Advances in Assessment and Management of Ocular Metabolic Disease

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Ocular disease in metabolic disorders

• Metabolic disorders are rare, genetic disorders
• Severe systemic problems may overshadow ocular issues- learning difficulties, multiple medical problems, shortened lifespan
• Ocular phenotype often unique and challenging to manage
Lysosomal storage disorders

• Willink Unit at Royal Manchester Children’s Hospital has largest cohort of LSD patients in Europe
• More than 50 very rare inherited metabolic diseases
• Result from deficiency of specific lysosomal enzymes required for normal cellular metabolism
• Incidence 1:7000
• New systemic treatments may prolong and improve quality of life
• New technologies lead to better understanding of ocular complications
Ocular disease in Lysosomal storage disorders

- Ocular features common, unique, challenging and may be present at early stage and give clue to diagnosis
The Mucopolysaccharidoses (MPS)

- **Defect of glycosaminoglycan degradation**
  - MPS I Hurler, Hurler-Scheie and Scheie
  - MPSII Hunter
  - MPSIII Sanfillipo A,B,C,D 1:70,000
  - MPSIVA and B Morquio
  - MPSVI Maroteaux-Lamy
  - MPSVII Sly
  - MPSIX Natowicz

- **Onset in infancy**- kyphoscoliosis, recurrent ENT infections, hernia

- **Skeletal, cardiac, respiratory, gastrointestinal and neurological manifestations**
The cornea in MPS

- Corneal opacification characteristic of
  - MPSI, IV, VI and VII
- Photophobia, reduced vision later
- Slowly progressive if untreated
- Exposure keratopathy, vascularisation

**Clinical Study**

**Abstract**

MPS is a group of rare disorders characterised by accumulation of glycosaminoglycans within multiple organ systems. This study aimed to determine the prevalence and severity of ocular complications in patients with MPS.

Methods: Clinical ophthalmic features and electrodiagnostic results of 50 patients with a diagnosis of MPS were retrospectively reviewed.

Results: A total of 70% of MPS patients had a visual acuity of less than
Corneal changes in MPS

• Central corneal thickness correlates with corneal opacification (Kottler et al Cornea 2010; Connell et al J AAPOS 2009)
• Progressive increase in peripheral corneal thickness with time (Casanova et al Cornea 2001)
• Variable central corneal thickness (Kottler et al Cornea 2010)
• Altered corneal hysteresis (Fahnehjelm et al Acta Ophthalmol 2011)
Anterior segment changes in MPS

- Biomarin funded study
- Anterior segment OCT in MPS
AS-OCT images in MPS

- Changes in anterior chamber; narrowing of angle, iris thickening
- Narrower angles in MPSVI compared to MPSI
- Central and peripheral corneal thickness greater in MPS VI than MPSI and MPSII
- May correlate with greater corneal clouding in MPSVI

From Ahmed et al, Eye 2014
AS-OCT findings in MPSI

- 32 year old, dense corneal clouding
- Vision of 1.0 LogMar both
Measurement of corneal opacity in metabolic disorders.

- Need to assess natural history and effect of treatments
- Previous assessment of corneal subjective
- Grading +,++,+++
- Photography variable illumination, focus, cooperation

New techniques for objective assessment of corneal opacity in metabolic disorders: Pentacam

Distribution of corneal opacity (slit lamp examination) in relation to density unit (Pentacam)—right eyes. Results from left eyes are similar.
Pentacam densitometry in MPS

Normal Cornea Values
12 to 17

MPSI Corneal Clouding
Up to 50
New techniques for objective assessment of corneal clouding in metabolic disorders

- Pentacam: Issues with positioning of patient and difficulties in dense corneal clouding
- Iris camera: Rapid, reliable objective measurement of corneal opacity
Iris camera technology to measure corneal clouding

Plot of corneal opacification measure (COM) score against clinical grading of corneal opacity (10 MPS and 9 normal).

