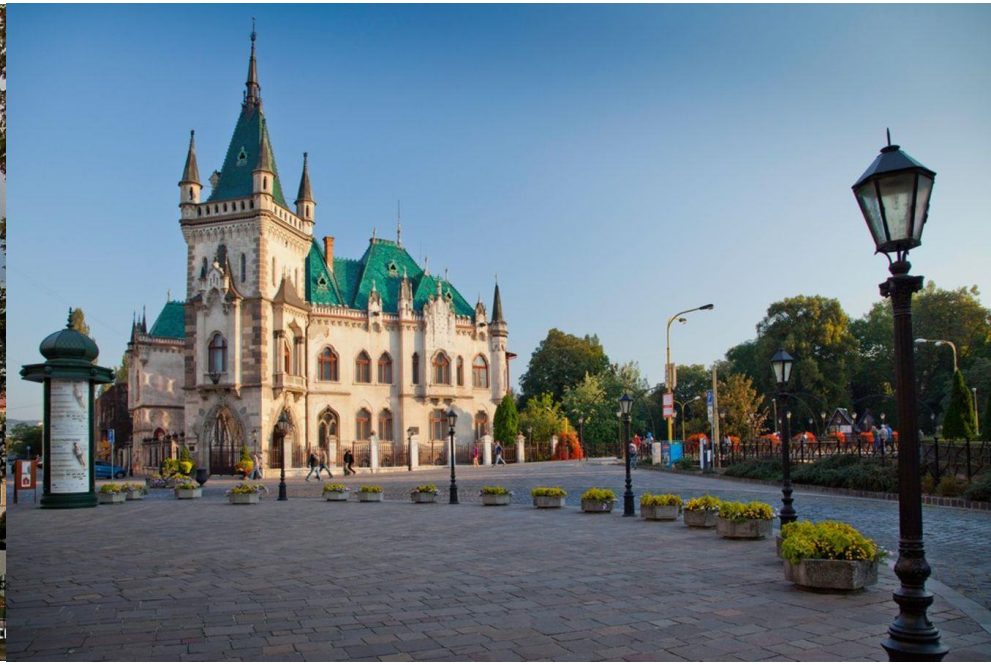


Diagnostic and therapeutic approach to patients with dystonia

Matej Škorvánek, MD, PhD
Dept. of Neurology and Center for Rare Movement Disorders
Safarik University and University Hospital, Kosice, Slovakia

