Choreas and paroxysmal disorders

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• Focus on:
  – Characteristic of the disorders (clues)
  – Phenomenology -> syndrome
  – Etiologies (diagnostic approach (clues/ tests)
  – Treatment (s)

Chorea

Bedside examination

• Definition
  – Erratic involuntary brief purposeless movements
  – Non repetitive, randomly distributed
  – Irregularly timed
  – Hypotonia

• Clinical clues
  – Age at onset
  – Acute progressive
  – Familial history
  – Associated clues
    • Septis/upper infectious
    • Pregnancy
    • APL, polyglobulia, etc.
    • Drugs
  – Associated signs:
    – Ataxia, behavioral, eye movements, neuropathy, clonus
  – Distribution (focal lesions)

Progressive onset, 40 years-old, behavioral disorders, cognitive decline

Huntington's disease
CAG repeat (huntingtin)

Facial chorea
Akinetic presentation

Dementia in HD
dysexecutive syndrome, reduced verbal fluency, apathy, bradyphrenia, relative preservation of language and memory, dementia of HD patients

Juvenile form
(large number of CAG repeats, paternal transmission)

Dyskinesia, may be also the first symptom in autosomal dominant ataxia (SCA1, SCA2, SCA3, SCA6, SCA7, DRPLA) or recessive EAO1 (Apraxia)

Dyskinesias, rigidity, akinesia

Not a treatment yet, but some hope

GPi-DBS attenuated chorea
Long term beneficial effect on chorea despite progression of other symptoms

dietary anaplerotic therapy: triheptanoin
replenishing the pool of metabolic intermediates in the Krebs cycle

Other types of hereditary chorea

- DRPLA
Huntington like syndromes
- HDL-1/PRNP (a few families)
- HDL-2/JPJH-3 junctophilin3 (Africa)
- HDL-3, SCA 17
- Rare: C9orf72 mutation, SCA2
- Neuro-acanthocytosis
- « Benin » hereditary chorea

Other types of chorea: Clues

- Variable age at onset
- Chorea, myoclonus, dystonia, parkinsonism
- Ataxia
- Dementia, psychosis
- Epilepsy (may be severe i.e. progressive myoclonus epilepsy)

Patients with progressive myoclonus epilepsy (PME) phenotype: larger expansions (62-79 repeats) earlier ages of onset (onset before age 20).

DRPLA Dentatorubral-pallidoluysian atrophy

Autosomal dominant CAG repeat (CTG-8-17 triplet repeat expansion) Atrophin-1 gene clinically overlaps with Huntington's disease combination of chorea, myoclonus, seizures, ataxia, and dementia.
**Other types of chorea: Clues**

- Young adult onset
- Chorea, myoclonus, dystonia, parkinsonism
- Ataxia
- Oromandibular dystonia
- Areflexia
- Dementia, psychosis

**Neuroacanthocytosis**

- **chorea-acanthocytosis (ChAc), autosomal recessive**
  - Rare autosomal recessive disorder, VPS13A gene, encoding chorein
  - Wide spectrum of symptoms that may vary over time
    - Dystonia lower face and tongue precipitated by eating, speech and swallowing difficulties
    - Neck ("head drops") and truncal flexion/extensions movements
    - Gait can appear bizarre and "rubbery," with buckling at the knees and hips
    - Bradykinesia usually develops later
    - Areflexia
    - Psychiatric symptoms, cognitive decline
    - Acanthocytes, increased CPK
  - Mac: Lesd similar features with neuropathy and myopathy  X-linked: XK gene

**Benign hereditary chorea**

- NKX2-1 gene (previously called TITF1), essential for organogenesis of the basal ganglia, thyroid lung
  - Rare autosomal dominant disorder
  - Childhood onset that tends to improve in adulthood.
  - Hypotonia and chorea in early infancy, with delayed walking ability
  - Dystonia, myoclonus, tics, ADHD may be associated over time
  - Learning difficulties in some, mental retardation may be present
  - Various combinations of thyroid (67%) and lung (46%) features
  - Beneficial effect of tetrabenazine (even in children)
Bedside examination

**Definition**
- Erratic involuntary brief purposesless movements
- Non-repetitive, randomly distributed,
  - irregularly timed,
  - Hypotonia

