Movement disorders in neurometabolic disorders

handout IN ADDITION to talk (extension of text slides, illustrative videos in talk)

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I have no financial relationships to disclose.

- and -

I will discuss several off-label treatments in my presentation:

- Off-label treatment differs between countries
- Given the rarity of the diseases I will discuss during this presentation, most if not all treatments are off-label or with orphan drug licences
Movement disorders

- Pyramidal
- Extrapyramidal (several)
- Cerebellar
- Pareses in neuromuscular disorders
Pyramidal System
Pyramidal movement disorder

- Spastic paresis
- Increase in tone
- Velocity dependent („clap-knife“)
- Reduction of muscular force and muscle wasting
- Pattern with flexors and pronators in arms
- Extensors and adductors in legs most involved
Spastic tetraparesis
Spastic tetra- and hemiparesis
Extrapyramidal movement disorders

- Chorea
- Dystonia
- Dystonia-parkinsonism
- Parkinsonism
- Myoclonus
- Tics
- Paroxysmal choreoathetosis
Thal

ST

PR

PC

N. accumbens

N. olfactorius

Caud

Put

GPe

GPi

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Dystonia features

- **Co-contraction** agonist + antagonist
- Twisting, slowish movements
- Abnormal postures
- “well-trained“ or hypertrophic muscles
- Patterns not stereotyped
- Routine movements often more dystonic than others
Opisthotonus with dystonia
Opisthotonus with spasticity
“well trained muscles“
Striatal toe
Dystonia variants

- **Athetosis** is distal dystonia
- **Myoclonic dystonia**, 
- “**jerky dystonia““ 
- **Dystonia-parkinsonism**
Examination

• Identify type of hypertonus

• Tendon reflexes: exaggerated with enlarged reflexogenic zones and cloni in pyramidal disorders

• But: dystonia in children often shows brisk or exaggerated reflexes and sometimes cloni. See patterns and tone for classification
Chorea

- Continuous Hyperkinesias
- Appear random, often all body parts
- Basic tone reduced
Cerebellar movement disorder

- Intentional tremor
- Dysdiadochokinesis *without other MD*
- Tone reduced
- Cerebellar ataxia:
  - gait wide-based with fluctuating width
  - grasping beside the target / dysmetria

➤ Sensory ataxia with loss of proprioceptive information (joint position sense)
Cerebellar handwriting (12 y.)
Confusions with „Ataxia“

• Specify „cerebellar“ or „sensory“ ataxia!

• With dystonia or parkinsonism normal diadochokinesi is usually impossible.

• Targeted movements are often severely abnormal.

➢ But do not diagnose a cerebellar disorder because of this!
Neurometabolic disorders with prominent movement disorders

- **Organic acidurias** (dystonia > others)
- **Disorders of biogenic amines** (parkinsonism-dystonia)
- **Creatine synthesis defects**: GAMT deficiency (dystonia)
- **Congenital disorders of glycosylation** PMM- cerebellar MD > others
- **Mitochondrial** (extrapyramidal but also cerebellar and pyramidal)
Neurometabolic disorders with prominent movement disorders

• **Lysosomal disorders** (GM gangliosidoses)
• **Vitamin transporter disorders** (thiamine transporter for ex.)
• **Metal accumulation disorders** (NBIAs, Wilson‘s d.)

• ....
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Organic acidurias

- Propionic acidemia \( (PA) \)
- Methylmalonic acedemia \( (MMA) \)
- Glutaric acidura typ I \( (GA\ I) \)
- L-2-OH-glutaric aciduria \( (L2-OH-GA) \)
- Maple-syrup-urine-disease \( (MSUD) \)
- Succinate-semialdehyde-dehydrogenase-deficiency \( (SSADH) \)
Common features

• Organic acids accumulate
• Neurological complications
• *Energy metabolism disturbed* (Neurons are extremely dependent on energy, especially basal ganlia neurons)
• *Toxicity of metabolites*

• Lesions are irreversible in most cases
Movement disorder and defect

- The movement disorders of MMA and PA are not systematically different, stable after crisis or very slowly progressive.

- Whereas the GA I movement disorder is distinguishable clinically, stable.

- In L2 OH- GA >> progressive course and mixed movement disorder.
Treatment organic acidurias

• Prevention of toxin accumulation and catabolic crises in PA, MMA, GA I, MSUD
  – Protein restriction, emergency regimens, carnitine (carnitine not MSUD)
  – newborn screening

!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

• SSADH and L2-OH-GA only symptomatic treatment (riboflavin trial L2-OH-GA!)
Biogenic amine’s and pterin disorders

- Biosynthesis disorders:
  - Clinical appearance depends more on the severity of dopamine deficiency than on biochemical defect!

