Approach to pediatric movement disorders.

Ali Nasreldien

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DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY CLINICAL PRACTICE GUIDE

Diagnostic approach to paediatric movement disorders: a clinical practice guide

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Paediatric movement disorders (PMDs) comprise a large group of disorders (tics, myoclonus, tremor, dystonia, chorea, Parkinsonism, ataxia), often with mixed phenotypes. Determination of the underlying aetiology can be difficult given the broad differential diagnosis and the complexity of the genotype–phenotype relationships. This can make the diagnostic process

Adapted international guidelines.

Diagnostic Approach to Paediatric Movement Disorders: a clinical practice guide. Brandsma et al. DMCN 2021 Mar;63(3):252-258.

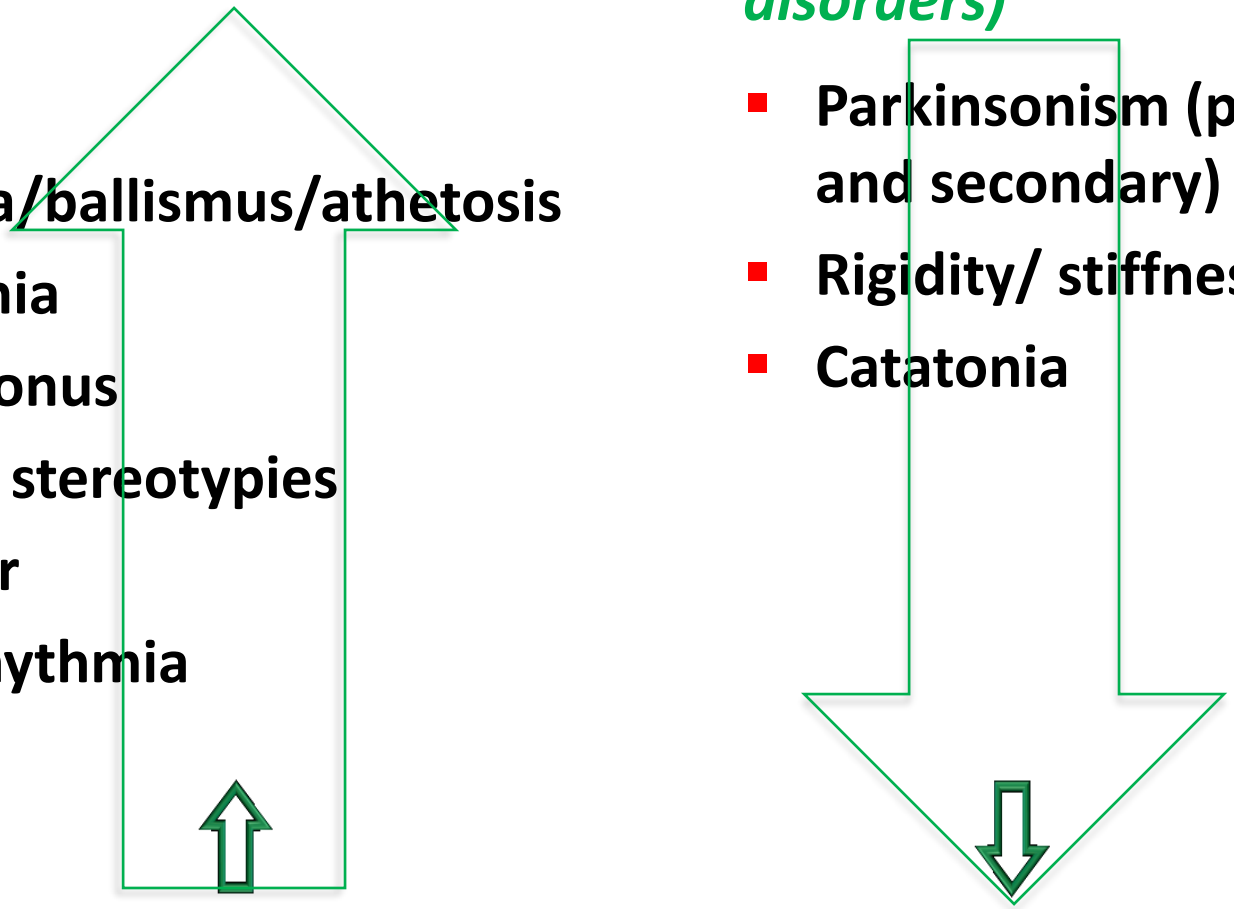
- Paediatric movement disorders (PMDs) are a large group of disorders.
- Often with mixed phenotypes.