**Clinical clues**
- Age at onset
- Acute/progressive
- Familial history
- Associated clues
  - Streptococcal infection
  - APL, polyglobulia, etc.
  - Drugs
- Associated signs:
  - dementia, bitemporal eye movements, neuropathy, ataxia
- Distribution (focal lesions)

Antiphospholipid syndrome (Lupus erythematosus)

- frequency ranges from 1% to 2%
- age at onset of chorea 20.6 years (9-62)
- may be the initial symptom or early in the course of LED
- female predominance (84%),
- high prevalence of antiphospholipid antibodies (91%)
  - heart valvulopathy during follow-up
  - Arterial thrombosis
  - Spontaneous abortions
  - Importance of prophylactic treatment of the APL syndrome (pregnancy)
  - beneficial effect of steroids (may also improve spontaneously)
  - Symptomatic treatment of chorea

Sydenham chorea

may have concomitant hyperactivity and OCD symptoms

Post-stroke

Paroxysmal disorders
Triggering factors

- **Paroxysmal kinesigenic dyskinesia (PKD)**
  - PRRT2

- **Paroxysmal exercise-induced dyskinesia (PED)**
  - SLC2A1 (Glut1 deficiency)

- **And paroxysmal non-kinesigenic dyskinesia (PNKD)**

  Rare troubles
  - Alternating hemiplegia ATP1A2 (and CACNA1A, SCN1A)
  - Episodic ataxia (EA1: KCNA1 mutations, EA2: CACNA1A mutations)

Becoming more complex over time: expanding spectrum

Paroxysmal Dyskinesia

- **PKD**
  - Onset in childhood
  - Triggering factor: sudden movement after rest (standing up)
  - Duration < 1 min.
  - No pain, no loss of consciousness, interictal examination normal
  - Frequent (up to 100/day), variable, often peaking in puberty, improvement in adulthood
  - Past history of benign infantile convulsions (before 1 year-old)

PRRT2 mutations and Kinesigenic paroxysmal Dyskinesias (PKD)

- **PRRT2 mutations**
- **Kinesigenic paroxysmal Dyskinesias (PKD)**

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Méneret & Roze, 2016

Dr. Méneret and Dr. Roze, 2016

Clinical spectrum of PRRT2 mutations

**PKD:** paroxysmal kinesigenic dyskinesias
**ICCA:** infantile convulsions with choreoathetosis syndrome
**BFIS:** benign familial infantile seizures
**PED:** paroxysmal exercise induced dyskinesias
**HM:** hemiplegic migraine
**EA:** episodic ataxia
**FS:** febrile seizures
**CAE:** childhood-absence epilepsy

### PKD
The most frequent among paroxysmal dyskinesias

- Onset childhood between 1 and 20 years-old
- Premonitory sensation* (aura)
- Triggering factor: initiation of movement after a period of rest
- Duration < 1 min.

No improvement by anti-epileptic drugs

Main cause: mutations SLC2A1

### PED
Exercise induced

- Onset in childhood
- Triggering factor: prolonged exercise
- Duration 5-30 minutes (variable frequency)
- No pain, no loss of consciousness, interictal examination normal
- No beneficial effect of antiepileptic drugs

Main cause: mutations SLC2A1 (GLUT 1 deficiency)

- Variable phenotype
- Microcephaly, mental retardation
- Complex movement disorders, ataxia, pyramidal signs
- Paroxysmal disorders (epileptic and non epileptic episodes)
- PED may be isolated
Significant reduction of non-epileptic paroxysmal manifestations when patients were treated with triheptanoin for 2 months (*p<0.05)

Ketogenic diets, standard of care in GLUT1 efficient on seizures control but less on movement disorders. Ketone bodies to the brain and compensate for the lack of glucose

**ATP1A3 mutations**
- Large spectrum:
  - Early infantile epileptic encephalopathy: seizures, dyskinesia followed a regression episode during a febrile episode during infancy.
  - Alternating hemiplegia of childhood (AHC): CAPOS (paroxysmal cerebellar ataxia, pes cavus, optic neuropathy, SN deafness).
  - Rapid-Onset Dystonia-Parkinsonism (RDP): Relapsing encephalopathy with cerebellar ataxia.