REVIEW

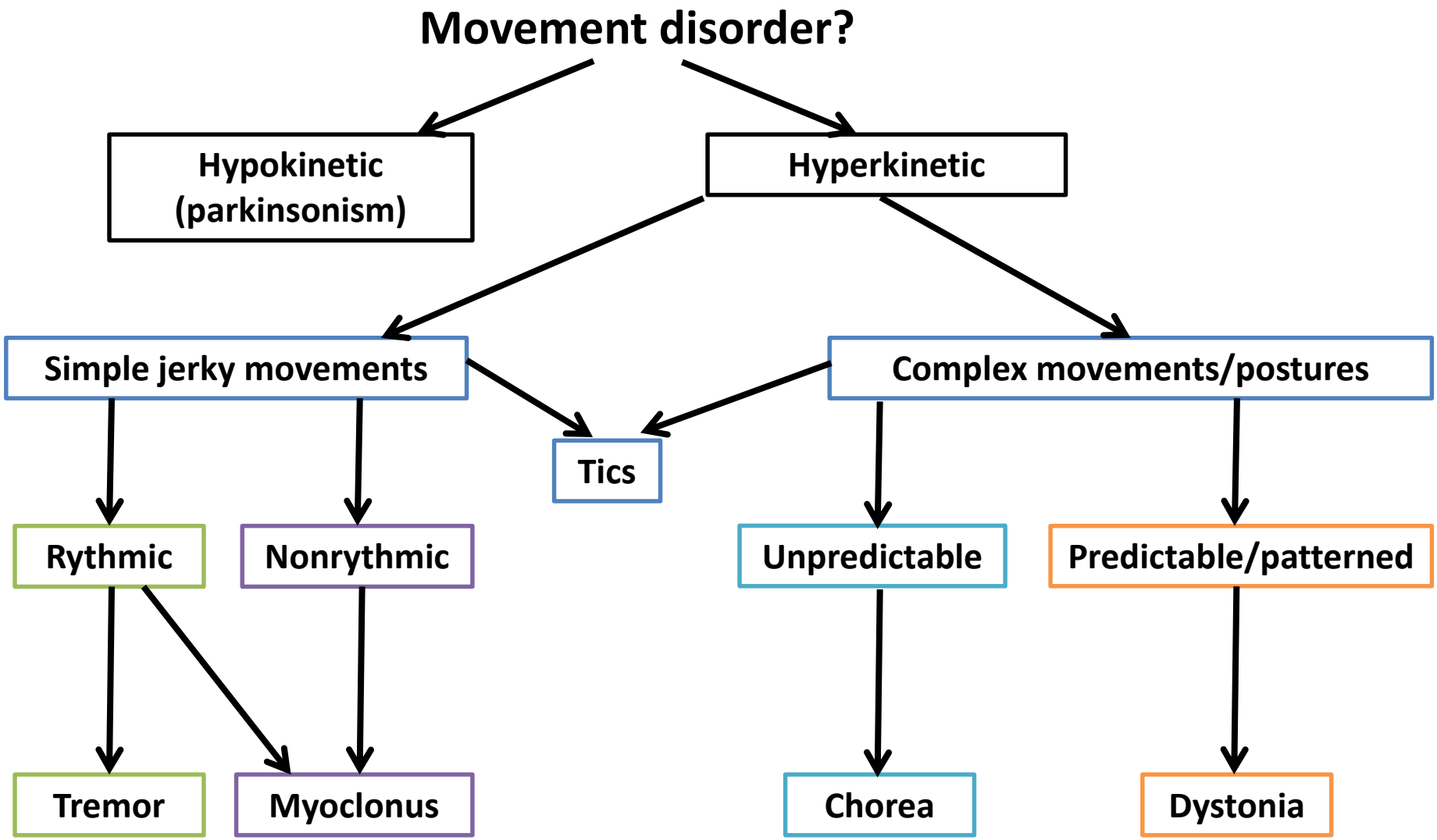
CME

Phenomenology and Classification of Dystonia: A Consensus Update

Alberto Albanese, MD,[1,2*] Kailash Bhatia, MD, FRCP,[3] Susan B. Bressman, MD,[4] Mahlon R. DeLong, MD,[5] Stanley Fahn, MD,[6] Victor S.C. Fung, PhD, FRACP,[7] Mark Hallett, MD,[8] Joseph Jankovic, MD,[9] Hyder A. Jinnah, PhD,[10] Christine Klein, MD,[11] Anthony E. Lang, MD,[12] Jonathan W. Mink, MD, PhD,[13] Jan K. Teller, PhD[14]

- Dystonia is defined as a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.
- Dystonic movements are typically patterned and twisting, and may be tremulous.
- Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

Albanese 2013


Movement disorder?
Hypokinetic (parkinsonism)
Hyperkinetic
Simple jerky movements
Complex movements/postures
Tics
Rythmic
Nonrythmic
Unpredictable
Predictable/patterned
Tremor
Myoclonus
Chorea
Dystonia

Differential diagnosis of hyperkinetic (rare) movement disorders

- 1. Phenomenology
- 2. Syndromological associations
- 3. Additional imaging/laboratory/genetic examinations

Phenomenology of dystonia

- Fixed dystonia
- Mobile dystonia
- Dystonic tremor/myoclonus
- Geste antagoniste

REVIEW CME

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Axis I: Clinical characteristics

I. Clinical characteristics
   I. Age of onset
   II. Body distribution
   III. Progression in time
      I. Disease course
      II. Variability

II. Associated features
   I. Dystonia isolated or combined with another movement disorder
   II. Other neurological or systemic disorders

Axis II: Etiology

I. Pathology of nervous system
   I. Proof of degeneration
   II. Proof of structural (often static) lesion
   III. Without proof of degeneration or structural lesion

II. Inherited or acquired disorder
   I. Inherited
   II. Acquired
   III. Idiopathic

According to age of onset

I. Infant (<2 years)

II. Childhood (3-12 years)

III. Adolescence (13-20 years)

IV. Younger adulthood (21-40 years)

V. Older adulthood (>40 years)

According to body distribution

- Focal – one muscle group or body segment
- Segmental – 2 neighbouring muscle groups or body segments (e.g. head+neck)
- Multifocal – 2 non-neighbouring muscle groups / body parts (e.g. neck + lower limb)
- Hemidystonia
- Generalized – affection of most or all body segments

Temporal pattern

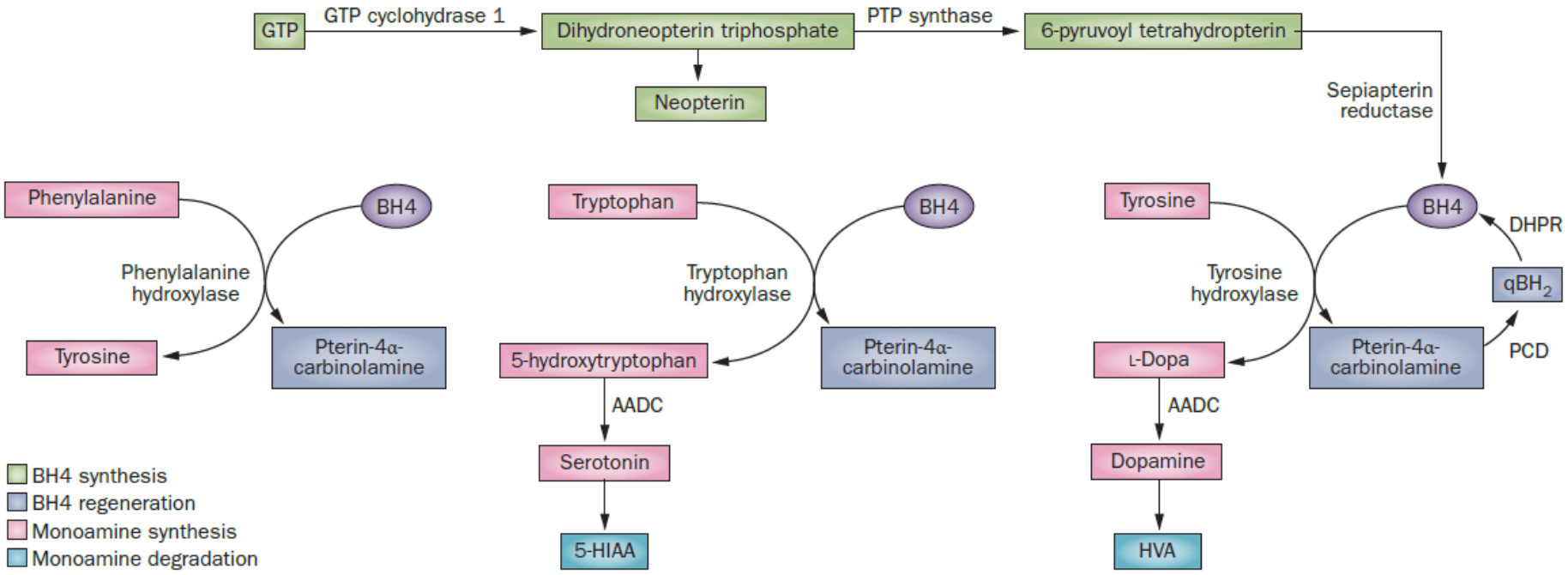
I. Disease course
    I. Static
    II. Progressive
II. Variability
    I. Persistent symptoms
    II. Action-specific
    III. Diurnal fluctuations
    IV. Paroxysmal dystonia

