Refsum Disease from an Ophthalmology Perspective

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DARE’S MISSION

Global DARE Foundation's mission is to promote world-wide awareness and better quality of life for all who are diagnosed with Adult Refsum Disease.
Webinar Housekeeping Details

- All participants are in listen only mode
- How to ask a question during the Q&A:
  - Participants following on Zoom can type their questions in the Q&A box at any time during the presentation or by raising their hand at the end to ask a question live.
  - Participants joining by phone can press *9 on their phone to raise their hand.
- Questions will be answered in the following order:
  - Q&A box in Zoom
  - Dial in participants
  - Online participants
- Today’s session will be recorded for later viewing on Global DARE Foundation Website (www.defeatadulttrefsumeverywhere.com)
Ophthalmological Features in Adult Refsum Disease

How to Make the Dx as an Ophthalmologist

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*No personal financial gain; all consultancy fees paid into Ghent Univ Hosp research accounts*
Outline

• Introduction
• Adult Refsum Disease
• Examples
• Conclusions
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Introduction

Basic Genetics

- Humans: 20,338 genes x 2 (= 3,200,000,000 bp (x2))
  - Non-coding genes 22,521
  - Pseudogenes 14,638
  - Gene transcripts 200,310
- Inherited retinal & ON diseases: 307 genes (271 cloned)
  https://sph.uth.edu/retnet/
Introduction
Basic Genetics

• 46 Chromosomes in somatic cells (diploid):
  M: 46,XY  F: 46,XX
• 23 Chromosomes in gametes (haploid)
• Mendelian inheritance patterns: AD, AR & XL
• Genotype & phenotype
• Individual has 4,5 million differences between him & reference human sequence
Normal Ocular Fundus

Optic disc
Retinal vein
Retinal artery
Fovea
Macula
Posterior Pole
Human Retina

Eye translates light into electricity
Introduction
Retinal Circuitry

Adapted from The Neurology of Vision by JD Trobe
Rods & Cones

- **Rods**
  - 120,000,000 to 130,000,000 per retina
  - Navigational vision at night
  - Do not function in daylight

- **Cones**
  - 5,000,000 to 7,000,000 per retina
  - Visual acuity in daylight
  - Colour vision in daylight
  - Navigational vision in daylight
  - Colour vision at night
Retinal Cells & Layers
## Rods & Cones

<table>
<thead>
<tr>
<th></th>
<th>Rods</th>
<th>Cones</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Numbers</strong></td>
<td>120 million per eye</td>
<td>5-7 million per eye</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Entire retina except fovea</td>
<td>High density in the macular region</td>
</tr>
<tr>
<td><strong>Sensitivity to light</strong></td>
<td>High sensitivity</td>
<td>Lower sensitivity</td>
</tr>
<tr>
<td></td>
<td>Separate discs</td>
<td>Continuous membrane</td>
</tr>
<tr>
<td><strong>Outer Segments</strong></td>
<td>Night vision</td>
<td>Daytime and colour vision</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Many rods link to a single retinal ganglion cell Larger</td>
<td>One cone to one ganglion cell in fovea</td>
</tr>
<tr>
<td><strong>Connections</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Receptive fields</strong></td>
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</tbody>
</table>
Retinitis Pigmentosa

Background

• **What?** Outer retinal dystrophy with rod, and secondary cone PR death by apoptosis

• **Signs:**
  • Progressive outer retinal atrophy
  • Intraretinal pigment migration
  • OD pallor & vessel attenuation

• **Symptoms:**
  • Night blindness
  • Peripheral VF constriction
  • Eventually loss of central vision
Retinitis Pigmentosa

Background

• Electrodiagnostically: rod-cone dystrophy
• Genetically:
  • Autosomal dominant
  • Autosomal recessive
  • X-linked
  • Most: simplex cases
**RHO-Related ADRP**

**Case**

M, 18 yrs  
BCVA RE 20/40 LE 20/30  
*RHO* c.403 C>T (p.Arg135Trp)
AD Retinitis Pigmentosa

Genes

RHO (25 to 40%)  HPRP3
PRPH2           PRPC8
RP1             FSCN2
NRL             PRPF31
RP9             IMPDH1

+ additional genes (total: 23; 22 cloned)
AR Retinitis Pigmentosa

Genes

- 43 genes
- 41 cloned
- 2 loci

Genes currently known: see RetNet

ABCA4, AGBL5, AHR, ARHGEF18, ARL6, ARL2BP, BBS1, BBS2, BEST1, C2orf71, C8orf37, CERKL, CLCC1, CLRN1, CNGA1, CNGB1, CRB1, DHDDS, DHX38, EMC1, EYS, FAM161A, GPR125, HSGNAT, IDH3B, IFT140, IFT172, IMPG2, KIAA1549, KIZ, LRAT, MAK, MERTK, MVK, NEK2, NEUROD1, NR2E3, NRL, PDE6A, PDE6B, PDE6G, PRCD, POMGNT1, PRCD, PROM1, RBP3, REEP6, RGR, RHO, RLBP1, RP1, RP1L1, RPE65, SAG, SAMD11, SLCA14, SPATA7, TRNT1, TTC8, TULP1, USH2A, ZNF408, ZNF513, ...
 Syndromic Retinitis Pigmentosa

