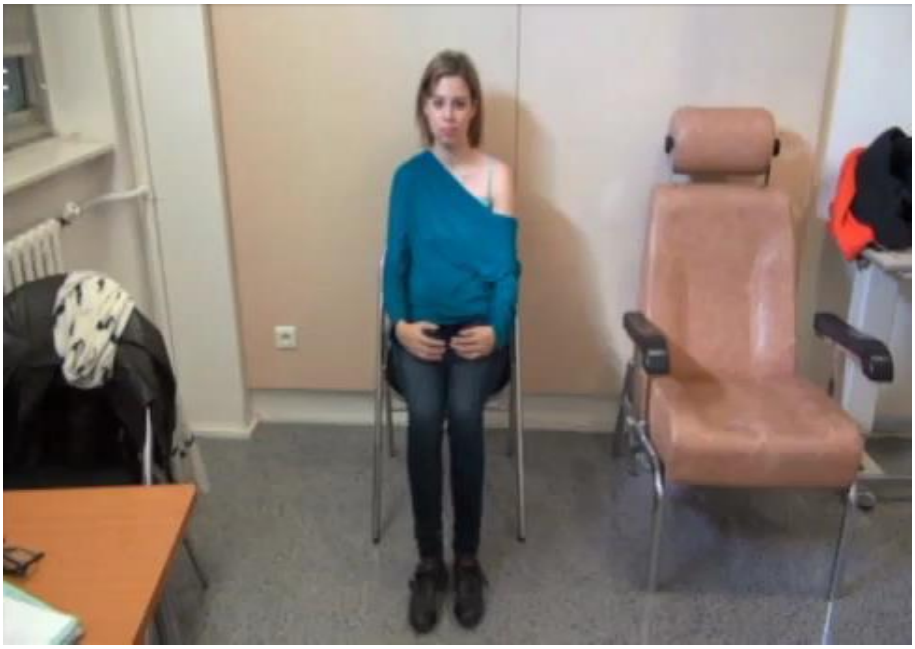
- **Very large phenotypic spectrum**
  - **Early infantile epileptic encephalopathy**
  - **Alternating hemiplegia of childhood**
  - **Relapsing encephalopathy with cerebellar ataxia**
  - **CAPOS (cerebellar ataxia/pes cavus/ optic neuropathy/SN deafness)**
  - **Rapid-Onset Dystonia-Parkinsonism**
- **AHC: episodic hemiplegia / dystonic or tonic attacks intellectual disability/ permanent movement disorders**
- **RODP: rapid onset of dystonia (hours to weeks) and parkinsonism**
- **Paroxysmal dystonia (PNKD +++)**
  - **in most AHC patients**
  - **In a few RDP patients**

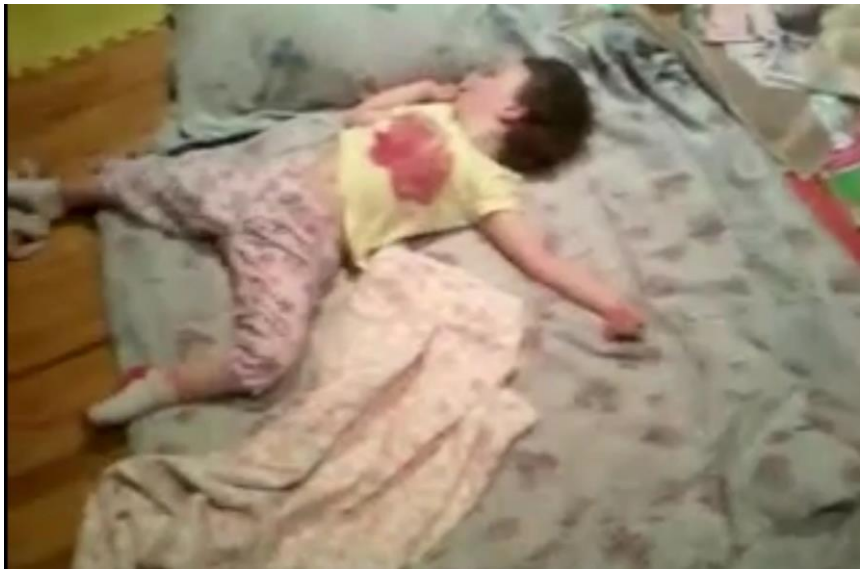
(Delorme et al., Ped Neurol, 2017)
Alternating plegic episode due to ATP1A3 mutation

PNKD due to *ADCY5* mutations

(Chang et al., 2016; Friedman et al., 2016; Chen et al., 2015; Mencacci et al., 2015, Méneret et al., 2019)