Dopa-responsive dystonia—clinical and genetic heterogeneity

Subhashie Wijemanne & Joseph Jankovic

Nature Reviews Neurology **11**, 414–424 (2015) | doi:10.1038/nrneurol.2015.86

Published online 23 June 2015



	Inheritance	Response to L-dopa	Dyskinesia	Other symptoms
GTP-cyklohydrolase 1 deficiency	AD	Excellent and persistent	Rare	Parkinsonism, brisk reflexes, scoliosis, anxiety, depression, OCD, sleep disorders
GTP-cyklohydrolase 1 deficiency	AR	Good, but high doses necessary	Rare	Spasticity, oculogyric crisis, excessive drooling, poor sleep, neonatal hyperphenylalaninemia
Tyrosine hydroxylase deficiency	AR	Good but can be incomplete	Frequent	Type A – progressive hypokinetic-rigid syndrome Type B – complex encephalopathy – tremor, ptosis, autonomic dysfunction, spasticity, hypotonia, delayed milestones, mental retardation
Sepiapterine reductase deficiency	AR	Good but can be incomplete	Possible	Oculogyric crisis, autonomic dysfunction, delayed milestones, microcephalia, growth retardation, mental retardation, hypotonia, spasticity, parkinsonism, hyperreflexia
PTP synthase deficiency	AR	Excellent and persistent	None	Early epileptic seizures, spasticity, mild cognitive dysfunction

Basically all subtypes

- Lower limb onset, generalize, diurnal fluctuations

Wijemanne Nat Rev Neurology 2015

How to treat dopa-responsive dystonia

Initial doses of L-dopa	0.5-1.0 mg/kg/day divided into 3-6 doses
Increasing of L-dopy	by 0.1-0.5 mg/kg/day according to tolerance
Management of dyskinesias	• Decrease L-dopa to last tolerated dose • Delay further increases of dose until dyskinesia dissapear • Increase frequency of dosing
Amantadine	If abovementioned points not effective
Doses of amantadine	4-6 mg/kg/day
Chronic doses of L-dopa	3-20 mg/kg/day according to tolerance
Dopamine agonists	If L-dopa not tolerated or does not provide sufficient clinical benefit

