Movement disorders in children

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First take home message:

**CHILDREN ARE NOT LITTLE ADULTS**

- Clinical history must investigate **age-specific elements** (birth weight, head circumference, developmental milestones, ...)

- Children may not be able to perform specific manoeuvres → «passive» **observation** is important (and takes time!)

- Semeiology is different (developing brain)

- Differential diagnosis of the same clinical entity (eg parkinsonism) largely differs from adults
In children, **hyperkinetic** movement disorders are much **more frequent** than hypokinetic ones.

Movement disorders are frequently **combined** (dystonia+parkinsonism, dystonia+chorea).

**Metabolic causes** (inherited disorders of metabolism) are more relevant than in adults.

**Treatable conditions** must be promptly recognized (it does not matter if you are not a child neurologist!!!)
Parkinsonism

✓ Parkinsonism in children is not frequently observed
✓ Rest tremor is rare and can have an episodic occurrence
✓ A combination of bradykinesia and rigidity is most frequently observed in children
✓ Bradykinesia and loss of postural reflexes cause delay in motor milestones achievement and can be challenging to identify
✓ Dystonia is frequently associated with parkinsonism regardless the underlying etiology
Paediatric parkinsonism

- Disorders of monamine neurotransmitter metabolism (GCH-1, TH, SpR, AADC) or **Dopamine transport** (SLC6A3)
- **Neurodegenerative disorders** (NBIA, Huntington, GM1, NPC, Fragile-X, Ceroidlipofuscinoses, mitochondrial diseases)

- **DYSTONIA**
- **PARKINSONISM**

- Drugs, toxic insult
- Basal ganglia lesions
Biosynthesis of monoamine neurotransmitters

[Diagram showing the biosynthesis pathway of monoamine neurotransmitters, including steps such as phenylalanine to tyrosine, tryptophan to serotonin, and tyrosine to dopamine, with key enzymes and intermediates labeled.]

Wijemanne & Jankovic, Nat Rev Neurol 2016
DOPA-responsive Dystonia (DRD)

A group of clinically and genetically heterogeneous disorders that typically manifest as
- **Limb-onset** dystonia
- With diurnal **fluctuations** (worsening during the day)
- And sustained **response to levodopa** treatment

- **Autosomal dominant GTP-CH-I deficiency**
- **Autosomal recessive GTP-CH-I deficiency**
- **Tyrosine Hydroxylase (TH) deficiency**
- **Sepiapterin reductase deficiency**
Autosomal dominant GTP-CH-I deficiency

✓ Also known as Segawa disease
✓ GTP-CH1 mutations show reduced penetrance (30%)

✓ Mean age at onset 8.5 years, range 0.2-48 years
✓ Onset with progressive dystonia in the lower limbs +/- parkinsonism
✓ DIURNAL FLUCTUATIONS 56-80% of patients (worse at evening)
✓ Brisk lower limb reflexes (DD spastic paraparesis!), striatal toe
✓ Normal motor and cognitive development
✓ Non-motor features increasingly recognized (anxiety, sleep disturbances, ...)
✓ Excellent and sustained response to Ldopa (1-10 mg/Kg/day in 3 doses)

✓ Patients with biallelic mutations (recessive form) show more severe dystonia, oculogyric crises, poor sleep, excessive drooling and require higher LD doses
Before LDopa

After LDopa
DRD: how to make a diagnosis

✓ Clinical suspicion

✓ Brain MRI and DAT-Scan are normal (but may be altered in adults)

✓ CSF neurotransmitters, pterins and metabolites (HVA, 5HIAA) dosage

✓ Blood Phenylalanine levels

✓ Phenylalanine loading test (100mg/Kg; blood phenylalanine:tyrosine ratio at different time intervals; increased in GHC-I deficiency)

✓ Genetic analysis (single gene vs customized gene panels vs WES)
**Table 2 | Characterization of DRD by CSF and blood analysis**

