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)
Adult Refsum Disease (ARD)

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Autosomal recessive peroxisomal disease due to deficiency in the phytanoyl CoA hydroxylase enzyme

Prevalence 1 in 1 million
ARD

Early diagnosis = improved outcome
ARD – Eye disease

Paper published in 1992
Adult Refsum Disease (ARD): Current practices in diagnosis and management
Simon Merrick, Wierzbicki, Ramachandran, McKibbin

Survey of practicing clinicians in ophthalmology departments across Europe (33 clinicians from 13 countries)
Adult Refsum Disease (ARD): Current practices in diagnosis and management

- Survey of practicing clinicians in ophthalmology departments across Europe (33 from 13 countries)

  70% of respondents had been involved in care of patients with ARD
  60% felt ARD was underdiagnosed
  ONLY 30% were confident of diagnosing ARD
ARD – corroborative history

- Anosmia
- Bony malformations
- Sensorineural deafness
- Cerebellar ataxia
- Cardiomyopathy/arrhythmia
- Peripheral neuropathy
- Icthiosis
- Family history
Clinical symptoms in ARD

Wierzbicki AS et al.; J Neurochem 2002; 80; 727
ARD: osteology in the hands & feet

Not always visually obvious – X-Ray needed
Present only in about 30% of patients
Case History

- 30 year old
- Retinopathy since 18 years
- Nil else suggestive of ARD
- No family history
- Entered into a research study – genetic panel analysed
Case History

- 2 mutations in the *PHYH* gene
- PA level – 10.62 umol/L (ref range 0-10)
- May have had blunted sense of smell
- No other history suggestive of ARD
- Skin biopsy - ARD (Prof Wanders)
- Initiated loose low PA diet – PA now < 5 umol/L
Case History

• Another referral from Eye Department
  – H/O retinopathy
  – no other symptoms/ family history
  – ARD on retinopathy gene panel

• PA levels – 22.5 umol/L (again only just above reference limit – 15)
Case History

• One case reported in literature

• Index case – retinopathy, cardiac failure – PA normal;

• Diagnosed ARD when older presented with cardiac failure, retinopathy and ↑ PA
ARD

- Retinopathy – may be the only clue
- Plasma PA levels – not always ↑↑
- Pristanic acid - undetectable
- Genetics
  – Likely higher pick up rate
ARD - Diagnosis

ARD diagnosis should be sought in all patients with retinopathy

Future diagnostic journey:

• Genetics as first line (ARD & phenocopies)
• Biochemical confirmation with plasma PA and pristanic acid
• Skin biopsy if needed
Pre-symptomatic diagnosis

Case report
Pregnancy outcome in Refsum disease: Affected fetuses and children born to an affected mother

Patricia Dubot1,2 | Léonardo Astudillo2,3 | Guy Touati4 | Julien Baruteau4 | Pierre Broué4 | Sandrine Roche4 | Frédérique Sabourdy1,2 | Thierry Levade1,2

Brought to my attention – courtesy Ms Kristie DeMarco
Phytanic acid levels in mum – mostly < 200 umol/L; P5 and P7 – higher levels up to 500 umol/L
## Outcome in affected children


<table>
<thead>
<tr>
<th>Girl II.4</th>
<th>Girl II.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>- PA at birth 31 umol/L</td>
<td>- PA at birth 24 umol/L</td>
</tr>
<tr>
<td>- PA normal at 3 weeks</td>
<td>- PA normal at 4 months</td>
</tr>
<tr>
<td>- On low PA diet since birth</td>
<td>- On low PA diet since birth</td>
</tr>
<tr>
<td>- PA ↑ 9 months, 158 μmol/L at age 5 yrs.</td>
<td>- PA ↑ 219 μmol/L at 3 years,</td>
</tr>
<tr>
<td>- Clinically, nystagmus observed that spontaneously regressed</td>
<td></td>
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</tbody>
</table>

- **Increase PA levels later on possibly because of deviation from diet.**
- **Normal physical & psychomotor development (5 yrs & 3 yrs respectively)**
- **Retinopathy not specifically mentioned**
Conclusion