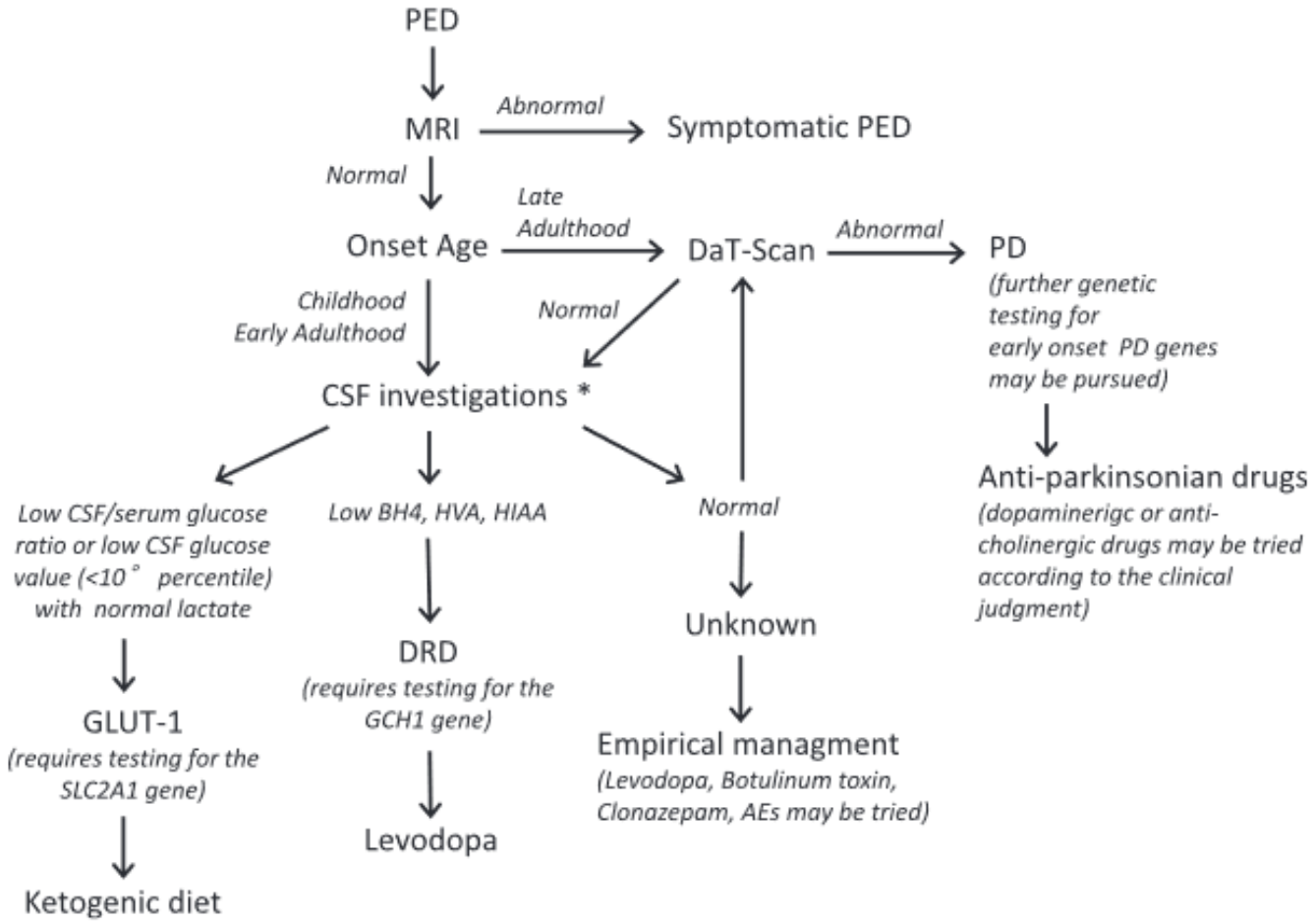
Wijemanne Nat Rev Neurology 2015

- Paroxysmal kinesigenic dystonia (PKD)
- Paroxysmal non-kinesigenic dystonia (PNKD)
- **Paroxysmal exercise-induced dystonia (PED)**
- Often normal neurological finding between attacks
- Non-epileptic

Movement Disorders
CLINICAL PRACTICE
ORIGINAL ARTICLE

The Clinical Syndrome of Paroxysmal Exercise-Induced Dystonia: Diagnostic Outcomes and an Algorithm

Roberto Erro, MD,[1,2,*] Maria Stamelou, MD, PhD,[1,3,4] Christos Ganos, MD,[1,5,6] Matej Skorvanek, MD,[7,8] Vladimir Han, MD,[7,8] Amit Batla, MD, PhD,[1] Kailash P. Bhatia MD, FCRP[1,*]



Associated features

- Dystonia isolated or associated with other movement disorder

Dystonia + myoclonus

Dystonia + parkinsonism

Dystonia + marked orobulbar involvement	Dystonia + peripheral neuropathy
Drug-induced (neuroleptics, antiemetics)	Niemann-Pick type C
PKAN (PANK2 mutations)	Metachromatic leukodystrophy
PLAN (PLA2G6 mutations)	Friedreich's ataxia
Choreo-akantocatosis	Ataxia teleangiectasia
Neuroferritinopathy	Spinocerebellar ataxies (esp. type 2/3)
Lesch-Nyhan syndrome	
Dystonia + oculomotor abnormalities	**Dystonia + retinitis pigmentosa**
Niemann-Pick type C	PKAN
Huntington's disease	GM2 gangliozidosis
Ataxia teleangiectasia, AOA1, AOA2	Metachromatic leukodystrophy
Dystonia + deafness	**Dystonia + progressive dementia**
Mitochondrial disorders	GM1 a GM2 gangliozidosis
Mohr-Tranebjaerg syndrome	Glutaric aciduria
Woodhouse-Sakati syndrome	Huntington's disease
	Huntington phenocopies

Schneider et al. 2010

REVIEW CME

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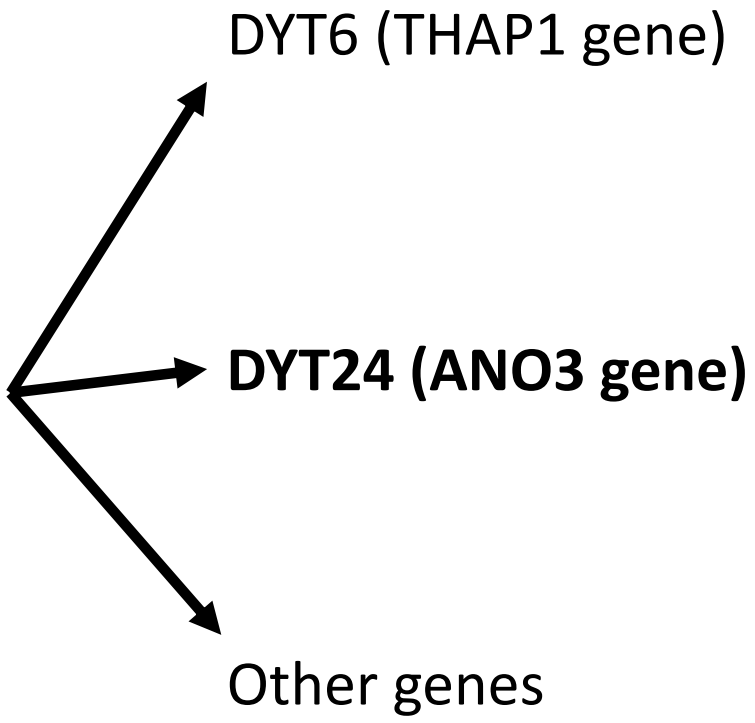
One phenotype many genes