- **Childhood-onset mixed hyperkinetic movement disorder**
- **Axial hypotonia**
- **Typically without ataxia or epilepsy**
- **Stable or progresses very slowly**
- **Diagnosis clues**
  - **Orofacial myoclonus/chorea**
  - **Marked fluctuations (over a day, weeks, months)**
  - **Paroxysmal dyskinesia**
- **Paroxysmal dyskinesia in ADCY5 patients**
  - **Pleiotropic paroxysmal dyskinesia**
  - **Mostly PNKD**
  - **Including paroxysmal dyskinesia during nighttime**





LETTERS | 11 JUNE 2019 Annals of Internal Medicine®

Caffeine and the Dyskinesia Related to Mutations in the *ADCY5* Gene

Aurélie Méneret, MD, PhD; Domitille Gras, MD; Eavan McGovern, MD, PhD; Emmanuel Roze, MD, PhD

- **ADCY5-related dyskinesia is due to gain-of-function mutations in ADCY5, coding for adenylate cyclase type 5.**
- **This enzyme is highly expressed within the striatum, where it is activated by adenosine through A2A receptors.**
- **Adenosine receptors are the major target of caffeine**
- **Using caffeine to antagonize A2A receptors, thus inhibiting adenylate cyclase type 5, makes sense to reduce the hyperkinetic movement disorder seen in patients with ADCY5-related dyskinesia.**

Pathogenesis of ADCY5 dyskinesia
Functionnal MRI + transcranial magnetic stimultaion

If you have ADCY5 patients, age > 15, who are interested to be involved please contact us

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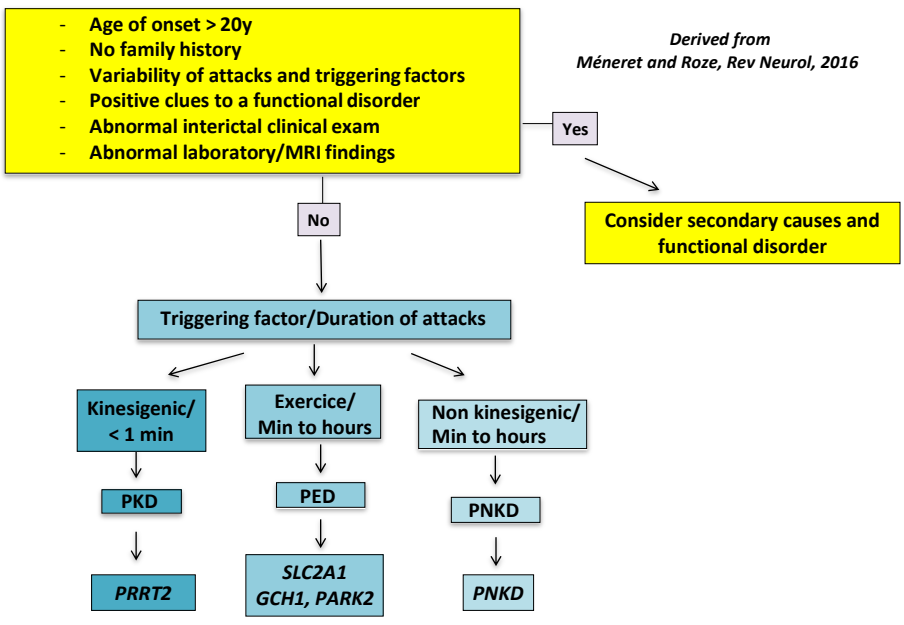
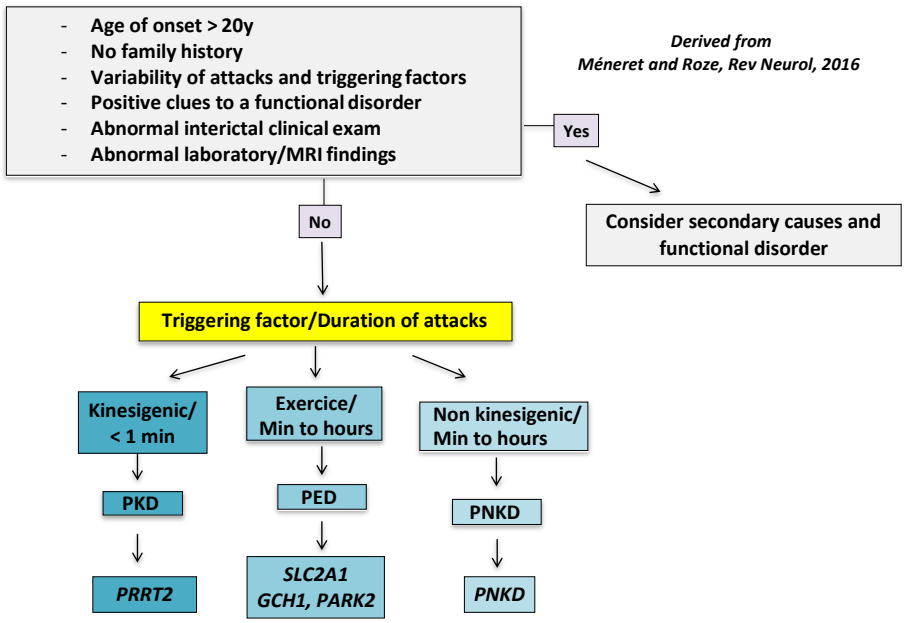
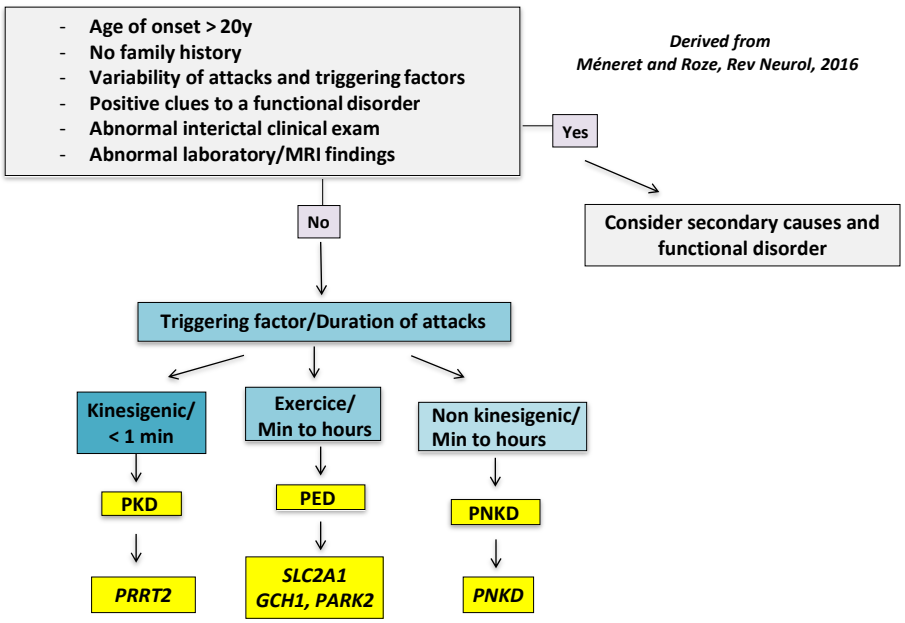