• Moderately elevated PA in mum – low fetal risk
• PA may rise during pregnancy – risk of acute decompensation – needs careful monitoring and management
• Some degree of trans-placental crossing occurs
Newborn screening

• ↑PA in baby - reflection of ARD in mum
• ARD babies of heterozygote mums unlikely to have ↑PA
• Biochemical newborn screening for the general population is not a option because
  – very low prevalence of ARD
  – unreliability of PA – false negatives
• High risk babies – genetic testing advised
Treatment

Low Phytanic acid (PA) diet - positive net elimination of PA
PA metabolism


Structure of a) phytanic acid which cannot be degraded via β-oxidation and initially has to be converted into b) pristanic acid via α-oxidation before further metabolism.

- β-oxidation: Mitochondria
- α-oxidation: Peroxisome

Omega oxidation by CYP 450 enzymes
Omega Oxidation

Wierzbicki AS et al; J Lipid Res 2003; 44 : 1481

Phytanic acid (umol/L)

Time (days)

PA expressed as PA equivalent
Omega oxidation

Wierzbicki AS et al; J Lipid Res 2003; 44 : 1481

- Omega oxidation - significant role in PA elimination
- can provide alternate pathway in ARD
- 3-MAA ↑ in patients with ARD vs normal
- 3-MAA correlates with plasma PA levels

- **However, threshold capacity of 6.9 mg of PA /day (2.8 – 19.4) – Hence PA in diet limited to 10 mg /day**
Fruit & Veg in ARD diet

• Fruit & Veg – not in original ARD diet – very restrictive
• Fruit & veg with high phytol but low free phytol were introduced into diet of one patient with ARD in 1988
• Clinical progress and plasma and adipose PA assessed after 18 months
• Clinically stable and PA levels – no change – Fruit & Veg introduced into ARD diet
• 30% - PA in normal range – **ideal scenario**
• A further 55% PA levels $<$10×ULN (150 umol/L)
• Mean half life of PA in patients on diet was 39 (20–78) months.
How quickly do plasma PA levels respond to treatment?


<table>
<thead>
<tr>
<th>Case</th>
<th>PA Intake</th>
<th>Protein</th>
<th>Fat</th>
<th>P.S Ratio</th>
<th>Plasma PA</th>
<th>3-MAA Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>1</td>
<td>14.0</td>
<td>0.0</td>
<td>96</td>
<td>78</td>
<td>27.5</td>
<td>33.6</td>
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<tr>
<td>2</td>
<td>10.0</td>
<td>0.0</td>
<td>127</td>
<td>59</td>
<td>32.5</td>
<td>36.1</td>
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<tr>
<td>3</td>
<td>0.46</td>
<td>0.0</td>
<td>72</td>
<td>114</td>
<td>26.0</td>
<td>37.6</td>
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<tr>
<td>4</td>
<td>1.3</td>
<td>0.9</td>
<td>67</td>
<td>49</td>
<td>28.9</td>
<td>31.6</td>
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<tr>
<td>5</td>
<td>2.7</td>
<td>0.5</td>
<td>89</td>
<td>119</td>
<td>23.4</td>
<td>38.1</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>5.3</td>
<td>86</td>
<td>84</td>
<td>21.6</td>
<td>27.0</td>
</tr>
<tr>
<td>7</td>
<td>0.8</td>
<td>2.1</td>
<td>68</td>
<td>99</td>
<td>21.7</td>
<td>18.0</td>
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<tr>
<td>8</td>
<td>52.4</td>
<td>16.0</td>
<td>82</td>
<td>85</td>
<td>29.2</td>
<td>31.4</td>
</tr>
<tr>
<td>9</td>
<td>5.8</td>
<td>0.0</td>
<td>66</td>
<td>62</td>
<td>25.2</td>
<td>27.4</td>
</tr>
<tr>
<td>Average (median)</td>
<td>2.7</td>
<td>0.5</td>
<td>82</td>
<td>86</td>
<td>27.6</td>
<td>30.8</td>
</tr>
</tbody>
</table>

P.S, polyunsaturated:saturated fatty acid intake. Two patients did not complete the assessment protocol and are excluded.

Roughly 23 days for levels to halve
Presence of non chlorophyll bound phytanyl esters in fruit and veg may be significant.