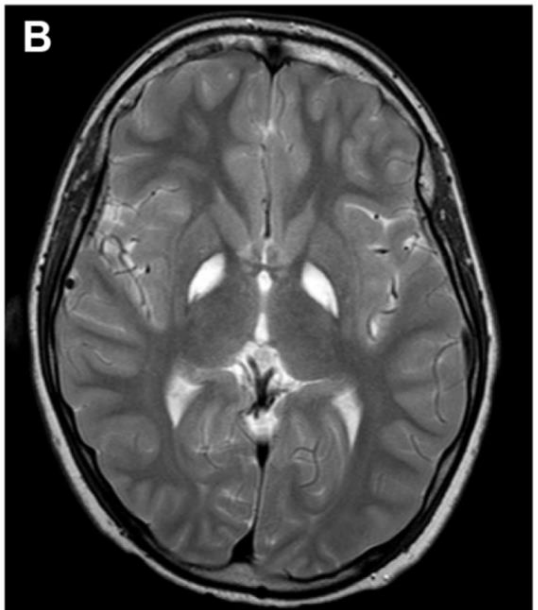


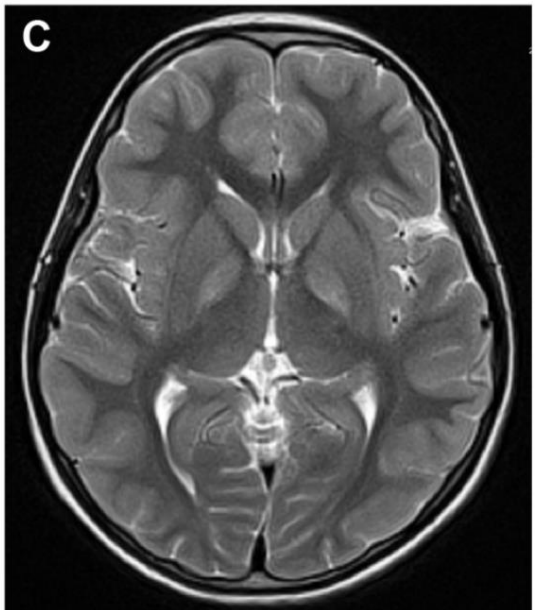
One gene many phenotypes

RESEARCH ARTICLE

Paroxysmal Exercise-Induced Dystonia Within the Phenotypic Spectrum of *ECHS1* Deficiency

Simone Olgiati, MSc,[1] Matej Skorvanek, MD, PhD,[2,3] Marialuisa Quadri, PhD,[1]
Michelle Minneboo, BSc,[1] Josja Graafland, BSc,[1] Guido J. Breedveld, BSc,[1] Ramon Bonte, BSc,[1]
Zeliha Ozgur, BSc,[4] Mirjam C.G.N. van den Hout, PhD,[4] Kees Schoonderwoerd, PhD,[1]
W. Verheijen, PhD,[1] Wilfred F.J. van IJcken, PhD,[4] Hsin Fen Chien, MD, PhD,[5] Egberto Reis Barbosa, MD, PhD,[5]
Hsiu-Chen Chang, BSc,[6] Szu-Chia Lai, MD,[6] Tu-Hsueh Yeh, MD, PhD,[6] Chin-Song Lu, MD,[6]
h-Huei Wu-Chou, PhD,[7] Anneke J.A. Kievit, MD, PhD,[1] Vladimir Han, MD,[2,3] Zuzana Gdovinova, MD, PhD,[2,3]
Robert Jech, MD, PhD,[8] Robert M.W. Hofstra, PhD,[1] George J.G. Ruijter, PhD,[1]
Wim Mandemakers, PhD,[1] and Vincenzo Bonifati, MD, PhD[1]*





Drug-induced dystonia (acute/tardive)

- Neuroleptics (antiemetics)
  - Therapy anticholinergics (biperiden) i.v.
- Antimalarics, late complications of L-dopa, dopamine agonists
- After overdosing - carbamazepine, fenytoin
- No safe neuroleptics, no safe dosis, no safe period of exposition
- Low rate of remission even after discontinuation

Cerebral palsy

- Overdiagnosed + often an escape diagnosis!
  - No more examinations needed, no specific treatment available...
- Prenatal and perinatal period!
  - Even if perinatal problems - still can have metabolic, mitochondrial or other disorder
- Many patients if properly diagnosed can have a treatable condition

