Update on the management of neurometabolic disorders in children.

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Neuro-metabolic disorders in children

- Rare, genetic disorders
- Ocular phenotype often specific and unique
- Severe systemic problems may overshadow ocular issues: learning difficulties, multiple medical problems, shortened lifespan
- New systemic treatments may prolong and improve quality of life
- New technologies lead to better understanding and treatment of ocular complications


- Update on the management of Lysosomal Storage Disorders (Jane Ashworth)  
- Corneal transplantation in MPS (Gail Summers)  
- Mitochondrial disease: LCHAD deficiency (Kristina Fahnehjelm)  
- Interesting cases (Jane Ashworth and Chris Lloyd)
Lysosomal storage disorders in children

- More than 50 very rare inherited metabolic diseases
- Result from deficiency of specific lysosomal enzymes required for normal cellular metabolism
- Life limiting
- Ocular features common, unique, challenging
- May be present at early stage and give clue to diagnosis
- New treatments improve prognosis, less certain effect on eyes and vision
## Common Lysosomal Storage Disorders and Current Treatments

<table>
<thead>
<tr>
<th>LSD</th>
<th>Function effected</th>
<th>Established treatment</th>
<th>Treatment in development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucopolysaccharidosis</td>
<td>GAG metabolism</td>
<td>ERT (I, II, IVa, VI), HSCT (I, VI)</td>
<td>Yes</td>
</tr>
<tr>
<td>Fucosidosis</td>
<td>Degradation of glycoproteins</td>
<td>No (HSCT)</td>
<td>ERT</td>
</tr>
<tr>
<td>Mannosidosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Sialidosis type 1</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Fabrys disease</td>
<td>Degradation of sphingolipids</td>
<td>ERT, Miglustat (SRT)</td>
<td>Yes</td>
</tr>
<tr>
<td>Gauchers disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niemann Pick type A and B</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Metachromic leukodystrophy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>Phenotype</td>
<td>Treatment</td>
<td>Status</td>
</tr>
<tr>
<td>---------------------------------</td>
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</tr>
<tr>
<td>Pompe disease</td>
<td>Degradation of glycogen</td>
<td>ERT</td>
<td>Yes</td>
</tr>
<tr>
<td>Cystinosis</td>
<td>Transport defect</td>
<td>Oral cysteamine</td>
<td>Yes</td>
</tr>
<tr>
<td>Neuronal Ceroid Lipofuscinosis</td>
<td>Lysosomal protein deficiency</td>
<td>No</td>
<td>Yes (ERT)</td>
</tr>
</tbody>
</table>

**Ocular manifestations of LSDs**

<table>
<thead>
<tr>
<th>Site</th>
<th>Phenotype</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cornea</td>
<td>Opacification</td>
<td>Mucopolysaccharidoses (MPSI, IV and VI, VII)</td>
</tr>
<tr>
<td></td>
<td>Crystals</td>
<td>Cystinosis</td>
</tr>
<tr>
<td>Location</td>
<td>Condition</td>
<td>Disease</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Verticillata</td>
<td>Fabry's disease</td>
<td></td>
</tr>
<tr>
<td>Localised opacity</td>
<td>Fucosidosis</td>
<td></td>
</tr>
<tr>
<td>Lens</td>
<td>Cataract</td>
<td>Fabry's disease</td>
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<tr>
<td></td>
<td></td>
<td>Mannosidosis, MPSIV</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>Vascular tortuosity</td>
<td>Fabry's disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Farber's disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gaucher's type 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fucosidosis</td>
</tr>
<tr>
<td>Retina</td>
<td>Cherry red spot</td>
<td>Niemann-Pick type A and B</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GM1 and 2 gangliosidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sialidosis type 1 and 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metachromic leukodystrophy</td>
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<tr>
<td></td>
<td></td>
<td>Ferber's lipogranulomatosis</td>
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<tr>
<td></td>
<td></td>
<td>Galactosialidosis</td>
</tr>
<tr>
<td>Retinopathy</td>
<td></td>
<td>MPSI, II, III</td>
</tr>
<tr>
<td>Bulls eye maculopathy</td>
<td>Neuronal ceroid lipofuscinosis</td>
<td></td>
</tr>
<tr>
<td>Retinal vascular tortuosity</td>
<td>Fabry's disease</td>
<td>Fucosidosis</td>
</tr>
</tbody>
</table>
| Optic nerve | Optic atrophy | Mucopolysaccharidoses  
Neuronal ceroid lipofuscinosis  
Niemann-Pick type A |
|-------------|---------------|-----------------------------|
| Ocular motility | Oculomotor apraxia  
(Saccadic Initiation Failure)  
Vertical supranuclear gaze palsy | Gauchers type 3  
Niemann-Pick type C |
The Mucopolysaccharidoses (MPS)