<table>
<thead>
<tr>
<th>Type of DRD</th>
<th>Levels in CSF</th>
<th>Levels in blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neopterin</td>
<td>Biopterin</td>
</tr>
<tr>
<td>Autosomal dominant GTP-CH-I deficiency</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Autosomal recessive GTP-CH-I deficiency</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Sepiapterin reductase deficiency</td>
<td>Normal</td>
<td>High</td>
</tr>
<tr>
<td>Tyrosine hydroxylase deficiency</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>PTP synthase deficiency</td>
<td>High</td>
<td>Low</td>
</tr>
</tbody>
</table>

*Abbreviations:* 5-HIAA, 5-hydroxyindoleacetic acid; CSF, cerebrospinal fluid; DRD, dopa-responsive dystonia; GTP-CH-I, GTP cyclohydrolase 1; HVA, homovanillic acid; PTP, 6-pyruvoyl tetrahydropterin.
✓ DRD is a treatable condition

✓ Response to Levodopa is excellent even many years after the onset

✓ Every patient with childhood-onset dystonia should be treated with a trial of Levodopa

✓ Levodopa-related motor complications (wearing-off, dyskinesias) are uncommon in patients with GTP-CH-I deficiency

✓ Available evidence indicates that levodopa can be used safely during pregnancy
Other diagnoses to consider

✓ **Metal deposition** in the basal ganglia (Copper, Iron, Manganese) → progressive dystonia and parkinsonism, no fluctuations

✓ **Lysosomal** storage disorders (GM1/GM2 gangliosidosis) → hepatosplenomegaly, bone alterations

✓ **Lipid** storage diseases (cerebrotendinous xanthomatosi) → chronic diarrhoea, liver disease, peripheral neuropathy, tendon xanthomas

✓ **Huntington’s** disease (Westphal variant) → CAG repeats on HTT gene
• 7 mo old boy
• Subacute onset of parkinsonism during chemotherapy for acute lymphoblastic leukemia
• Rest tremor R>L
• Irritability

Enterovirus encephalitis with extensive bilateral basal ganglia lesions
Wilson’s disease

- Biallelic ATP7B mutations
- Dystonia involving the facial muscles (risus sardonicus), parkinsonism, chorea, liver disease, (flapping) tremor, Kayser Fleischer ring
- Diagnosis: serum ceruloplasmin (↓), 24h urinary copper (↑), brain MRI, liver biopsy, slit-lamp exam, gene testing
- Treatment: penicillamine, tirientine, zinc

On LD/Carbidopa 300 mg/day + Artane 6 mg/day
Neurodegeneration with Brain Iron Accumulation (NBIA)

*Pantothenate Kinase-Associated Neurodegeneration (eye of the tiger sign)*
(PKAN; PANK2 mutations)

*Beta-propeller protein associated neurodegeneration*
(BPAN; WDR45 mutations)
## Main NBIA syndromes

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Gene</th>
<th>Transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pantothenate Kinase-Associated Neurodegeneration (PKAN)</em></td>
<td>PANK2</td>
<td>AR</td>
</tr>
<tr>
<td>Phospholipase 2, group VI-associated neurodegeneration (PLAN)</td>
<td>PLA2G6</td>
<td>AR</td>
</tr>
<tr>
<td><em>Beta-propeller protein associated neurodegeneration (BPAN)</em></td>
<td>WDR45</td>
<td>X-linked</td>
</tr>
<tr>
<td>Mitochondrial membrane protein-associated neurodegeneration (MPAN)</td>
<td>C9Orf12</td>
<td>AR</td>
</tr>
<tr>
<td>Fatty acid hydroxylase-associated neurodegeneration (FAHN)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COASY protein-associated neurodegeneration (CoPAN)</td>
<td>CoASY</td>
<td>AR</td>
</tr>
<tr>
<td>Kufor–Rakeb syndrome</td>
<td>ATP13A2</td>
<td>AR</td>
</tr>
<tr>
<td>Woodhouse–Sakati syndrome</td>
<td>C2Orf37/DCAF17</td>
<td>AR</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td>FTL</td>
<td>AD</td>
</tr>
<tr>
<td>Aceruloplasminemia</td>
<td>CP</td>
<td>AR</td>
</tr>
</tbody>
</table>
PKAN