Hyper- kinetic (dyskinesias)

- Tics
- Chorea/ballismus/athetosis
- Dystonia
- Myoclonus
- Motor stereotypies
- Tremor
- Myorhythmia

Hypo- kinetic (akinetic/rigid disorders)

- Parkinsonism (primary and secondary)
- Rigidity/ stiffness
- Catatonia



- Identifying the underlying aetiology is challenging
  - broad differential diagnosis
  - complex genotype–phenotype relationships.

- This can make the diagnostic process time-consuming and difficult.

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- This study present a diagnostic approach for PMDs, with emphasis on genetic causes.
- This approach can serve as a framework to lead the clinician through the diagnostic process in eight consecutive steps.
- The aim of this approach is to increase the recognition and diagnostic yield in PMDs.

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- (NGS) techniques can facilitate the diagnosis.
  - enhance the diagnostic process,
  - prevent unnecessary additional investigations,
  - shorten the time of uncertainty in patients and caregivers.
- In some disorders, early treatment options are crucial to prevent further neurological decline.

Step 1. Is it a movement disorder?

- Mimics are common.
- Understand the milestones of normal movements from birth through childhood.
  - Ie normal toddler movements are abnormal if expressed in older children!
  - Some “odd” movements are normal e.g. shuddering, infantile gratification, benign neonatal sleep myoclonus.
- Evaluate how movement pattern develop with age.

- Always be aware of the overlap between the PMD and epilepsy.

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Step 2. Classify the movement disorder phenotype and which movement disorder is most prominent.

- Movement disorders are classified into three major groups:

1-Hyperkinetic.

2-Hypokinetic.

3-Ataxia.

- Mixed MD.

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Step 3. Could the movement disorder be functional?

- Diagnosing a functional movement disorder is
  - no longer a diagnosis of exclusion,
  - but should be a positive diagnosis,
  - Supported by the history and examination.

- Functional PMDs are usually hyperkinetic.

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Step 4. Determine the clinical syndrome

- Clinical syndrome = constellation of all clinical features, different movement disorders, and additional neurological signs e.g
  - spasticity, epilepsy, polyneuropathy, deafness, blindness, cognitive difficulties
- and non-neurological signs e.g.
  - dysmorphism,
  - neurocutaneous markers
  - psychiatric manifestations.
- So detailed history and examination essential.

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Outcome of first assessment

- The clinical findings may strongly point to a specific diagnosis and prompts directed genetic testing.
- Other cases may have no clear phenotype or genotype indicators.

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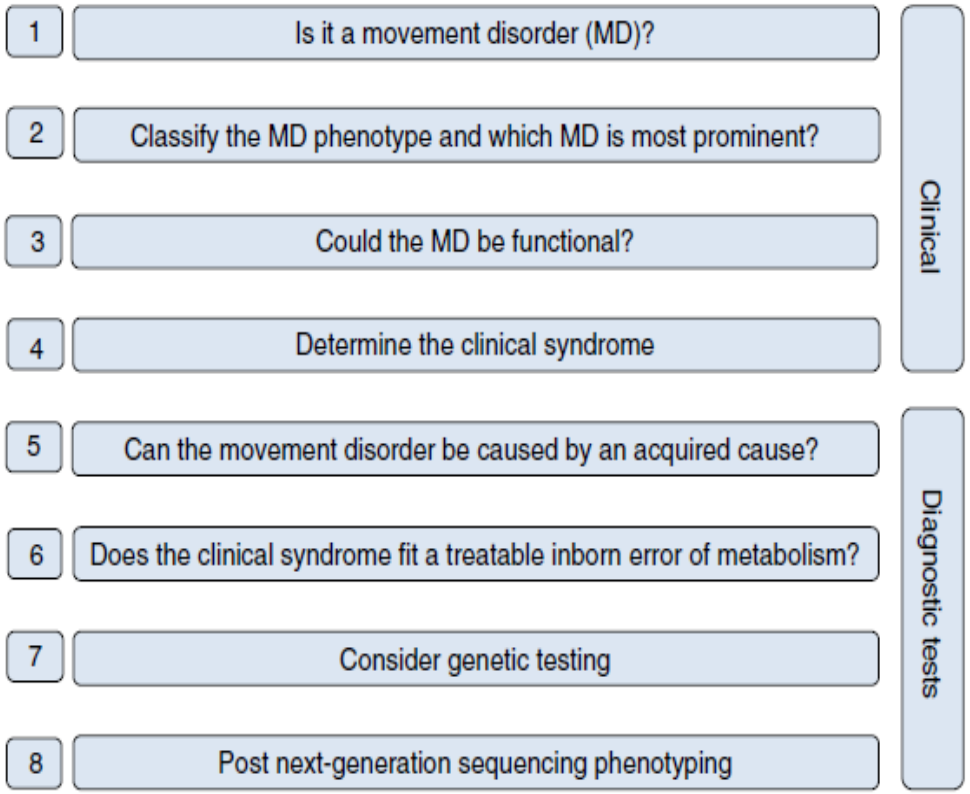

Figure 1: A diagnostic approach to paediatric movement disorders (PMDs). The diagnostic approach of PMDs divided in a clinical part (history and examination) and diagnostic part (diagnostic testing). Each step of this approach is explained in the text. [Colour figure can be viewed at wileyonlinelibrary.com]

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Step 5. Can the movement disorder be caused by an acquired cause?

