


Movement Disorders and their etiologies

Dr. Britton Zuccarelli MD
Child Neurologist
Clinical Assistant Professor of Pediatrics and Neurology
University of Kansas School of Medicine



Disclosure

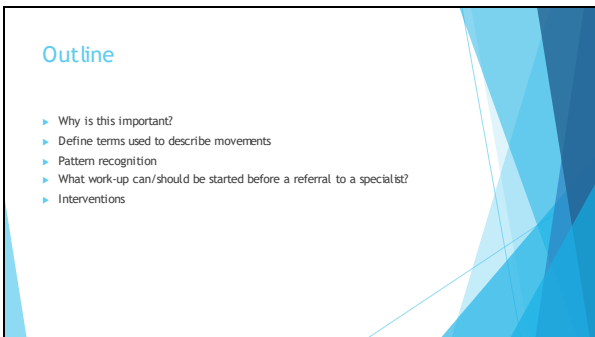
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- ▶ I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation
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Let's start with a case

- ▶ Chief complaint: 8 year old boy with progressive balance disturbances and frequent falls
- ▶ HPI: slowly progressive difficulty with balance, "trips" over nothing
 - ▶ No preceding febrile illness, obvious trauma or trigger
- ▶ PMH: term, uncomplicated twin pregnancy, mild gross motor delay
- ▶ FH: twin brother does the same thing
- ▶ Exam:
 - ▶ General exam: unremarkable
 - ▶ Neurological examination:
 - ▶ Very broad based gait, severely unsteady
 - ▶ Fast, abrupt jerks of the extremities and trunk causing him to become off balance







Background

- ▶ Movement disorders are common
 - ▶ Tourette syndrome, essential tremor: 1%
 - ▶ Functional Neurological Disorders: 2nd most common reason to see a neurologist
- ▶ Sometimes lifelong impact, life-limiting
- ▶ Some are uncomfortable, embarrassing, cause occupational dysfunction
- ▶ Cost of treatment

Bennett et al 2021

Definitions

- ▶ Hypokinetic
 - ▶ Catatonia
 - ▶ Parkinsonism/extrapyramidal symptoms
 - ▶ Some tics
- ▶ Hyperkinetic
 - ▶ Akathisia
 - ▶ Ataxia
 - ▶ Athetosis
 - ▶ Ballism
 - ▶ Chorea
 - ▶ Dyskinesia
 - ▶ Dystonia
 - ▶ Hyperexplexia
 - ▶ Mirror movements
 - ▶ Myoclonus
 - ▶ Myokymia
 - ▶ Myorhythmia
 - ▶ Restless leg
 - ▶ Spasms
 - ▶ Stereotypy
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Catatonia

<https://youtu.be/zAE1-lundms>

Zerati 2010

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Parkinsonism

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Tic

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Dystonia

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 - ▶ Dystonia
 - ▶ Hyperplexia
 - ▶ Mirror movements
 - ▶ Myoclonus
 - ▶ Myokymia
 - ▶ Myorhythmia
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 - ▶ Spasms
 - ▶ **Stereotypy**
 - ▶ Tic
 - ▶ Tremor

Stereotypy

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Definitions

- ▶ Akathisia
 - ▶ inability to stay still, restless, muscle quivering
 - ▶ Common side effect of antipsychotic or antidepressant medications
- ▶ Athetosis
 - ▶ Slow, writhing movements, worm like
- ▶ Ballism
 - ▶ Twisting, swinging, jerking movement
- ▶ Chorea
 - ▶ Sudden, jerky irregular, dance-like, often corticuous
- ▶ Dyskinesia
 - ▶ Erratic writhing movements with or without dystonic component

Definitions

- ▶ **Hyperekplexia**
 - ▶ Exaggerated startle resulting in hypertonia
- ▶ **Mirror movements**
 - ▶ Simultaneous contralateral identical movement accompanying voluntary movement
- ▶ **Myokymia**
 - ▶ Localized quivering of a few muscles or bundles within a small muscle
- ▶ **Myorhythmia**
 - ▶ Repetitive, rhythmic, slow, coarse tremor
 - ▶ Example: oculomasticatory (pathognomonic for Whipple's disease of the CNS)
- ▶ **Restless leg**
 - ▶ Uncontrollable urge to move the legs accompanied by unpleasant sensation

Definitions

- ▶ **Spasms**
 - ▶ Sustained involuntary muscular contraction
- ▶ **Tremor**
 - ▶ Rhythmic low amplitude to and fro movement around a joint of variable frequency
 - ▶ Various subtypes: kinetic, postural, intention