REVIEW

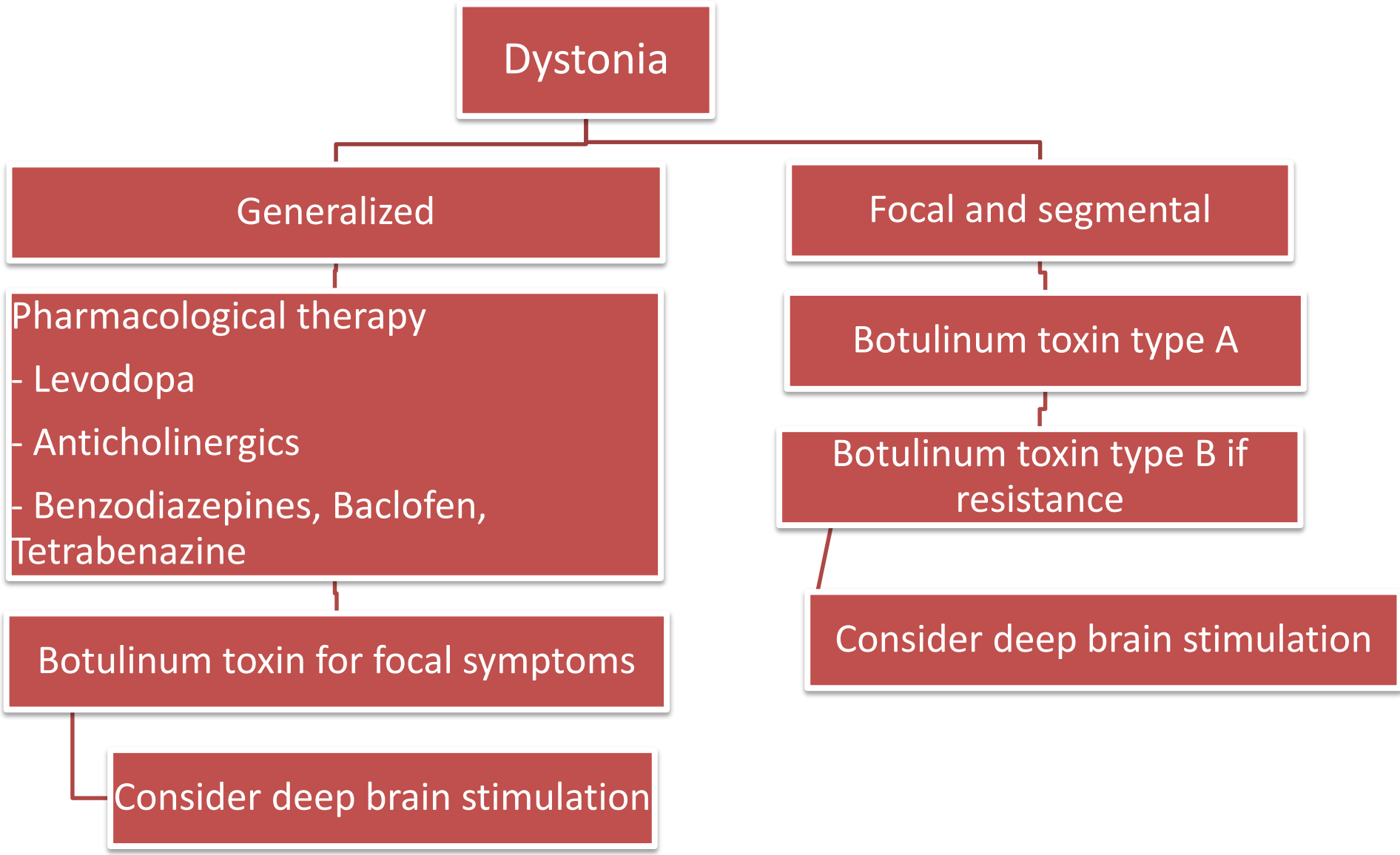
CME

Treatable Inherited Rare Movement Disorders

H. A. Jinnah, MD, PhD,[1*] Alberto Albanese, MD,[2,3] Kailash P. Bhatia, MD,[4] Francisco Cardoso, MD,[5] Gustavo Da Prat, MD,[6,7] Tom J. de Koning, MD, PhD,[8] Alberto J. Espay, MD,[9] Victor Fung, PhD, FRACP,[10]

- **Reduction of toxic products** – Cerebrotendinous xanthomatosis, Dystonia/parkinsonism with manganese accumulation, Gaucher disease, Niemann Pick type C, Wilson disease
- **Dietary interventions** – Abetalipoproteinemia, Cerebral creatine def, GLUT-1 def, Glutaric aciduria type 1, Homocystinuria, Maple syrup urine disease, Methylmalonic aciduria, Phenylketonuria, Propionic acidemia, Pyruvate dehydrogenase complex def, Refsum disease
- **Vitamin supplements** – Abetalipoproteinemia, AADC def, Ataxia with vit E def, Biotin-thiamin responsive basal ganglia disease, Biotinidase def, Cerebral folate def, Cobalamin def, Coenzyme Q10 def, Homocystinuria, Pyruvate dehydrogenase complex def
- **Trigger avoidance** – Alternating hemiplegia of childhood, Biotin-thiamin responsive basal ganglia disease, Episodic ataxia type 2, Glutaric aciduria type 1, Maple syrup urine disease, Methylmalonic aciduria, Paroxysmal kinesigenic / nonkinesigenic dyskinesia, Propionic acidemia, Rapid onset dystonia parkinsonism
- **Specific drugs** – AADC drugs, Dopa-responsive dystonia, Episodic ataia type 2, GLUT-1 defficiency, Molybdenum cofactor defficiency, Paroxysmal kinesigenic dyskinesia

Therapy algorithm for dystonia



ORIGINAL ARTICLE

Management of dystonia in Europe: a survey of the European network for the study of the dystonia syndromes