- Intoxication- medications.
- Infectious and Para infectious conditions.
- Autoimmune disease.
- Post traumatic.
- Brain SOL.
- etc…

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Step 6. Does the clinical syndrome fit a treatable inborn error of metabolism?

- Clues: Deterioration after dietary changes, fasting, or fever ie episodic MVD.

- Early recognition of a treatable IEM is crucial as timely treatment can prevent or lessen (brain) damage.

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Examples of genetic disorders to consider – each with unique features

Cerebrotendinous xanthomatosis
Hypermanganesemia with dystonia 1 and 2
Gaucher disease (type III)
Niemann-Pick type C
Wilson disease
Abetalipoproteinemia
Ataxia with vitamin E deficiency
Biotin-thiamine responsive basal ganglia disease
Biotinidase deficiency
Cerebral creatine deficiency 2 and 3
Cerebral folate deficiency
Cobalamin defiency
CoEnzyme Q10 deficiency
GLUT1 deficiency
Glutaric aciduria type 1

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And more!!

Homocystinuria
Maple syrup urine syndrome
Methylmalonic aciduria
Classic phenylketonuria
Propionic acidemia
Pyruvate dehydrogenase complex deficiency
Refsum disease
Aromatic amino acid decarboxylase defiency
Dopa-responsive dystonia, classic (AD)
Dopa-responsive dystonia, complex
Dopa-responsive dystonia, complex
Dopa-responsive dystonia, complex
Molybdenum cofactor deficiency
Krabbe disease
Metachromatic leukodystrophy
X-linked adrenoleukodystrophy

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Management

- Therapeutic options for IEMs
  - Reduction of toxic substances,
  - Dietary interventions,
  - Vitamin supplementation,
  - Avoidance or management of triggers,
  - Specific medications.

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Step 7. Consider genetic testing

- If acquired causes are excluded, genetic testing should be the next step.
- Options – dependent on suspected condition:
  - Single gene test.
  - Genomic hybridization.
  - NGS.
  - WES.

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Step 8. Post-NGS phenotyping

- The results of NGS techniques can be difficult to interpret frequently,
- results reveal variants of unknown significance or heterozygotic mutations in a gene associated with a recessive disease.

- *NB we do not know all the variants in our setting….*

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Treatment

- With or without a diagnosis
  - always consider viable treatment options

- Consider mechanism based treatment modalities for specific metabolic disorders or symptomatic treatments.

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PMDs:

- Involve many disorders with heterogeneous phenotypes and genotypes.
- Diagnostic work-up can be challenging and time-consuming.
- This paper provided
  - up-to-date overview of PMDs
  - diagnostic framework to facilitate early recognition of movement disorder phenotypes.

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Illustrative example:
Rare pediatric movement disorder

History:

- 14-year-old male.
- Right upper limb abnormal movements 2019.
- Continuous rhythmic involuntary hyperkinetic movement involving the Rt upper limb more distally.
- Disappeared in sleep.
- No muscle pain or cramps.

Cont.

- Not suppressible.
- Associated with action dystonic posturing.
- No diurnal variations.
- Unable to use his Rt upper limb for his daily activity.

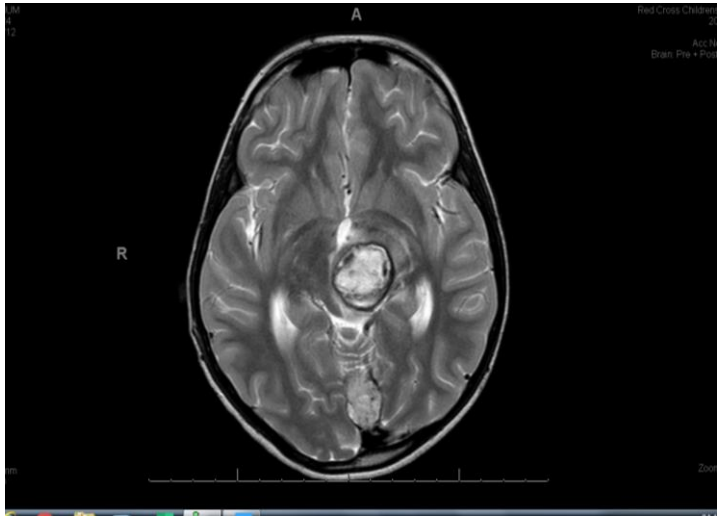
Cont..