**Alternating hemiplegia childhood**
- Age at onset before 18 months
- Triggering factor: temperature, bath-induced paroxysmal events
- Duration: minutes to days.
- All patients experience hemiplegic attacks: 86.5% episodes of bilateral weakness, 86% dystonic attacks, 53% epileptic seizures, 72% developed chorea and/or dystonia and 92% mental retardation
- Other: hemiplegia or quadriplegia, seizures, nystagmus, autonomic disturbances, dysnea, altered consciousness, seizures
  - Paroxysmal eye movements by the age of 3 months in 80%
  - Hemiplegic episodes appeared by 6 months of age in 96% of infants.

Ataxia (96%), cognitive impairment (100%) frequent nonepisodic symptoms

**Dopa-responsive dystonia (DRD)**
- Due to heterozygous mutation (++) or deletion GTP cyclohydrolase gene, GCH1, in 70% cases
- AD, incomplete penetrance, female predominance (3:1)

**Typical form**:
- Onset first decade,
- Initial involvement of one limb,
- Dystonic fluctuations (70%),
- Exercise-related worsening,
- Excellent response to L-Dopa

**Atypical forms**
- Adult-onset generalized dystonia
- Dystonia that remains focal over decades
- Exercise-induced dystonia
- Task-specific dystonia
- Dysarthria-dystonia
- Isolated parkinsonism
- Spastic paresis
- Additional signs: cerebellar features, axial hypotonia, ocular motor

**Dopa-responsive dystonia**

**Other**
- Payed football all day with his friends
dystonia when walking +/- akinesia
- After treatment

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**Triheptanoin dramatically reduces paroxysmal motor disorder in patients with GLUT1 deficiency**

Mochel F et al JNPP 2016
**ADCY5**

- Onset in childhood
- Hyperkinetic movement disorders (mixed chorea/dystonia), some fluctuations
- Axial hypotonia
- Orofacial myokimia/myotonia
- No ataxia, no marked cognitive deficiency,
- Slow progression
- Paroxysmal nocturnal movement disorders at night

**Episodic Ataxia**

- Recurrent ataxia
- +/- dysarthria, tremor, dizziness and vertigo, diplopia,
- Duration: Seconds to several days
- No loss of consciousness
- Sometimes improvement by acetazolamide

**Episodic ataxia type 1: EA1**

- Mutation on the KCNA1 gene
- Onset in childhood or adolescence
- Duration: brief, seconds to minutes
- Triggering factor: movement, startle
- Myokimia (facial)
- +/- mental retardation, epilepsy, myotonia
- May be improved by acetazolamide or anti-epileptic drugs
**Paroxysmal episode**

Started at the age of 25
Duration: 3 sec to 5 min
Variable frequency: 3/day to 1/month
Triggered by a movement or when he is surprised

**Symptomatic episodic ataxia**

<table>
<thead>
<tr>
<th>Symptomatic episodic ataxia</th>
<th>Episodic ataxia 1</th>
<th>Episodic ataxia 2</th>
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<tbody>
<tr>
<td>Onset (years)</td>
<td>Adulthood</td>
<td>Childhood (2-15)</td>
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<tr>
<td>Usual attack duration</td>
<td>Minutes</td>
<td>Hours to days</td>
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<tr>
<td>Attack signs</td>
<td>Ataxia, dysarthria, vertigo</td>
<td>Ataxia, dysarthria, diffuse tremor; myokimias</td>
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<tr>
<td>Possible interictal signs</td>
<td>Signs related to the underlying disorder</td>
<td>Myokimias</td>
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<td>Brain MRI</td>
<td>Brainstem lesion</td>
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<td>Response to acetazolamide</td>
<td>++</td>
<td>++</td>
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<td>Response to carbamazepine</td>
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<td>++</td>
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<tr>
<td>Inheritance</td>
<td>Sporadic</td>
<td>AD</td>
</tr>
</tbody>
</table>

**Episodic ataxia type 2: EA2**

- Mutation in the CACNA1A gene
- Onset in childhood or adolescence
- Duration: a few hours to a few days
- Triggering factor: stress, exercise, coffee, alcohol
- Between episodes: persistence of ataxia, nystagmus, epilepsy, migraine
- May be improved by acetazolamide or 4-aminopyridine

**Ataxie épisodique de type 2 (EA2)**

- Mutations hit du gène CACNA1A
- Début dans l'enfance ou à l'adolescence
- Durée des attaques: qq heures à qq jours
- Facteurs déclenchant: stress, exercice, caféine, alcool
- En interictal: ataxie + nystagmus +/- épilepsie, migraine, dystonie...
- Tit: acetazolamide, 4-aminopyridine

**Thank you for your attention**