- Progressive generalized dystonia severely affecting the OM region and the trunk
- Parkinsonism more prominent in adolescents-young adults
- Frequent, drug-resistant status dystonicus in childhood
- T2* sequences show pallidal iron accumulation and «eye of the tiger sign»
- No disease-modifying treatment; pallidal DBS can improve dystonia and SD
HYPERKINETIC MOVEMENT DISORDERS
✓ TICS
✓ CHOREA
✓ DYSTONIA
✓ MYOCLONUS
✓ DYSKINESIAS
✓ TREMOR
✓ STEREOTYPIES
TICS DISORDERS
Sudden, brief, repetitive and stereotyped movements (motor tics) or sounds (phonic tics) that typically mimic a usual motor behavior (e.g.: eye blinking)
How to approach a patient with tics

1) Tics or other movement disorders? (myoclonus, chorea, stereotypies)
2) Age of onset (under-recognized in infancy)
3) Primary or secondary to an underlying disorder (neurogedenerative, post-infectious ecc)?
4) Family history
5) Psychiatric comorbidity (OCD, ADHD, etc)
6) Tics course (waxing and vaning?) and time from onset
7) Monomorphc or polymorphc?
8) Degree of disability and social impairment
9) Full neurological examination (secondary tics?)

- SINGLE MONOMORPHIC TIC
- NO WAXING AND VANING COURSE
- ADDITIONAL SIGNS ON EXAMINATION

RED FLAGS FOR SECONDARY TICS
Spectrum of tic disorders

Provisional tic disorder
• Single or multiple motor and/or vocal tics
• Tics have been present for <1 year
• Age of onset < 18 years
• No secondary causes

Chronic (persistent) tic disorder
• Single or multiple motor or vocal tics have been present for >1 year, but not both motor and vocal tics

Gilles de la Tourette (GTS) syndrome
• Both motor tics (2 +) and phonic tics (1 +)
• Duration > 1 year
• Age of onset <18 years
• Psychiatric comorbidity in 90% of patients

Prevalence in childhood 0.3%-0.9%

M 1.06% : F 0.25%
DYSTONIA
Classification of dystonia

- Isolated
  - Generalised
  - Focal / segmental

- Combined
  - + Myoclonus
  - + Parkinsonism
Childhood-onset DYSTONIA

✓ Typically starts in the limbs (++ lower limbs)
✓ Frequent generalization (unlike adults)
✓ Onset in the cranio-cervical region is atypical (THAP1, VPS16)
✓ Dystonic tremor is very rarely observed
✓ Oromandibular dystonia is often suggestive of an underlying neurodegenerative disease (NBIA)
✓ Always investigate diurnal fluctuations (DRD)
✓ If possible, examine the child’s parents
Isolated dystonia

✓ DYT1 (Tor1A)
✓ DYT4 (TUBB4a)
✓ DYT5 (GCH1)
✓ DYT6 (THAP1)
✓ DYT24 (ANO-3)
✓ DYT25 (GNAL)
✓ DYT2 (HPCA)
✓ DYT30 (VPS16)
✓ VPS11

Combined dystonia

✓ DYT11 (SGCE)
✓ DYT12 (ATP1A3)
✓ DYT3 (TAF1)
✓ DYT28 (KMT2B)
✓ VPS41
✓ TSPOAP1
DYT1 (TOR1A)

- AD, 30% penetrance
- early-onset (first three decades) usually in a limb
- frequent generalization (in about 5 years)
- ++ sparing of cranial-cervical region
- good response to Gpi-DBS

**del GAG** recurrent mutation
- founder mutation in Ashkenazi Jews
- also arisen *de novo* several times
KMT2B

- Early-onset **lower limb dystonia**
- Prominent oro-mandibular and **laryngeal** involvement (→ anarthria)
- Severe **axial** dystonia
- **Generalization** in almost all patients
- Very good response to DBS
- *De novo* mutations in most cases, but evidence of incomplete penetrance

**Additional features**
- **Microcephaly**
- **Dysmorphic features** (enlongated face and bulbous nasal tips)
- Mild-to-moderate **intellectual disability**
- Brisk reflexes in the lower limbs

Subtle, symmetrical hypointensity of the globus pallidi (with a hypointense streak of bilateral globus pallidus externa) on MR images
KMT2B