- Defect of glycosaminoglycan degradation leading to accumulation in systemic and ocular tissues
- MPS I (Hurler, Hurler-Scheie and Scheie), MPSII (Hunter’s), MPSIII (Sanfillipo’s), MPSIV (Morquio’s), MPSVI (Maroteaux-Lamy), MPSVII Sly’s, MPSIX Natowicz
- Onset in infancy- kyphoscoliosis, recurrent ENT infections
- Skeletal, cardiac, respiratory, gastrointestinal and neurological manifestations
- Ocular manifestations variable but corneal clouding may be present from birth

The cornea in MPS

- Corneal opacification characteristic of
  - MPSI (Hurler’s, Hurler-Scheie and Scheie’s)
  - MPSIV (Morquio’s)
  - MPSVI (Maroteaux-Lamy)
  - MPSVII (Sly’s)
- Photophobia, reduced vision later
- Slowly progressive if untreated
- Exposure keratopathy, vascularisation

Anterior segment changes in MPS

- Central corneal thickness correlates with corneal opacification (Kottler et al Cornea 2010; Connell et al J AAPOS 2009)
- Variable central corneal thickness (Kottler et al Cornea 2010)
- Progressive increase in peripheral corneal thickness with time (Casanova et al Cornea 2001)
- Progressive thickening of cornea and altered hysteresis
  (Fahnehjelm et al Acta Ophthalmol. 2011)
- Changes in anterior chamber; narrowing of angle, iris thickening (Ahmed et al Eye 2014)
Optic neuropathy in MPS

- “Full” appearance of optic nerves in MPS
  - Increased thickness of sclera
  - More susceptible to damage from raised ICP

Raised ICP may have optic atrophy as only manifestation and may result in profound visual loss

Glaucoma in MPS

- Rare- prevalence 2.1-12.5%
- May result in profound loss of vision
- Challenging to diagnose and monitor
- IOP affected by
  - technique (i-care)
  - corneal thickness and hysteresis
- Optic discs may be effected by GAG deposition, poor view due to corneal opacity and poor dilation
- Visual fields effected by cooperation and retinopathy

Retinopathy in MPS

- MPSI, II and III

- Later onset of nyctalopia and peripheral visual field loss
- Later central vision effected
- ERG progressive attenuation in dark then light adapted conditions
Retinal detachment (MPSII)

Enzyme replacement therapy in MPS
- Weekly infusion MPSI (laronidase), II (elaprase), IVa (elosulfase) and VI (galsulfase)
- Improvement in systemic parameters (walking ability, endurance and pulmonary function) and reduced urine GAG excretion in MPSI and MPSII (Jameson et al Cochrane Database Syst Rev 2013; da Silva et al Cochrane Database Syst Rev 2014)
- Early treatment in MPSI, II and VI may improve clinical course in family studies (Lampe et al JIMD Rep 2014, Jones et al.....)
- Lifelong treatment, disease progression can still occur
- Immune reactions, difficult delivery to brain, bone, heart valves and eye

Other treatments for MPS
- HSCT
  - Pre and peri-HSCT ERT in MPSI Hurler’s diagnosed before age 2 years (neurological effect)
  - MPSVI rarely
- Gene therapy
  - Phase I/II clinical trails of intra-cerebral gene therapy in MPSIIIA (Tardieu et al Hum Gene Ther 2014) and intrathecal in MPSII and IIIa (refs)
  - Stem cell gene therapy in MPSI and IIIa (autologous bone marrow transplantation with gene therapy-cures MPSIII mice)- has been done in MLD

Effect of systemic treatment on the eye in MPS
- Lack of objective assessment of ocular condition
  - poor correlation with visual acuity, variability in VA measurements
  - Subjective clinical grading of opacification
  - Photography-depend on illumination, focus, cooperation
- Iris camera imaging and Pentacam densitometry used to quantify corneal clouding (Aslam et al BJO 2012, Elflein et al BJO 2013)
Effect of early treatment on the eye in MPS

- MPSI L490P case series 12 patients (Chan et al Eye 2013 Does the timing of treatment affect the ocular phenotype in patients with Mucopolysaccharidosis I homozygous for the L490P mutation?)
- Limitations- unknown variability in phenotype, subjective assessment of corneal clouding, variable follow-up
- Dog model- high dose iv ERT prevented or improved ocular features (Newkirk et al IOVS 2011)

Local treatment for corneal clouding in MPS

- Corneal keratocytes stable population
- Dendritic cells from limbal blood vessels (and aqueous)
- Adenoviral transduction of keratocytes in canine MPSVII cornea (J Control Release 2014)
- Human umbilical mesenchymal stem cells intra-stromally transplanted into corneas of MPSVII mice reduced corneal haze and decreased GAG content (Stem cells 2013 31(10)2116-26)

Summary

- Wide range of ocular phenotypes
- Helpful in diagnosis
- Need to be aware of new treatments- ERT, HSCT, substrate reduction, gene therapy
- Visual problems more relevant when improved quality of life and life expectancy
- New technologies for ocular assessment to assess new treatment effects