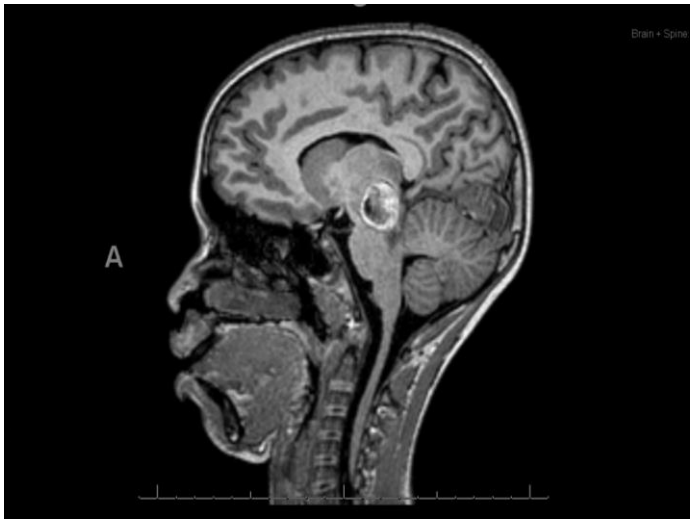
- PMHx: brain stem cavernoma.
  - Surgical intervention 2019.
  - VP shunt was inserted.
- Clinically also has Rt sided hemiplegia more affecting UL.

Cont…

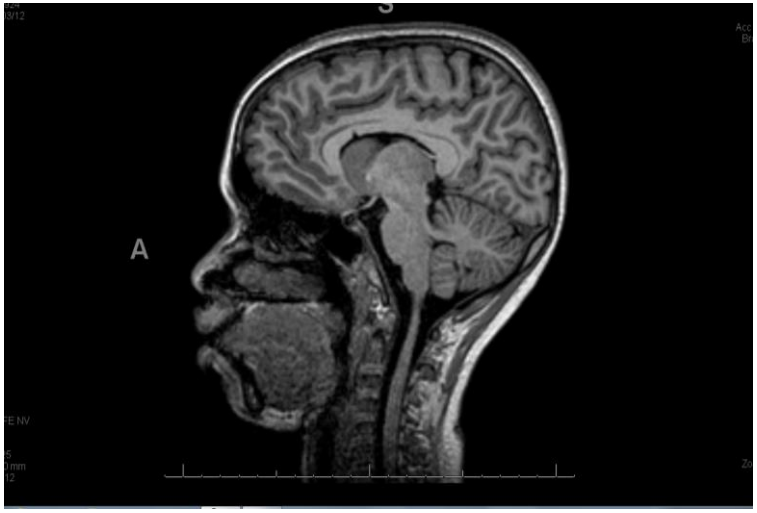
- PMH: single focal motor seizure.
- Med: Valproate (for MVT disorder)
  - NB: no improvement.
- Currently in grade 9 mainstream school
  - some learning difficulties.

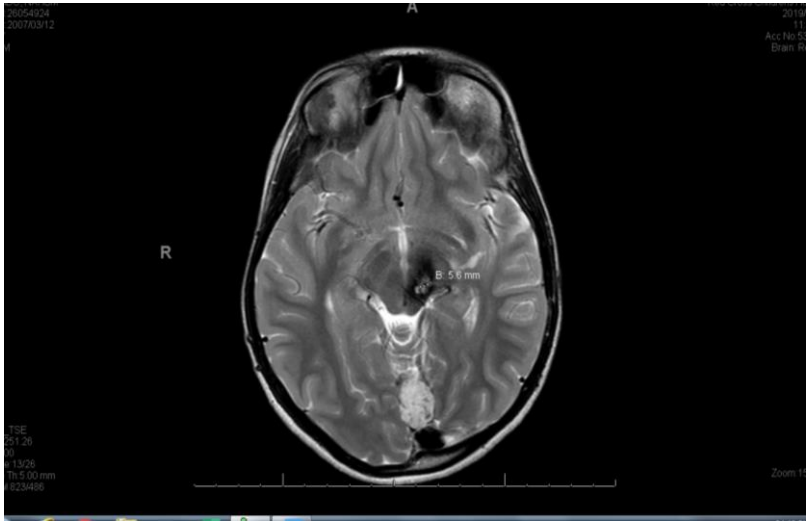
Brain MRI before surgery
T2 axial – T2 Flair sagittal





Post operative brain MRI





REVIEW

Myorhythmia: Phenomenology, Etiology, and Treatment

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Thank You