- Future aim to compare iris camera and Pentacam
Assessment and management of glaucoma in MPS

- Rare- prevalence 2.1-12.5% in MPS (submitted to Acta Ophthalmologica)
- IOP affected by
  - corneal thickness and hysteresis
  - technique (i-care)
- Optic discs may be effected by GAG deposition, poor view due to corneal opacity and poor dilation
- Visual fields effected by cooperation and presence of retinopathy
Severe visual loss from glaucoma in MPSVI (Maroteaux-Lamy)

- MPSVI diagnosed age 1
- Age 5 (1998) vision 3/60 OD, 1/60 OS
- Dense corneal clouding
- IOP 32 OD, 33 OS with air-puff
- Pink discs
- EUA 1999 C:D ratio 0.7 L and R
- Started on betoptic
- Later azopt/lumigan
Glaucoma in MPSVI (Marotaux-Lamy)

- CCT 931 OD, 996 OS (2003)
- 2007 IOP 38OD and 41 OS
- No red reflex or fundal view
- 2011 AS-OCT CCT 1099um
- B-scan advanced disc cupping
- Preception of light vision left and right
Challenging glaucoma in MPSI Hurler (L490P)

- 2009 Age 5 MPSI on ERT
- Parents consanguinous, dad has Ushers syndrome
- Vision 0.475 left and right crowded LogMar
- IOP with i-care 38 and 42
- Moderate bilateral corneal clouding
- Low hypermetropia
- Normal central corneal thickness
- Topical glaucoma medications started
Narrow angle glaucoma in MPSI

• January 2011 IOP right 38 left 56 i-care (26 R and 27L Goldman)
• Started on trusopt

• Pilogel then xalatan added
Glaucoma in MPSI

- May 2012-EUA and UBM

- Diagnosis of aqueous misdirection
- Right surgical PI May 2012, started on atropine both eyes
- Left surgical PI Sept 2012
Glaucoma in MPSI

- June 2012 after PI, on atropine

  OD

- Oct 2012 AS-OCT after PIs without atropine

  OD  OS
Glaucoma in MPSI

- Nov 2012 IOP 30 OD and 25 OS on Cosopt/xalatan/iopidine/atropine
- Jan 2013 bilateral cyclodiode
- Post-treatment scleritis
- IOP right 40 left 17 Goldman
- Right lensectomy and ant vity (and through PI) April 2013
- Now vision 0.5 right and 0.4 left with glasses
- (+20.00 R, +1.50/+2.50X75 L)
- IOP 15 R and 11L on Cosopt/iopidine/latanprost both eyes
- Considering right secondary IOL
Optic neuropathy in MPS

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

- MPSII Hunters aged 15 years noted poor vision in left eye
- Seen 2010, vision hand movement left and 0.1 right
- Left RAPD and optic nerve pallor, left exotropia
- Right temporal pallor
- MR scan showed raised ICP
- Treated with VP shunt
- Vision stabilised
Retinopathy in MPS

- MPSI (Hurler, Hurler-Scheie and Scheie), II (Hunter) and III (Sanfillipo)

- Retinal detachment (MPSII)

Progressive deterioration in dark and light adapted ERG in MPSI (from Neil Parry)
Maculopathy in MPSII Hunter

- Choroidal folds and maculopathy in MPSII (Anawis Ophthalmic Genet 2006; Yoon et al Ophthalmic Surg Lasers Imaging 2007)
- 25 year old with MPSII
- Vision 0.1 left and right
- Pallor of discs and macular ‘pucker’
Systemic treatment in MPS

- **Bone marrow transplantation**
  - MPSI Hurler’s diagnosed before age 2 years

- **Enzyme replacement therapy**
  - Weekly infusion MPSI (laronidase), II (elaprase), IVa (elosulfase) and VI (galsulfase)
  - Improvement in systemic parameters (walking ability, endurance and pulmonary function)

- Disease progression can still occur
- Difficult delivery to brain, bone, heart valves, eye

- **Gene therapy**
  - Phase I/II clinical trails of intra-cerebral gene therapy in MPSIIIA and intrathecal in MPSII and IIIa (Tardieu et al Hum Gene Ther 2014)
  - Stem cell gene therapy in MPSI and IIIa mice (autologous bone marrow transplantation with gene therapy)
Effect of early treatment for MPS on eye findings

- MPSI L490P case series 12 patients

- Limitations- unknown variability in phenotype, subjective assessment of corneal clouding, variable follow-up
Local treatment for corneal clouding in MPS

- Penetrating keratoplasty or DALK

- Animal MPS models
  - 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)
Summary: Advances in Assessment and Management of Ocular metabolic disease

• Unique and challenging ocular phenotypes
• New systemic treatments (ERT, BMT) lead to improved quality of life and lifespan
• AS-OCT, UBM, Pentacam, iris camera all may have a role
• Objective assessment of ocular disease needed to determine phenotype, disease progression and treatment effect
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