- Age of onset > 20y
- No family history
- Variability of attacks and triggering factors
- Positive clues to a functional disorder
- Abnormal interictal clinical exam
- Abnormal laboratory/MRI findings
Derived from
Méneret and Roze, Rev Neurol, 2016
Yes
Consider secondary causes and functional disorder
No
Triggering factor/Duration of attacks
Kinesigenic/ < 1 min
Exercice/ Min to hours
Non kinesigenic/ Min to hours
PKD
PED
PNKD
PRRT2
SLC2A1 GCH1, PARK2
PNKD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Consider secondary causes and functional disorder
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Triggering factor/Duration of attacks
Kinesigenic/ < 1 min
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PKD
PED
PNKD
PRRT2
SLC2A1 GCH1, PARK2
PNKD

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- Positive clues to a functional disorder
- Abnormal interictal clinical exam
- Abnormal laboratory/MRI findings

Derived and updated from
Méneret and Roze, Rev Neurol, 2016

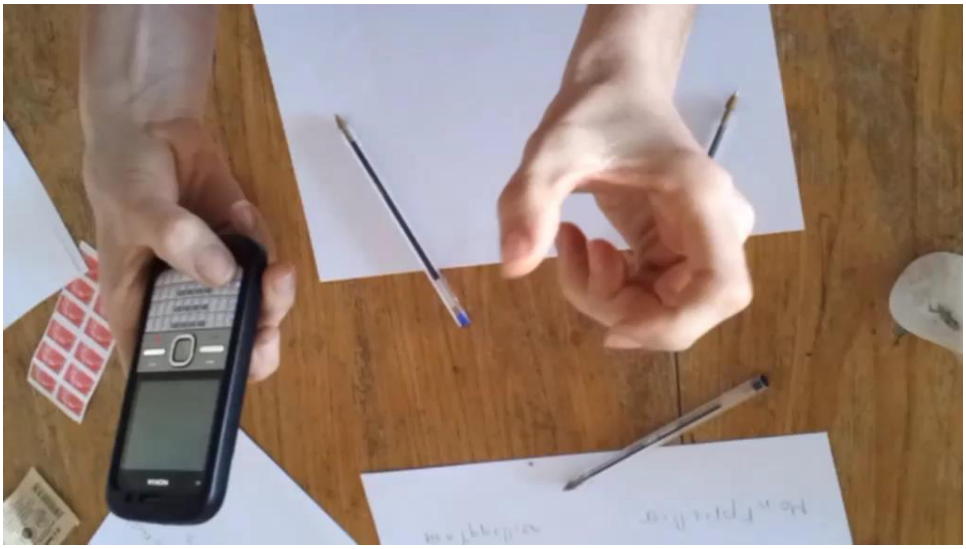
Yes → Consider secondary causes and functional disorder