A. Valadas[1,2,*], M-F. Contarino[3,4,*], A. Albanese[5], K. P. Bhatia[6], C. Falup-Pecurariu[7], L. Forsgren[8], A. Friedman[9], N. Giladi[10], M. Hutchinson[11,12], V. S. Kostic[13], J. K. Krauss[14], A. Lokkegaard[15], M. J. Marti[16], I. Milanov[17], Z. Pirtosek[18], M. Relja[19], M. Skorvanek[20,21], M. Stamelou[22,23], A. Stepens[24], G. Tamás[25], A. Taravari[26], C. Tzoulis[27,28], W. Vandenberghe[29], M. Vidailhet[30,31], J. J. Ferreira[32] and M. A. Tijssen[33]

frontiers in Neurology

REVIEW
published: 24 February 2017
doi: 10.3389/fneur.2017.00035

Check for updates

Clinical Practice: Evidence-Based Recommendations for the Treatment of Cervical Dystonia with Botulinum Toxin

Maria Fiorella Contarino[1,2], Joost Van Den Dool[3,4], Yacov Balash[5,6], Kailash Bhatia[7], Nir Giladi[5,6], Johannes H. Koelman[8], Annemette Lokkegaard[9], Maria J. Marti[10], Miranda Postma[8], Maja Relja[11], Matej Skorvanek[12,13], Johannes D. Speelman[8], Evelien Zoons[8], Joaquim J. Ferreira[14], Marie Vidailhet[15,16,17,18,19], Alberto Albanese[20,21] and Marina A. J. Tijssen[3]**

Factors of DBS success

- Selection of appropriate candidates!!!
- Precise placement of electrodes

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bilateral Deep-Brain Stimulation of the Globus Pallidus in Primary Generalized Dystonia

Marie Vidailhet, M.D., Ph.D., Laurent Vercueil, M.D., Jean-Luc Houeto, M.D., Ph.D., Pierre Krystkowiak, M.D., Alim-Louis Benabid, M.D., Ph.D., Philippe Cornu, M.D., Christelle Lagrange, Ph.D., Sophie Tézenas du Montcel, M.D., Ph.D., Didier Dormont, M.D., Ph.D., Sylvie Grand, M.D., Ph.D., Serge Blond, M.D., Olivier Detante, M.D., Bernard Pillon, Ph.D., Claire Ardouin, Ph.D., Yves Agid, M.D., Ph.D., Alain Destée, M.D., and Pierre Pollak, M.D., Ph.D., for the French Stimulation du Pallidum Interne dans la Dystonie (SPIDY) Study Group*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pallidal Deep-Brain Stimulation in Primary Generalized or Segmental Dystonia

Andreas Kupsch, M.D., Reiner Benecke, M.D., Jörg Müller, M.D., Thomas Trottenberg, M.D., Gerd-Helge Schneider, M.D., Werner Poewe, M.D., Wilhelm Eisner, M.D., Alexander Wolters, M.D., Jan-Uwe Müller, M.D., Günther Deuschl, M.D., Marcus O. Pinsker, M.D., Inger Marie Skogseid, M.D., Geir Ketil Roeste, M.D., Juliane Vollmer-Haase, M.D., Angela Brentrup, M.D., Martin Krause, M.D., Volker Tronnier, M.D., Alfons Schnitzler, M.D., Jürgen Voges, M.D., Guido Nikkhah, M.D., Ph.D., Jan Vesper, M.D., Markus Naumann, M.D., and Jens Volkmann, M.D., for the Deep-Brain Stimulation for Dystonia Study Group*

DBS for dystonia

- Isolated generalized dystonia
  Vidailhet 2005; Kupsch 2006; Bronte-Stewart et al, Mov Disord 2011
- Myoclonus dystonia
  Cif et al, Mov Disord 2004
- Cervical dystonia / Meige syndrome refractory to BoNT
  Ostrem et al, Mov Disord 2007
- Selected secondary dystonias
  - X-linked parkinsonism-dystonia DYT3 (Lubag)
    Evidente et al, Mov Disord 2010
  - PKAN
    Timmermann et al, Brain 2010
  - Cerebral palsy without cognitive deficit and only mild spasticity
    Vidailhet et al, Lancet Neurol 2009
  - Tardive dystonia
    Trottenberg 2001

DBS for dystonia

- Isolated > Combined
- Mobile > Fixed
- No MRI abnormalities > MRI structural changes
- Axial > Limb
- Shorter > Longer duration (> fixed skeletal deformities)

DBS in status dystonicus

- Potentially life threatening situation, variable outcomes
- ICU management, sedation, ventilation?, usually pharmacotherapy as first line (benzodiazepines, propofol, barbiturates, anticholinergics, neuroleptics, levodopa, intrathecal morphine, intrathecal baclofen) Fasano, Mov Disord 2012
- In refractory cases acute DBS should be considered
  - Good results shown in DYT1, DYT6, PKAN, tardive dystonia, etc

Mariotti 2007; Jech 2009, Kovacs 2011, Fasano 2012

DBS in myoclonus dystonia

- GPi > VIM
  - Myoclonus 75.7% vs. 70.4%
  - Dystonia 60.2% vs 33.3%

Andrews 2010; Rughani 2013

- worsening of psychiatric symptoms?

Contarino 2011

DBS in hyperkinetic cerebral palsy

- In selected patients improvement of dystonia 24-49.5% (BFMDRS-m)

Vidailhet Lancet Neurol 2009; Keen J Neurosurg Ped 2014; Marks J Child Neurol 2013; Romito Eur J Neurol 2015;

- Inclusion criteria
  - Neonatal hypoxic or ischaemic encephalopathy, delayed milestones
  - No other cause of dystonia including metabolic and genetic disorders, focal vascular lesions, head trauma, neuroleptic treatment
  - Little or no spasticity (Ashworth scale <2 for each segment)
  - No more than slight abnormalities seen on T1 MRI images
  - No psychiatric disorders
  - Little or no cognitive impairment
  - Optimised treatment (tried highest tolerated doses of levodopa and anticholinergics)

Vidailhet Lancet Neurol 2009

DBS for PD-related dystonia

- dystonia responsive to levodopa?
- dystonia present only in OFF state?

