Dysmorphology And The Paediatric Eye

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Why Make A Syndrome Diagnosis?

• Why did it happen?
• What does the future hold?
• How can you treat/manage it?
• Will it happen again and can you test for it?
• Where can we access support and information?
Diagnosing Syndromic Eye Disease

• Most geneticists have limited expertise in ophthalmology

• Ophthalmologists tend to concentrate on eyes

• Parents might not mention other problems at the ophthalmology appointment

• Overall a joint approach may work best
Gorlin Syndrome

De novo mutation in PTCH1

Screening for jaw cysts and basal cell carcinoma
Ocular Findings In Gorlin Syndrome


Ragge et al. B J O 2005
Syndrome Diagnosis Impacts On Management

Stickler Syndrome
Stickler Syndrome

- Risk of retinal detachment
- Cleft palate and airway obstruction
- Feeding difficulties
- Congenital hip dislocation
- Joint hypermobility and pain
- Hearing loss
- Premature arthritis
- COL1A2, COL11A1, COL11A2
- COLL11A2 no ocular signs
- Screening of family members
Making a syndrome diagnosis

Family and medical history

Full examination

Investigations (genetic, biochemical, X-rays etc.)

Synthesis - putting it all together

Photographs

Review of literature, case discussion
Clues From The Pregnancy History

Fetal alcohol syndrome

Cytomegalovirus

optic n. hypoplasia, vessel tortuosity
Clues From The Family History

Facial asymmetry
Hypernasal speech
Clues From The Family History

Facial asymmetry
Hypernasal speech

Sclerocornea Associated With the Chromosome 22q11.2 Deletion Syndrome

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Clues from the Medical History

• Unilateral microphthalmia

• Limbal dermoid

• Unusual nasal tip

• Operation on nose as a baby
Pai Syndrome

- Ocular anomalies (anterior segment dysgenesis, microphthalmia, coloboma)
- Nasal polyps
- Bifid or notched nasal tip
- Midline brain lipoma
- Autosomal dominant

Winter-Baraitser database
Clues From The Natural History

• Many metabolic causes of eye disease
• Progressive course
• Juvenile onset cataracts
• Other metabolic disturbance eg liver disease or enlargement, skeletal features
• Family history
• Possibilities for treatment
Clues From Examination

2 brothers
Retinal dystrophy
Slim build
One has a son
Normal IQ
The Clue:
The Skin As A Clue

- Alström
- Acanthosis
- Retinal dystrophy
- Hearing loss
- Diabetes
- Normal IQ

Branchio-ocular facial syndrome
Mosaicism And Eye Disorders

Incontinentia Pigmentii

Schimmelpenning Syndrome

Wang et al Paediatrics and Neonatology 2013
Amato et al Am J Neuroradiology 2010
A Case Of Unilateral Microphthalmia
Behavioural Clues; Lowe syndrome

Congenital cataracts
Epicanthic folds
Renal tubular acidosis
Hypotonia
Arthropathy
Abnormal Eye Movements

Okihiro

Moebius

ROBO3 mutation
The Importance of Follow-Up

- Learning disability
- Joint laxity
- Myopia
- Truncal obesity
- Slender extremities
- Neutropenia
- Retinal dystrophy

Cohen Syndrome
Some Phenotypes Evolve......
Investigations

Chromosome analysis

Skin biopsy for RNA synthesis

MRI

Cockayne Syndrome

Joubert Syndrome
Microarrays for autozygosity mapping

Homozygosity at 4p16.1

Oculoauricular syndrome, HMX1
Microphthalmia; Which gene?

SOX2
OTX2
STRA6
BCOR
HCCS
PAX6
VSX2
SIX3
GJA1

Good review on microphthalmia;
Slavotinek AM
Mol Genet Metab September 2011
Think in Groups; Cilliopathies

- Retinal dystrophy
- Apnoeas
- Oculomotor apraxia
- Cerebellar abnormalities
- Renal cysts
- Chest infections (ciliary dyskinesia)
- Polydactyly
- Situs inversus
Gene Panels v Exomes/Genomes

- At present better coverage of specified genes
- Less risk of incidental findings
- Less data to analyse
- More acceptable to patients

- Larger number of genes
- Chance to identify novel genes
- More extensive pre-test counselling required
- More expensive (for now)
A Role For Epigenetics In Dysmorphology

same genes, different expression
Environmental Agents Modify Gene Expression

- Environmental agents cause ocular developmental defects
- Alcohol and valproic acid cause histone modification and affect gene expression
- Preventable
Environmental Agents Modify Gene Expression

- Environmental agents cause ocular developmental defects
- Alcohol and valproic acid cause histone modification
- Preventable
- Some genetic disorders are due to mutations in genes involved in histone modification
Syndrome Diagnosis Facilitates Genetic Counselling

First baby, first cousin parents
No family history
Cataracts
Mild microphthalmia
Not feeding well
Hypotonia
Global delay
MICRO Syndrome

First baby, first cousin parents
No family history
Cataracts
Mild microphthalmia
Not feeding well
Hypotonia
Global delay

RAB3GAP1 gene
The Importance of Working Together; Baby K

- Brain abnormality noted prenatally
- Infarct of middle cerebral arteries
- Baby born with congenital cataracts
- Evidence of anterior segment changes
- Post-natal MRI shows porencephaly
- DNA sequenced on NGS cataract panel
- Discussed at MDT meeting
Novel COL4A1 Mutations Associated With HANAC Syndrome: A Role for the Triple Helical CB3[IV] Domain

Emmanuelle Plaisier,¹,²,³* Zhiyong Chen,² Florian Gekeler,⁴ Safa Benhassine,² Karine Dahan,¹ Béatrice Marro,⁵ Sonia Alamowitch,⁶ Michel Paques,³,⁷ and Pierre Ronco¹,²,³
The Ophthalmic Dysmorphologist Of The Future...

- Continued role in diagnosis; Current exome sequencing studies are providing results in around 40% of patients

- Role in reporting of NextGeneration sequencing results

- Natural history studies and “deep phenotyping”

- Evidence-based management guidelines

- Treatment and prevention trials
Summary

- There are many benefits to making a syndrome diagnosis
- A structured, multidisciplinary approach
- Newer genetic technologies including microarray analysis and NextGen sequencing are facilitating diagnosis
- Further role for ocular deep-phenotyping
- If it doesn’t fit, don’t force it! It’s difficult to get rid of an incorrect label
Summary

• There are many benefits to making a syndrome diagnosis
• A structured, multidisciplinary approach
• Newer genetic technologies including microarray analysis and NextGen sequencing are facilitating diagnosis
• Further role for ocular deep-phenotyping
• If it doesn’t fit, don’t force it! It’s difficult to get rid of an incorrect label
• Ophthalmic dysmorphismology is not dead!
Quiz
Which Eyebrows?
Which Eyebrows?

A: Kabuki Syndrome
B: Fraser Syndrome
C: Waardenburg Syndrome
Thank-you!