- Dopamine transporter defect: heterogeneous in infancy and preschool-age, later parkinsonian
Legend to figure, only defects discussed

- 2: Tyrosine hydroxylase, TH
- 3: Aromatic-L-aminoacid decarboxylase, AADC
- 8: Guanosine cyclohydrolase I, GTPCH I
- 9: 6‘-Pyruvoyl tetrahydropterin synthase, PTPS
- 11: Sepiapterin reductase, SR
- 13: Dihydropteridin reductase, DHPR
Mild dopamine deficiency

• **Segawa phenotype**: manifestation at school-age, lower legs, after exercise, over the day (diurnal variation)

• **Spastic paraparesis** responsive to L-Dopa (GTPCI-Hydrolase deficiency and TH deficiency)
Severe dopamine deficiency

- Severe hypotonia in infancy
- Reduced voluntary movements
- Ptosis
- Miosis
- Hypersalivation/ reduced swallowing
- Distal tremor or chorea
- Oculogyric crises
Dopamintransporter deficiency syndrome, infantile onset

- **infancy**: hyper- or hypokinetic
  - with and without tremor
- **Eye movement disorders**: ocular flutter, saccade initiation failure, oculogyric crises (few patients)
- **Anarthria**
- **School-age**: parkinsonism with some dystonia predominant
- **Mental progress** continues
VMAT 2 deficiency

• Defect: Vesicular monoaminetransporter 2
• Vesicles (presynaptic) contain less dopamine and serotonin, no clear biochemical marker
• 1 familiy (2013, Rilstone)
• Parkinsonism-dystonia spectrum + autononomic functions
• L-Dopa worsens, Dopamine agonists improve symptoms !!!
Treatment of biogenic amine's disorders

- L-Dopa/Carbidopa 4:1 up to ~ 400mg/day, then 10:1
- Severe deficiency: start ~ 0.5 mg/kg/d in (4-) 6 dosages. Increases at individual pace (2-5 days, maybe longer - esp. later in course)
- Side effects: chorea, myoclonus, VOMITS (cave aspiration !)
- Mild: start 1-2 mg/kg/day in 4 dosages, 1-2 wks
- Not effective for AADC and DAT deficiency
Treatment of biogenic amine’s disorders

• Full replacement: ~10 (-12) mg/kg/day L-Dopa
• But in severe cases less tolerated >>
  equilibrium dystonia-parkinsonism
  and chorea or myoclonic jerks
• If 10:1 is used (L-Dop/Carbdop.), more L-Dopa
  is lost in the gut membranes and nominal
  dosage may exceed this.
• 5-OH-Tryptophane ~2 mg/kg/d less than
  L-Dopa (no additional carbidop)
Cofactors and diet

- Recessive GTPCH I and PTPS: **BH4 5-10 mg/kg/d in 2-3 dos.**
  - controversial in DHPR: (BH2) accumulates and inhibits NO synthase, possibly AADC)
- If BH4 (Kuvan) unavailable >PHE reduced diet

- Phe-check at least once per month (no clearly defined target range available, therefore according to national PKU recommendations)
- DHPR: folinic acid **15-20 mg/day in 1-2 dos.** and low-Phe diet
Pterin defects without hyperphenylalaninemia

- Aut. dominant GTPCH I and Sepiapterin reductase deficiency:
  - Usually no BH4 supplementation >> high dosages to cross blood-brain-barrier, no effect on biogenic amines, much more efficient with neurotransmitter supplementation
Argument for more than 3 dosages of L-Dopa in addition to hypersensitivity of receptors


Hyperprolactinemia, a Tool in Treatment Control of Tetrahydrobiopterin Deficiency: Endocrine Studies in an Affected Girl

Robert Birnbacher¹, Susanne Scheibenreiter¹, Nenad Blau³, Christian Bieglmayer², Herwig Frisch¹ and Franz Waldhauser¹
At 5¾ y, 24-h hormone profiles in our patient with severe BH₄ deficiency while on three doses of L-DOPA/carbidopa (“D”). Prolactin profile;
At 6½ y, 24-h hormone profiles in our patient while on six doses of L-DOPA/carbidopaa ("D"). Prolactin profile, dosage 6-10-12-14-16-18 o’clock

8 o’clock pm
At 10¼ y, 24-h prolactin profile in our patient with severe BH$_4$ deficiency while on three doses of L-DOPA/carbidopa slow release preparation. DS, L-DOPA/carbidopa slow release preparation.
AADC deficiency

- L-Dopa / 5-Hydroxytryptophan without effect (exception with special mutation)

- **Dopamine agonists**: Pramipexole, Bromocriptine, Rotigotine, Ropinirole

- **MAO (B) inhibitors**: Selegeline, Tranylcypromine

- Pyridoxine to boost residual activity

- Symptomatic: trihexyphenidyl
Symptomatic treatment of Dystonia

• Medication

• Botulinum toxin

• Intrathecal Baclofen (catheter up to C 4-7)

• deep brain stimulation – preferably in unlesioned pallidum, ongoing studies
Medication focussed at reduction of tone

- **Dantrolen** (peripheral muscle)
- **Tizanidine** (central α-agonist)
- **Baclofen** (GABA $B$ receptors)
- **Benzodiazepines** (GABA $A$ receptors, *status dystonicus*)
Medication focussed at dystonia and involuntary movements

• **L-Dopa/Carbidopa**, dopamine agonists
• **Trihexyphenidyl** (anticholinergic)
• **Tetrabenazine** (antidopaminergic, presynaptic, inhibits vesicular transporter)
• **Tiapride** (antidopaminergic, D2 receptor inhibitor as are atypical neuroleptics)
• **Zopiclon** (atypical tranquilizer)
Zopiclón

- Atypical Tranquilizer
- GABA A receptor agonist but α₁-subunit
- Chemical structure different from Benzodiazep.
- Helps well for bad hyperkinesias without too much sedation and without /less tolerance
My way for off-label dosage

• Recommended dosage for Adults transformed to dosage per 1,73 m²

• Calculation of dosage for child’s surface

• Start with 10-20% of this