No → Triggering factor/Duration of attacks

Kinesigenic/ < 1 min → PKD → ***PRRT2***
- *ADCY5*
- *SCN8A*
- *SCL16A2*

Exercice/ Min to hours → PED → ***SLC2A1***
- *GCH1, PARK2*
- *ADCY5, PDE2A*
- *PRRT2*
- *ATP1A3*
- *PDHA1, PDHX, DLAT*
- *ECHS1*
- *CACNA1A*

Non kinesigenic/ Min to hours → PNKD → ***PNKD***
- *PRRT2*
- *ADCY5, PDE2A*
- *SLC2A1*
- *ATP1A3*
- *KCNMA1*
- *KCNA1*
- *FGF14*
- BCKD complex
- *PDHA1, PDHX, DLAT*
- *SLC20A2, PDGFB*

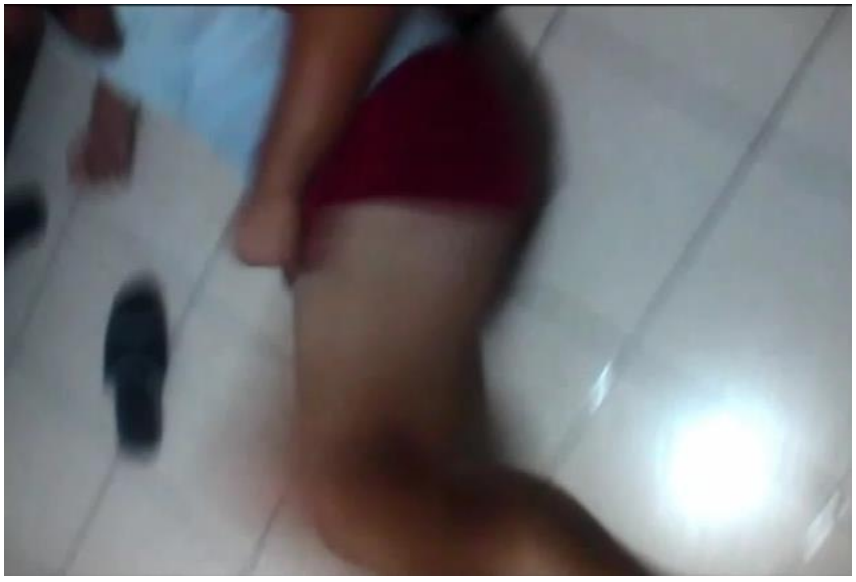


1 year history of reccurent paroxysmal episodes lasting for a few minutes

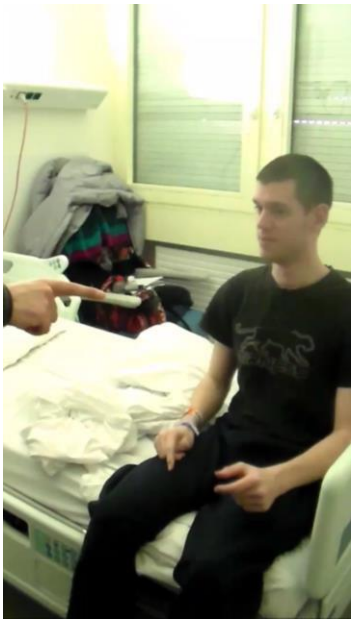
No ictal abnormality on EEG

Courtesy of Pr* Roongroj Bhidayasiri *(Bangkok)

Courtesy of Pr* Beomseok Jeon *(Seoul)



(Pozzi et al., Mov Disord Clin Pract, 2015)



Paroxysmal dystonia in neuromyelitis optica spectrum disease

Sleep in ADCY5-related dyskinesia: prolonged awakenings caused by abnormal movements