Cicarechio et al., MDJ 2019
MYOCLONUS DYSTONIA (DYT11/SGCE mutations)

**MYOCLONUS**
- Brief, shock-like jerks
- Upper body involved (head, trunk, upper limbs)
- Worsens with action, posture, stress, emotions
- Non stimulus-sensitive
- Lower limbs affected in 25% patients

**PSYCHIATRIC DISTURBANCES**
- OCD
- Generalized anxiety disorder
- Social phobia
- Agorafobia

**DYSTONIA**
- Mild-to-moderate
- Cervical dystonia/writer’s cramp
- Spontaneous improvement during adolescence
- Lower limbs are rarely affected

- Normal brain MRI
- **Alcohol-responsive myoclonus** with subsequent rebound
Myoclonus dystonia
CHOREA
Main causes of chorea in childhood are:

- **Metabolic diseases** (inherited disorders of metabolism – organic acidurias, aminoacidopathies, ...)

- **Autoimmune/post-infectious causes** (Sydenham’s chorea, autoimmune encephalitides)

- **Genetic disorders** (degenerative/non neurodegenerative)
Chorea in Inborn Errors of Metabolism (IEMs)

**Methylmalonic aciduria**

- **23-year-old female**
- **Born full term after uncomplicated pregnancy**
- **Healthy until 18 months of age → acute comatose state**
- **Laboratory tests → metabolic acidosis**
- **Generalized hypotonia, mild hepatomegaly**
- **High urinary concentration of methylmalonic acid (MMA)**
- **Genetic testing: compound heterozygous mutations in MMAB gene**

**Metabolic diseases:**
- Acute onset
- Generalized distribution of chorea
- Metabolic decompensation (catabolic state) with/without acidosis
- Basal ganglia lesions on brain MRI
Autoimmune causes: Sydenham’s chorea

- The most common acute-onset chorea in childhood
- Onset within **4-8 weeks** after streptococcal infection
- Rapid generalization, BUT hemichorea in 20% of cases
- Hypotonia, motor impersistence
- 60-80% carditis (mitralic valve); arthritis in 20-30% cases
- Behavioural abnormalities (OCD) in 14 to 24% cases

1) Look for present or recent streptococcal infection (serum ASLO titer, anti-DNAase Ab, ESR, RCP, pharyngeal swab+colture)
2) Cardiac ultrasounds
3) Exclusion of alternative causes
Sydenham’s chorea
# Genetic causes

<table>
<thead>
<tr>
<th></th>
<th>ADCY5</th>
<th>NKX2-1</th>
<th>PDE10A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Delayed milestones</strong></td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Axial hypotonia</strong></td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Intellectual disability (mild)</strong></td>
<td>Y</td>
<td>Y/N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Inheritance</strong></td>
<td>AD (mostly de novo)</td>
<td>AD (mostly de novo)</td>
<td>AD (mostly de novo)</td>
</tr>
<tr>
<td><strong>Brain MRI alterations</strong></td>
<td>No</td>
<td>No</td>
<td>Yes (basal ganglia)</td>
</tr>
<tr>
<td><strong>Additional features</strong></td>
<td>Paroxysmal exacerbations, brisk reflexes</td>
<td>Lung and thyroid disease, myoclonus</td>
<td>Rapid onset</td>
</tr>
<tr>
<td><strong>Disease course</strong></td>
<td>Non progressive</td>
<td>Non progressive (spontaneous improvement in some adults)</td>
<td>Non progressive, possiblendiurnal fluctuations</td>
</tr>
</tbody>
</table>
Genetic causes: NKX2-1

«Brain-Thyroid-Lung disease» («Benign Hereditary Chorea»)

- 10 year-old boy
- Pulmonary hypertension at birth
- Subclinical hypothyroidism
- Recurrent upper respiratory tract infections
- AD history of hypothyroidism and subtle chorea

c.1204dupT; p.*402Leuext*37

(A) I/1 I/2

(B) II/1 II/2 II/3

(C) III/1
PDE10A c.1000T>C (p.Phe334Leu), de novo

Bilateral putaminal lesions WITHOUT metabolic alterations

Esposito, Carecchio et al., MDJ 2017