Conditions

- Ciliopathies
  - Bardet-Biedl syndromes
  - Joubert syndrome & JSRD
  - Senior-Loken syndrome
  - Alström syndrome
- Mitochondrial disorders
  - Kearns-Sayre syndrome
- Usher syndromes
- Peroxisomal disorders
  - Zellweger syndrome
  - Adult Refsum disease
- Spinocerebellar ataxia 7
- Neuronal ceroid lipofuscinosis
- Abetalipoproteinemia (Bassen-Kornzweig syndrome)
Outline

• Introduction
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Adult Refsum Disease

Original Description

Sigvald Refsum, 1946:

- Retinitis pigmentosa
- Peripheral polyneuropathy
- Cerebellar ataxia
- High protein in CSF
Adult Refsum Disease

Clinical Signs

- Sensorineural hearing loss (70%)
- Pupillary abnormalities
- Short metacarpals & -tarsals (30%)
- Non-specific ECG changes
- Anosmia (50% by age 50)
- Ichthyosis (15%)
Adult Refsum Disease

Ocular Signs & Symptoms

• Retinitis pigmentosa
  – Night blindness
  – Constricted visual fields
  – Decrease of central vision
• Pupillary abnormalities
• Iris atrophy
• Cataract
Autosomal recessive

Biallelic mutations in $PHYH$

Deficiency of peroxisomal enzyme Phytanoyl-CoA Hydroxylase leads to accumulation of unusual branched 20-carbon fatty acid of exogenous origin: 3,7,11,15-tetramethylhexadecanoic acid or phytanic acid

Probably accumulates in RPE
Adult Refsum Disease

Eye Problems Bring Patient to Eye Doctors

- Rare disease w/ estimated population frequency of 1/1,000,000
- Problem: under diagnosed & often diagnosed too late
- But... if only the eye doctor would see...
- “...average delay of 11 years (range 1-28 yrs) between the patient presenting to the ophthalmologist and being diagnosed as having Refsum disease.”

Adult Refsum Disease
Issues Regarding Eye Problems

- Neurological & dermatological symptoms improve w/ Rx
- Retinal function seems to decline over time despite Rx

Claridge KG, Gibberd FB, Sidey MC: Refsum Disease: The Presentation and Ophthalmic Aspects of Refsum Disease in a Series of 23 Patients. Eye, 6, 371-375, 1992
Adult Refsum Disease

Study Purpose

- To study clinical manifestations
- To characterise retinal function and evaluate its evolution over time using ERG
Adult Refsum Disease
Study Methods

- 12 Caucasian patients / 8 families
- Clinically fully ascertained
- 8 British / 3 Belgian / 1 Dutch
- 7 men / 5 women
- Mean age at Dx 28 yrs (16-37)
- Mean age of 1st symptoms: +/- 16 yrs
- 9 patients at least 1 ERG (ISCEV)
- 3 patients at least 2 ERGs (ISCEV)
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Adult Refsum Disease

Patient 1

- M, 27 yrs
- Slow decrease VA
- Balance problems
- Decreased sensitivity lower extremities
- Anosmia
Adult Refsum Disease

Patient 1

- BCVA BE 6/9 w/ -1.0 D
- SLE BE miosis ++
- OF BE chorioretinal atrophy more pronounced in periphery
Adult Refsum Disease

Patient 1

Anterior Segment
Adult Refsum Disease

Patient 1

Posterior Pole
Adult Refsum Disease

Patient 1

- DA BE increased threshold +++
- ERG BE absent responses
- pVEP BE good responses for 60’, 30’ & 15’
- Serum Phy Ac 1039µg/ml (no. 0.4-4.0)
Adult Refsum Disease Patient 1 ERG

RE
Scotopic
LE
Maximal
Photopic
30Hz Flicker
Patient 2

Clinical Data

- F, 28 yrs, history of psychiatric mismanagement
- Slow decrease VA
- Balance problems
- Decreased sensitivity lower extremities
- Anosmia
Patient 2
Clinical Data

- VA BE 6/18 w/o correction
- SLE BE normal
- OF BE mild chorioretinal atrophy in periphery & macula & macular oedema
- Normal pupillary dilatation
Patient 2
Fluorescein Angiography

RE

LE
Patient 2
Hands & Feet
Patient 2
Clinical Data

- ERG BE  rod-cone dystrophy
- Serum Phytanic Acid: 1506 µmol/l (no. < 15 µmol/l)
- Initially: stabilization of ERG traces under plasmapheresis
Patient
ISCEV Standard ERG
Patient 2

Evolution of Pre-Ganzfeld DA ERG

[Graph showing the evolution of ERG measurements over years.]
Patient 3
Clinical Data

- F, 29 yrs
- Moderate decrease VA since 5 yrs
- Has unsuccessfully worn braces for dorsal displacement 4\textsuperscript{th} toes
- Stubby thumbs
- No balance problems
- No decreased sensitivity lower extremities
- Lost sense of smell & taste after delivery
Patient 3