Aurélie Méneret, MD, PhD,[1,2*] Emmanuel Roze, MD, PhD[1,2*] Pauline Dodet, MD,[3] Jean-Baptiste Maranci, MD,[3] Diane Doummar, MD,[4] Florence Riant, PharmD,[5,6] Christine Tranchant, MD, PhD,[7,8,9] Valérie Fraix, MD, PhD,[10] Mathieu Anheim, MD, PhD,[7,8,9] Asya Ekmen,[2] Eavan McGovern, MD,[1] Marie Vidailhet, MD,[1,2] Isabelle Arnulf, MD, PhD,[2,3] Smaranda Leu-Semenescu, MD[3]

- *ADCY5*-related nocturnal paroxysmal dyskinesias are not elicited by sleep or due to a sleep disorder. They rather emerge after arousals and prevent patients to resume sleep immediately.
- The frequency of episodes of abnormal movements was increased after morning awakening

A simple blood test expedites the diagnosis of GLUT1 deficiency syndrome

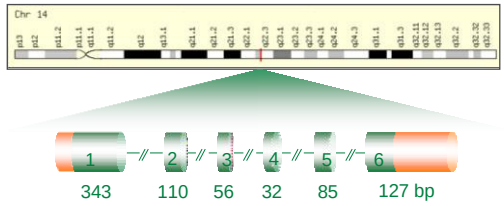
Domitille Gras, Christelle Cousin, Caroline Kappeler, Cheuk-Wing Fung, Stéphane Auvin, Nouha Essid, Brian Hy Chung, Lydie Da Costa, Elodie Hainque, Marie-Pierre Luton, Vincent Petit, Sandrine Vuillaumier-Barrot, Odile Boespflug-Tanguy, Emmanuel Roze, Fanny Mochel

Annals of Neurology in press.

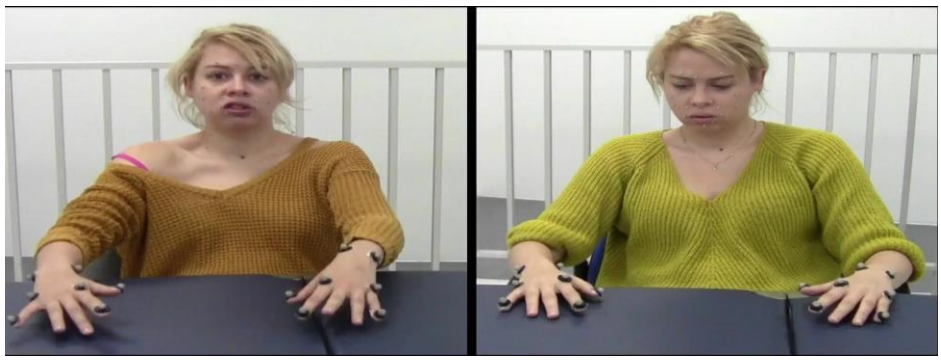
- We tested a novel simple and rapid blood test in 30 patients with GLUT1-DS with predominant movement disorders, 18 patients with movement disorders due to other genetic defects and 346 healthy controls.
- We detected significantly reduced GLUT1 expression only on red blood cells from patients with GLUT1-DS (23 patients, 78%), including patients with inconclusive genetic analysis.
- This test opens perspectives for the screening of GLUT1-DS in children and adults with cognitive impairment, movement disorder or epilepsy.

Dopa-reponsive dystonia (DRD)

- **Due to heterozygous mutation (+++) or deletion within the GTP cyclohydrolase gene, GCH1, in 70%**



- **Autosomal dominant with incomplete penetrance and female predominance (3:1)**



Triheptanoin (UX007; Ultragenyx Pharmaceuticals Inc; Novato; USA) is a medium odd-chain triglyceride containing three 7-carbon fatty acids. Its metabolism yields appropriate substrates for both fatty acid metabolism and anaplerosis. Triheptanoin is well tolerated and has been shown to improve clinical manifestations and/or brain metabolism in various disorders associated with patent brain energy deficits, such as glucose transporter deficiency, pyruvate carboxylase deficiency, and Huntington's disease.

Paroxysmal neurological disorders

- **Paroxysmal neurological disorders**
  - **isolated**
  - **part of a more complex disorder, with interictal manifestations**
- **They encompass apparently heterogeneous disorders**
  - **migraine**
  - **epilepsy**
  - **periodic paralysis**
  - **paroxysmal movement disorders (PD/EA primary/secondary)**
- **They are linked by**
  - **a common pathophysiological feature = neuronal hyperexcitability**
  - **overlapping genetic causes.**