STN vs. GPi stimulation

- Camptocormia
  - Improvement 34.6-78.2%
  - Both STN and GPi used
  - Better if shorter duration (<1.5 years)
- Pisa syndrome
  - DBS generally less effective

Umemura 2010; Schulz-Schaeffer 2015; Chieng 2015

DBS for tardive dystonia

- 80+ patients reported (4pts STN, other Gpi)
- Mean improvement 74% on motor score of BFMDRS
- Usually rapid improvement (days – weeks) phasic > tonic movement
- Long-term good effect of stimulation
- Very good cognitive and psychiatric tolerability (1pt worsening of depression, 1pt worsening of psychosis)

Welter 2010; Mentzel 2012; Pouclet-Courtemanche 2016; Sobstyl 2016

Side-effects of Gpi DBS

- Hardware and surgery related
- Stimulation related
  - Especially dysarthria
  - Occasionally hypokinetic gait disorder with freezing of gait
    - Stimulation dependant

Other targets

- STN DBS for dystonia associated with PD (off dystonia with good response to levodopa)

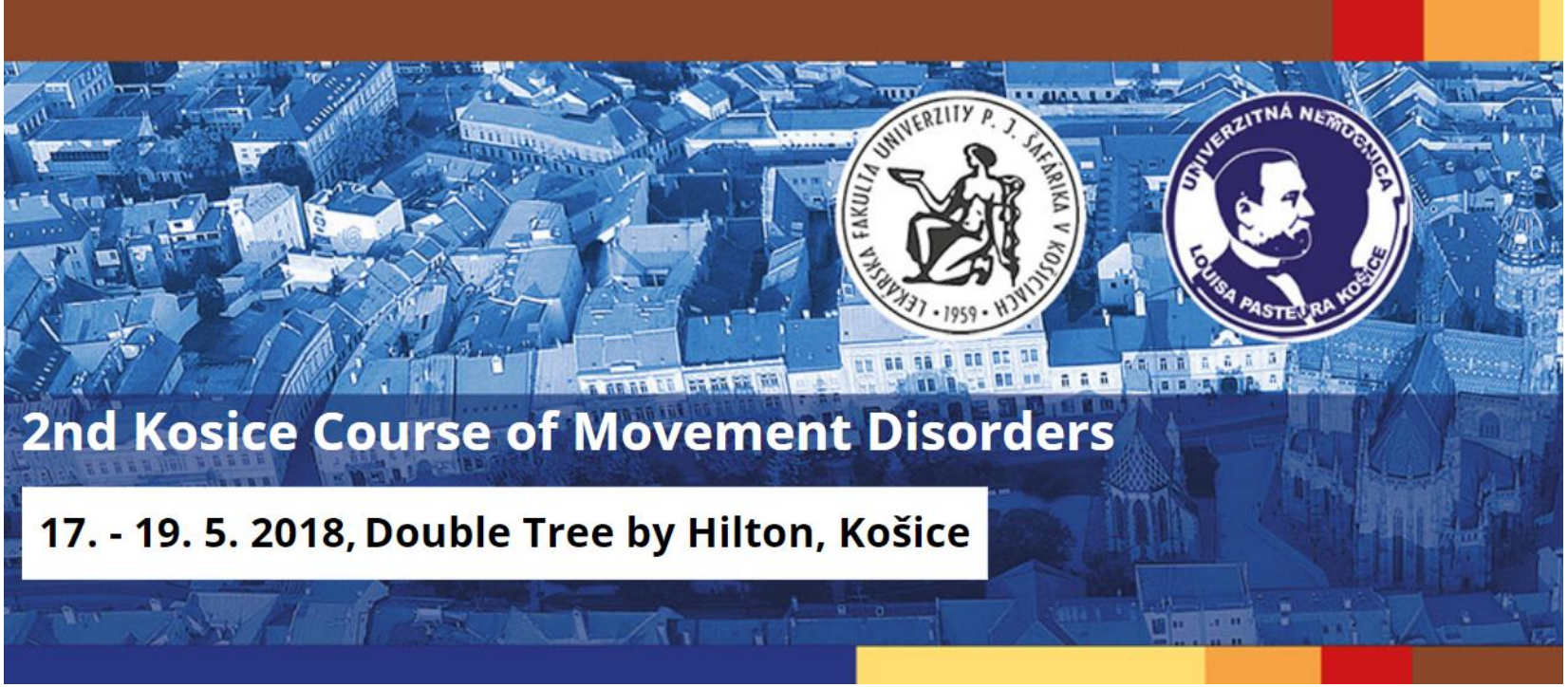
- STN for focal, segmental and generalized isolated dystonia
  - comparable results with Gpi stimulation in a limited number of studies
  - Without neuropsychiatric and cognitive side effects seen in PD

Ostrem 2011; Schjerling 2013, Mills 2015

- VIM/subthalamic area for dystonic tremor

Fasano 2014; Pauls 2014

- VIM for Myoclonus dystonia



www.expy-ke.sk

www.movementdisorders.org