How a slit lamp can save lives

The crucial role of optometrists
In the early diagnosis of Lysosomal Storage Disorders

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Goals

To Review and to understand:
- Pathophysiology of Fabry Disease and MPS
- Characteristics and clinical signs of these diseases
- The role of optometrists in the early detection and timely diagnosis of these diseases

What is a Lysosome?

- Subcellular organelle found in all eukaryotic cells
  - Responsible for the cell’s digestion of macromolecules, old cell parts and microorganisms

Normal production of lysosomal enzymes

Correctly folded, stable enzyme

Misfolded lysosomal enzymes

- Misfolded, unstable enzyme
- Incorrect amino acid sequence
- Substrate accumulates in lysosomes

What do these disorders have in common?

- They are hereditary and progressive in nature
- They lead to irreversible damage to organs and can thus be considered as life-threatening and potentially fatal disorders
- Timely identification and early treatment are therefore crucial
**INCIDENCE**

- Individually rare but collectively common
  - Individual incidence (each): 1:40,000 to 1:1,000,000 births
  - Collective incidence (40 diseases): 1: 7,700 to 1:10,000 births (= 100/1M)

- Ethnical incidence
  - Some diseases affect more particular ethnical groups:
    - Ashkenazes Jews—Gaucher, Niemann-Pick type A
    - Afro-Americans—Infantile-onset Pompe disease (POM-PAY)

**Prevalence among LSD**

- Mucopolysaccharidosis Type I (MPS I)
- Hurler (MPS I)
- Sanfilippo B
- Fahey
- Fabry
- Gaucher type I
- Sanfilippo A
- Sanfilippo D
- Hurler/Scheie (MPS)
- Scheie (MPS)
- Hurler (MPS I)
- Hunter (MPS I)

**Transmission**

- All MPS are autosomic recessive except Hunter disease which is X-linked
- Chromosomal abnormalities and mutations
- In utero screening possible

« If it is in your chair…. It is not rare anymore »

–Lou Catania O.D.

The crucial role of eye care professionals

- Many patients with LSDs have visible eye disorders which may be among the first symptoms to occur
- Recognition of these eye disorders is very important for timely diagnosis
- ECPs play a crucial role as they may be the first to identify and refer a patient
- If necessary, treatment can then be started to prevent irreversible damage to vital organs

By making a timely diagnosis, ECPs can have an enormous impact on the quality and possibly also the duration of a patient’s life
MPS I disease spectrum of severity

**Hurler**
- Severe phenotype (rapidly progressive)
- Psychomotor regression
- Death before age 10*
- Little or no effect on the intellect

**Hurler-Scheie**
- Little or no effect on the intellect
- Death before age 30*

**Scheie**
- Mild phenotype (slower progression)
- Normal intelligence
- Death before age 30*

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**What is MPS I Disease?**

- Progressive, debilitating lysosomal storage disorder belonging to Mucopolysaccharidoses
- Autosomal recessive inborn error of metabolism due to deficient α-L-iduronidase enzyme activity
  - Inability to break down heparan sulfate and dermatan sulfate

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**Frequencies of the 5 most common symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Severe Phenotype</th>
<th>Mild Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coarse Facial Features</td>
<td>298 (94%)</td>
<td>114 (83%)</td>
</tr>
<tr>
<td>Hernia</td>
<td>237 (75%)</td>
<td>41 (65%)</td>
</tr>
<tr>
<td>Kyphosis</td>
<td>259 (81%)</td>
<td>99 (72%)</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>265 (83%)</td>
<td>111 (81%)</td>
</tr>
<tr>
<td>Corneal Clouding</td>
<td>279 (88%)</td>
<td>54 (86%)</td>
</tr>
</tbody>
</table>

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**Corneal opacities**

- Recurrence of corneal opacities post-graft

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**Ocular Manifestations in MPS I**

Ocular complications causing significant reduction in vision are common in MPS I patients.

- Corneal clouding
- Optic disk swelling (papilledema)
- Subsequent optic atrophy
- Retinal degeneration

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**MPS diseases and cornea**

Corneal manifestations:
- Gradual loss of transparency
  - 2nd to lack of uniform density of the tissue
  - Excessive amounts of dermatan sulfate accumulate in the corneal stroma producing fine punctate opacities
Ocular Manifestations in MPS I

Others

- Peripheral neovascularization
  - Response to increased IOP
  - Cornea can become thicker; check pachymetry
- Exophthalmia possible
  - Induced dryness of the ocular surface

Optic disk swelling and subsequent optic atrophy

- Optic disk abnormalities are common in MPS I Hurler and Hurler/Scheie phenotypes:
  - Optic disk swelling: Hurler: 57% / Hurler/Scheie: 43%
  - Optic atrophy: Hurler: 14% / Hurler/Scheie: 19%

- Optic disk swelling and subsequent optic atrophy can occur secondary to:
  - Raised intracranial pressure and hydrocephalus or
  - Compression of the optic nerve by GAG in thickened dura and sclera, resulting in compression of axons at the level of lamina cribrosa or and
  - Accumulation of GAG within retinal ganglion cells which could eventually lead to their degeneration and optic atrophy.