Neurodiagnostic evaluation

1	Is it a movement disorder (MD)?	Clinical
2	Classify the MD phenotype and which MD is most prominent?	
3	Could the MD be functional?	
4	Determine the clinical syndrome	
5	Can the movement disorder be caused by an acquired cause?	Diagnostic tests
6	Does the clinical syndrome fit a treatable inborn error of metabolism?	
7	Consider genetic testing	
8	Post next-generation sequencing phenotyping	

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Table 1: Medication with movement disorders as side effects

Medication	Parkinsonism	Myoclonus	Dystonia	Ataxia	Tremor	Chorea
Anticonvulsants	✓	✓	✓	✓	✓	✓
Antipsychotics	✓	✓	✓	✓	✓	✓
Antidepressants	✓	✓	✓	✓	✓	✓
Antihypertensives	✓	✓	✓	✓	✓	✓
Antiparkinson drugs	✓	✓	✓	✓	✓	✓
Antibiotics	✓	✓	✓	✓	✓	✓
Antineoplastic	✓	✓	✓	✓	✓	✓
Opiates	✓	✓	✓	✓	✓	✓
Anaesthetics	✓	✓	✓	✓	✓	✓
Oral contraceptives	✓	✓	✓	✓	✓	✓
Anti-emetics	✓	✓	✓	✓	✓	✓
Immunosuppressants	✓	✓	✓	✓	✓	✓
Corticosteroids	✓	✓	✓	✓	✓	✓

The table shows groups of medication known to cause different movement disorders. The list is not complete and only shows the main classes of drugs that may induce movement disorders.

Brandsma et al 2020

Laboratory testing

- ▶ Serology:
 - ▶ Infectious
 - ▶ Autoimmune
- ▶ Spinal fluid
 - ▶ Infectious
 - ▶ Autoimmune
 - ▶ Neurotransmitter disorder

Treatable inborn errors of metabolism

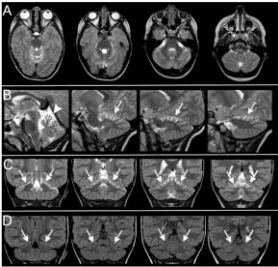
Gene	OMIM phenotype	Max age of onset of MD	MD	
Cerebrotendinous xanthomatosis	CYP27A	213700	Adolescence-childhood	Ataxia, dystonia, myoclonus, chorea, tremor, parkinsonism
Hyperparathyroidism with dementia 1 and 2	SLC5A10 and SLC19A1	613280, 617013	Infancy-adulthood	Dystonia, tremor, parkinsonism
Gaucher disease (type III)	GBA	231000	Childhood-adulthood	Ataxia, dystonia, myoclonus, tremor, parkinsonism
Niemann Pick type C	NPC1 and NPC2	257220	Infancy-adulthood	Ataxia, dystonia, myoclonus, chorea, tremor, parkinsonism
Wilson disease	ATP7B	277900	Childhood-adulthood	Ataxia, dystonia, myoclonus, chorea, tremor, parkinsonism
Abetalipoproteinemia	MTPP	200100	Childhood	Ataxia, dystonia
Ataxia with vitamin E deficiency	TTPA	277460	Adolescence-childhood	Ataxia, dystonia
Benign disease responsive basal ganglia disease	SLC15A3	607483	Childhood	Ataxia, dystonia
Biotinidase deficiency	BTD	253260	Infancy-adolescence	Ataxia
Cerebral creatine deficiency 2 and 3	GAMT and GATM	612795, 612718	Infancy-adolescence	Ataxia, dystonia, chorea
Cerebral folate deficiency	FOLR1 and SLC46A1	611068, 229020	Childhood	Ataxia, chorea, dystonia
Caldesmon deficiency	Multiple genes	Multiple numbers	Infancy-adulthood	Ataxia, dystonia
Collapsin Q10 deficiency	Multiple genes	Multiple numbers	Childhood	Ataxia, dystonia, myoclonus, tremor
GLUT1 deficiency	SLC1A1	606777	Infancy-adulthood	Pharyngeal ataxia, dystonia, myoclonus, chorea
Onyiah acylase type 1	ONYH1	211670	Infancy-childhood	Ataxia, dystonia, chorea, parkinsonism

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MRI

- ▶ Trauma
- ▶ Vascular
- ▶ Autoimmune
- ▶ Genetic/metabolic
- ▶ Infectious

Back to our case



Romaniello et al 2022

Genetic testing

- ▶ Specific gene panels for ataxias, dystonias, channelopathies
- ▶ Whole exome sequencing
 - ▶ Limitations:
 - ▶ Does not detect large deletions/duplications (microarray)
 - ▶ Does not detect triplet repeat expansions
 - ▶ Does not detect heteronic mutations
 - ▶ Diagnostic yield ~30%