Limitations – dietary therapy

• Information on PA levels in food limited
• Omega oxidation capacity varies
• Residual phytanoyl CoA hydroxylase enzyme varies
• Further research to enable personalised dietetic advice
Reasons for high PA levels

Non-modifiable
Severity of disease
  – varying degree of residual enzyme activity
Omega oxidation of PA
  – varying capacity for omega oxidation

Modifiable (episodes)
• Weight loss (12)
• Diet compliance (patient reported) (10)
• Surgical/medical admission (4)
• Infection (3)
• Unknown (4)

Monitoring - PA

• 6 monthly in our clinic
• More often if likely to impact management
  – Symptoms (neurological) – for decision re plasmapheresis
  – Weight loss – planning/intended/unintended
  – Other inter-current illness that may impact on levels
Plasmapheresis

• Not routine in our service
• We would consider if
  – Acute/worsening neurological symptoms
  – Or cardiac symptoms
  – If PA levels > 1000 umol/L
• Further research needed
Emergency Regime

Aim
To prevent catabolic state that may lead to release of stored PA into circulation
Emergency Regime Rationale

• Standard practice for other disorders of fatty acid oxidation
• Data from this paper below

Metabolism of phytanic acid and 3-methyl-adipic acid excretion in patients with adult Refsum disease

Anthony S. Wierzbicki,⁎,† Phillip D. Mayne,⁎ Matthew D. Lloyd,§ David Burston,⁎ Guam Mei,⁎ Margaret C. Sidey,¹ Michael D. Feher,† and F. Brian Gibberd†

Department of Chemical Pathology⁎ and Refsum Disease Clinic,† Chelsea & Westminster Hospital, 369 Fulham Road, London, United Kingdom; and Department of Pharmacy & Pharmacology,§ University of Bath, Claverton Down, Bath, United Kingdom
PA in 5 patients fasted for 56 hours

Wierzbicki AS et al; J Lipid Res 2003; 44 : 1481

- Plasma PA doubling time 29 hours
- 1 patient lost 8 kgs
- 1 patient - unwell for 12 weeks
- 1 patient - leg cramps for 3 days after

Higher the baseline – higher the risk
Emergency Regime

• Oral
  – 20% glucose polymer at regular intervals until eating and drinking normally

• IV
  – 10% glucose at 2ml/kg/hour
  – Maintain blood glucose at 6-10 mmol/L; if levels persistently high – start insulin sliding scale (dry will suffice) rather than slowing rate of infusion
  – Normal saline to correct fluid deficit
Emergency Regime - Caution

- ARD patients’ median age significantly higher than most of our patients with other fatty acid oxidation defects
- Co-morbidities like diabetes, reactive hypoglycaemia, hypertension, IHD can co-exist – Multidisciplinary approach to management recommended
Surveillance
Neurological manifestations

• Mixed motor and sensory neuropathy
  - Chronic
  - Asymmetric
  - Progressive
  - Initially often waxing and waning with PA levels
  - Later fixed with disabling muscle atrophy and weakness
  - Can present acutely as demyelinating with albumin-cytological dissociation in CSF
Surveillance

• Hearing – regular audiology scans from age 50 or earlier if symptoms
• Neurology – guided by symptoms- physical examination/Nerve conduction studies
• ? baseline Brain MRI scan
• Eyes – already discussed by Prof Leroy
Cardiac Manifestations

Cardiomyopathy – very late presentation – heart failure secondary to hypokinetic myocardopathy
Arrhythmias – rare – mostly an acute presentation related to very high PA levels – may also occur as a complication of plasmapheresis
Cardiac Monitoring

- Symptom based management
- Cardiac monitoring in the acute phase
- Perhaps a baseline cardiac MRI when stable
Other co-morbidities – case reports

- Renal Tubulopathy
- Leukodystrophy
- Vestibular neuropathy
Acknowledgments

Patients
Dr Mike Feher, Ms Eleanor Baldwin, Ms Sarah Firman and Prof Tony Wierzbicki
Refsum Disease Clinic formerly at Chelsea and Westminster Hospital
Centre for Inherited Metabolic Diseases
Guys and St Thomas’ NHS Foundation Trust
Q&A

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