Retinal Degeneration

- Retinopathy is known to occur to a variable degree in all MPS I phenotypes:
  - Hurler: 69%
  - Hurler/Scheie: 56%
  - Scheie: 66%

- Electroretinogram abnormalities, particularly in the rod-mediated response, indicate a progressive retinal pigmentary degeneration

- Patients may complain of night blindness and problems of peripheral vision

- Histiopathology shows accumulations of heparan sulfate in the retinal ganglion cells and pigment epithelium

MPS I differential diagnosis in a nutshell

- Corneal clouding
- Joint contracture
- No clinical inflammatory signs
- History of surgical intervention for hernias

= MPS I

Fabry Disease
Historical perspective (1)

- 1898 1st description of the disease by Johann Fabry et William Anderson.
- 1963 Enzymatic base is found. Primary lipid is identified: GL-3 (Globotriasylceramide) (Sweeley and Kilionsky, 1963)
- 1967 Enzyme deficiency is known: galactosyl hydrolase. (Brady et al., 1967)
- 1979 First success in the treatment of the disease by enzyme substitution. (Desnick et al., 1979)
- 1990s Alpha-GAL is synthetically produced
- 2000 Phase III completed (Eng et al. 2001)

What is Fabry Disease?

- Under-recognized, genetic (X-linked) LSD
- Progressive and ultimately life-threatening
  - Symptoms early in childhood
- Characterized by deficiency of the lysosomal enzyme alpha-galactosidase A (α-GAL A)

Impact on quality of life

Cardiopathy
CNS involvement
Kidney function
Acroparesthesia

Symptoms
[Age] 0 40+ 40+
Quality of life

Fabry Disease Manifestations
By Average Age of Onset

Ocular manifestations
- Corneal and reticular opacities

Neurological involvement
- Acroparesthesia, episodic pain crisis
- Recurrent fever

Hypohidrosis
Heat and cold intolerance

Gastrointestinal manifestations
- Post-prandial abdominal pain
- Diarrhea and vomiting
- Associated with nausea and vomiting

Renal involvement
- Proteinuria
- Renal dysfunction
- Dialysis
- Transplantation

ENT involvement
- Hearing loss
- Tinnitus

Cardiovascular manifestations
- Early Transient Ischemic Attacks
- Renal and vascular disease (PR)

Cardiac involvement
- Left Ventricular Hypertrophy
- Conductive abnormality (long PR)
- Repolarisation abnormalities
- Valvular disease (Mitral Insufficiency)

Systemic signs - angiookeratomes

(a) (b) (c)

Fabry – edema of feet/hands
Diagnosis is a journey

- Patients can consult up to 13 GPs and specialists before an appropriate diagnosis of their condition
- Dx will take more than 6 years for 1/7 patients
- If not diagnosed/treated, Fabry is life-threatening
  - Affected men’s life expectancy: 55 y.o.

Ocular Manifestations in Fabry Disease

Ocular findings are considered a hallmark of Fabry Disease and may result in diagnosis.

- Corneal involvement: Cornea verticillata
- Lens opacities: anterior cataract and posterior “Fabry” cataract
- Conjunctival vessel anomaly
- Retinal vessel tortuosity

Ocular Manifestations in Fabry Disease
Corneal Involvement: Cornea Verticillata

- Cornea verticillata is considered to be the most characteristic and usual ocular findings in hemizygous males. Also considered as a marker of carrier status in heterozygous females.¹
  - Whorl-like corneal opacities
  - Usually in the inferior part and deriving from a unique point of the cornea
  - Most typically cream-colored
  - Generally do not impair visual function¹

- Related to a deposition and accumulation of glycosphingolipids in the epithelial and sub-epithelial layer of the cornea near or at the level of Bowman’s membrane. ⁴

Ocular Manifestations in Fabry Disease
Corneal Involvement: Cornea Verticillata

- Brother no.1 – 17 y.o.
- Brother no.2 – 15 y.o.

Always asymmetrical on the same individual
More easily seen under pupil dilation

A patient screened by an optometrist
Ocular Manifestations in Fabry Disease

Lens Opacities: Anterior /posterior cataracts

- Granular anterior capsular or sub-capsular deposits
- Bilateral and symmetrical
- Mild white triangular opacities whose vertex points toward the center of the lens (older patients)
- Usually associated with a posterior sub-capsular cataract
- 9% of women; 23% of men

Patient sent for screening

Corneal Haze + trace of verticilata

Vortex – easily seen

Patients under treatment

Patient under dialysis and enzyme replacement. 45 y.o.
Fabry’s cataract

Anterior vs posterior

Subcapsular cataract.

Ocular Manifestations in Fabry Disease
Conjunctival Vessel Anomaly

- Tortuosity or micro-aneurysms of the conjunctival vessels
- Sometimes limited to a few vessels dilatations

Conjunctival vessel tortuosity
Inferior sector of the conjunctiva in a male patient affected with Fabry disease

Micro-aneurysms

WCM, 57 y.o.
Ocular Manifestations in Fabry Disease

Retinal Vessel Tortuosity

- Retinal vascular tortuosity predominant in the posterior pole of the eyes
- In the more severe involvement, these vessels have a “corkscrew-like” appearance

Increase in the tortuosity of both retinal arteries and veins all over the retina but mainly in the posterior pole.

Retinal photos

Fabry Disease differential diagnosis in a nutshell

- Cornea Verticillata
- Acroparesthesia - Pain crisis
- Hypohidrosis - Anhidrosis
- Angiokeratoma
- Proteinuria

Fabry Disease

The crucial role of optometrists

Your early recognition of these eye symptoms can potentially save lives.

Refer all patients with corneal clouding or cornea verticillata to a metabolic lab for testing.

Contact Genzyme Medical Information to locate a testing facility in your area (euemedinfo@genzyme.com)
In your area... where to refer patients

- University Health Network and Mount Sinai Hospital
  - Adults genetics Program
  - 416-586-4800 #4220

- Hospital for Sick Children
  - Clinical and Metabolic Genetics Clinic
  - 416-813-6390

- QUESTIONS ????
- Thank you !!!
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