Pedigree

- Refsum S
- Fam Angioneurotic Edema
Patient 3
Clinical Data

- VA RE 6/12  LE 6/18
- SLE BE iris atrophy
Patient 3
Fundus Pictures
Patient 3

Hands & Feet
Patient 3
Clinical Data

- ERG: BE: severe RCD
- High Serum Phytanic Acid
Patient 3
ISCEV Standard ERG

[Graphs showing scotopic rod, maximal, 30Hz flicker, photopic, and PERG responses for R eye, L eye, and Normal conditions.]
Adult Refsum Disease

Patient 4

- F, 39 yrs
- Age of Dx 24yrs
- Slow decrease VA
- Balance problems
- Decreased sensitivity lower extremities since jaw-wiring for chin operation
- Anosmia
Patient 4
Clinical Data

• BCVA  RE 6/9 w/ -6,5D  LE 6/6 w/ -6,5D
• Inspection anisocoria LE>RE & miosis
• SLE BE shallow AC (-> YAG-iridotomy)
Patient 4
Fundus Pictures

RE

LE
Patient 4
Goldmann-Weekers Dark Adaptometry

- Patient's curve
- Normal curve
Patient 4

Goldmann Visual Fields

RE

LE
Patient 4

Hands & Feet
Patient 4
Clinical Data

- ERG BE rod-cone dystrophy
- Serum Phy Ac 382 µg/ml (no. 0.4-4.0)
- insertion 3 bp (576-577 insGCC): in frame insertion extra Ala
- Initially stabilisation of ERG traces under strict dietary Rx
- Then progressive rod-cone degeneration
Patient 2
ISCEV Standard ERG

Rod
Max
Cone
30HzFl

1993 (LE)

2002 (BE)
# Adult Refsum Disease Study Results

<table>
<thead>
<tr>
<th>FEATURE</th>
<th>NUMBERS</th>
<th>FRACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ret dyst/Narr VF</td>
<td>12</td>
<td>100%</td>
</tr>
<tr>
<td>Iris atrophy</td>
<td>9Y/3N</td>
<td>75%Y/25%N</td>
</tr>
<tr>
<td>ERG abnos</td>
<td>8RCD/4Flat</td>
<td>67%RCD/33%Flat</td>
</tr>
<tr>
<td>Skeletal abnos</td>
<td>8Y/4N</td>
<td>67%Y/33%N</td>
</tr>
<tr>
<td>Anosmia</td>
<td>8Y/4N</td>
<td>67%Y/33%N</td>
</tr>
<tr>
<td>Miosis</td>
<td>7Y/5N</td>
<td>58%Y/42%N</td>
</tr>
<tr>
<td>Parental Consang</td>
<td>6Y/6N</td>
<td>50%Y/50%N</td>
</tr>
<tr>
<td>Periph Neuropathy</td>
<td>6Y/6N</td>
<td>50%Y/50%N</td>
</tr>
<tr>
<td>Balance Probs</td>
<td>5Y/7N</td>
<td>42%Y/58%N</td>
</tr>
<tr>
<td>Ichthyosis</td>
<td>4Y/6N/2?</td>
<td>33%Y/50%N/17%?</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>2Y/10N</td>
<td>17%Y/83%N</td>
</tr>
<tr>
<td>Cardiac Abnos</td>
<td>1Y/6N/5?</td>
<td>8%Y/50%N/42%?</td>
</tr>
</tbody>
</table>

N = 12
Adult Refsum Disease

Results

- Variable electrophysiological & clinical inter- & intrafamilial expressivity
- Moderate to severe bilateral retinal degeneration (RP-RCD)
- Relatively slow evolution of disease when PhyAc is controlled
- Two patients: no obvious decline of ERG for considerable period
**7 Extra Patients Clinical Data**

- M, 9 yrs, no ocular symptoms & signs
- M, 58 yrs, fairly normal macula, BCVA BE 20/40, discrete border of chorioretinal atrophy, miosis
- F, 48 yrs, fairly good macula with central PEA & BCVA of RE 20/30 & 20/40 LE despite CMO
- F, 41 yrs, normal feet, but short 4th metacarpal bone both hands, classic RP *
- M, 57 yrs, consecutive bilateral acute deafness, successfully Rx w/ cochlear implants, severe RP
- M, 49 yrs, night blindness since age 15 yrs, SNHL since age 30 yrs, good BCVA RE 20/30 LE 20/25
- M, 46 yrs, severe RP despite strict diet

* F, 41 yrs
  short 4th metacarpal bone both hands; normal feet
Adult Refsum Disease

Treatment

• Special diet w/ restriction of phytanic acid (products from ruminants)
• FU by cardiologists (cardiomyopathy)
• FU by ophthalmologists
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Adult Refsum Disease

Conclusions

• Rare & variable disease
• Early Dx enables Rx to reverse life-threatening complications
• Rod-cone dystrophy is moderate to severe
• Early Rx may be effective in limiting disease progression in eye
Adult Refsum Disease

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