Vernetti et al 2022

Back to our case

- ▶ Whole exome sequencing revealed a heterozygous known pathogenic mutation in the *KCNK3* gene compatible with autosomal dominant spinocerebellar ataxia type 13.
 - ▶ Phenotypic spectrum
 - ▶ Includes progressive and nonprogressive types
 - ▶ May feature learning disabilities and/or psychiatric manifestations
 - ▶ Treatment: therapies
 - ▶ Perhaps medication, based on gain- or loss-of-function
 - ▶ Avoid: alcohol (may exacerbate ataxia)
 - ▶ Not generally thought to be life-limiting (unless dysphagia is present)
 - ▶ Parent/patient support groups

Summary

- ▶ Pediatric movement disorders are common, debilitating, costly
- ▶ Phenomenology is paramount for classification, guiding work-up
 - ▶ Encourage parents to get a video (and share with you in a HIPPA-compliant fashion)
- ▶ Metabolic, genetic testing, and neuroimaging can be revealing
- ▶ Treatments are available

Functional Neurological Disorders

- ▶ Motor, sensory, other symptoms that are
 - ▶ Genuinely experienced
 - ▶ Related to a functional (rather than structural) problem with the nervous system
- ▶ Huge historical burden (hysteria, conversion disorder)
- ▶ Not necessarily a diagnosis of exclusion
 - ▶ Functional neuroimaging and neurophysiology can help in the diagnosis
- ▶ Represents 5-10% of new neurology consultations
- ▶ Incidence ~12/100,000/year
- ▶ Disproportionately affects females ~3:1 but this decreases with age
- ▶ Rare before age 10

Bennett et al. 2021

Functional Neurological Disorders

- ▶ Associated with high levels of disability
- ▶ Higher frequency of psychological comorbidities than other neurological disorders
- ▶ Can co-occur with other functional disorders (abdominal or chronic pain)
- ▶ Can co-occur with other neurological disorders (~20% of cases)
- ▶ Symptoms typically persist for many years
- ▶ Estimated total annual healthcare cost is ~\$900 million

Bennett et al. 2021
Stephen et al. 2019

Functional Neurological Disorders

- ▶ Make a thorough list of symptoms
- ▶ Investigate for mechanism of onset
- ▶ Diagnostic pitfalls
 - ▶ Failure to consider comorbidity of another medical condition
 - ▶ Reliance on unusual clinical features
 - ▶ Focus on psychiatric features/recent stress
 - ▶ Dependence on normal investigations
 - ▶ Misinterpretation of abnormal investigations

Bennett et al. 2021

Functional Neurological Disorders

- ▶ Physical exam pearls
 - ▶ Hoover's sign
 - ▶ Splitting the forehead
 - ▶ Entrainable movements
 - ▶ Distractibility
 - ▶ Suggestibility
 - ▶ Retained consciousness with whole-body convulsions
 - ▶ Spontaneous resolution of prolonged whole-body convulsions without confusion
 - ▶ Astasia abasia



Bennett et al. 2021

Functional Neurological Disorders

- ▶ Pathophysiology hypotheses
 - ▶ Changes in brain networks
 - ▶ Altered predictive processing
- ▶ Treatment
 - ▶ Validation
 - ▶ Confident delivery of diagnosis
 - ▶ Education/Support
 - ▶ www.cmc.org/ncmt/ncmt.asp
 - ▶ www.fnh.org.uk
 - ▶ www.fnhc-tan.org.uk
 - ▶ Therapies
 - ▶ Medication
 - ▶ Alternative treatments



Bennett et al. 2021



Thank you!



Google Images

Questions?

References

- ▶ Bennett et al. A practical review of functional neurological disorder (FND) for the general physician. *Clinical Medicine*, 21(1):28-36, January 2021.
- ▶ Brandsma et al. Diagnostic approach to paediatric movement disorders: a clinical practice guide. *Developmental Medicine & Child Neurology* 63(3):252-258, November 2020.
- ▶ Fenichel, G.M. *Clinical Pediatric Neurology: A Signs and Symptoms Approach*, 6th Edition, Saunders Elsevier, 2009, Chapter 14 (Movement Disorders).
- ▶ Romaniello et al. Superior cerebellar atrophy: an imaging clue to diagnose *ITPR1*-related disorders. *International Journal of Molecular Sciences* 23(12):6723-6736, June 2022.
- ▶ Stephen et al. Healthcare utilization and emergency department inpatient costs in adult and pediatric functional neurological disorders. *Movement Disorders International Congress*, 2019.
- ▶ Verneti et al. Genetic diagnosis in movement disorders: use of whole exome sequencing in clinical practice. *Tremor and Other Hyperkinetic Movements*, 12:12-21, April 2022.
- ▶ Zerati, E. Neuroscience channel, [youtube.com/@churroITPR](https://www.youtube.com/@churroITPR), 8/15/2010, accessed 3/22/23. <https://www.youtube.com/@churroITPR>
