EKG Webcast Fabry

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27.05.2020 – Webcast
DISCLOSURES

• Speaker Fees/Honoraria/Travel Grants
  – Bayer, Biosense Webster, Biotronik, Boston Scientific, Daiichi Sankyo, Medtronic, Sanofi Genzyme, Shire (now part of Takeda)

• Advisory Boards
  – Amicus, Bayer, Biotronik, Boston Scientific, Daiichi Sankyo, GBc, Sanofi Genzyme, Shire (now part of Takeda)

• Investigatorships
  – Biotronik, Daiichi Sankyo, Biosense Webster, Boston-Scientific, Sanofi Genzyme

• Research/Fellowship Grants
  – Abbott, Biotronik, Biosense Webster, Sanofi Genzyme, Shire (now part of Takeda)

• Presidency
  – CHAR (Swiss Arrhythmia Foundation)
Dynamic disease course

ECG, electrocardiogram; MRI, magnetic resonance imaging.

- Subclinical
- Diagnostic
- Macro
- Organ damage
- Reversibility
- Disease-specific signs

Micro:
- MRI
- Biopsy
- ECG

Fabry disease genotype–phenotype correlations

- > 900 GLA variants have been reported to date\(^1\)
  - Due to the large number of de novo variants, there is often not enough evidence across enough individuals for full phenotypic characterization\(^2\)
  - This accounts for extensive heterogeneity of Fabry disease manifestations\(^3\)

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GLA, galactosidase alpha.
Two major phenotypes: classic and later-onset Fabry disease

**Classic disease – early manifestations**
- Angiokeratoma
- Hyperthermia/fever
- Neuropathic pain
- Hypohidrosis/anhidrosis
- Exercise/heat/cold intolerance
- Gastrointestinal symptoms
- Cornea verticillata
- Cardiac conduction abnormalities
- Occult kidney injury

**Later-onset disease – general lack of early manifestations, such as**
- Neuropathic pain
- Gastrointestinal symptoms
- Angiokeratoma

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Organ failure is not common in later-onset disease.

Gb3, globotriaosylceramide.

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**Male and female manifestations can differ significantly within these phenotypes**

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Simplified course of disease pathogenesis in Fabry disease

LVH, left ventricular hypertrophy; SMC, smooth muscle cell.

THE ELECTROCARDIOGRAM IS...

a highly sensitive *electro-anatomical* tool, i.e. whatever happens in the myocardium → electrical signature with a considerable temporal and spatial resolution

highly reproducible & not expensive at all

...old & beautiful...

...REGARDER N’EST PAS VOIR...
WHAT DO WE SEE AND WHY DO WE SEE WHAT WE SEE?
ELECTRO-ANATOMICAL PRELUDE...

...WHY DO WE SEE WHAT WE SEE...
DYNAMIC DISEASE COURSE

- Subclinical
- Organ damage
- Signs, symptoms
- Disease-specific signs
- Reversibility

- micro
  - MRI
  - Biopsy
  - ECG

- diagnostic

- macro

ECG ABNORMALITIES IN CARDIOMYOPATHIES

- Intracellular glycolipid deposits
- Extracellular amyloid deposits
- Myocellular content and volume
- Diastolic function
- Localization of myopathic process
- Effects of mutated protein on myocardium and conduction system
- Interstitial expansion and fibrosis

ECG, electrocardiogram.

Courtesy of Dr. M. Pieroni
Was mache ich bei einem Morbus Fabry Verdachtsfall?

Mittels Trockenblutkarte (DBS) zur Messung von

- Enzymaktivität von α-Galaktosidase A
- Krankheitsmarker lyso-GL3 (= lyso-Gb3)
- Gen-Analyse

Erhältlich z.B. von:
Archimed Life Science GmbH
unter der Service-Hotline
0800 / 1115200 (kostenfrei)
oder per eMail
Archimed-Diagnostikinitiative@viluacare.de

Sanofi-Aventis Deutschland GmbH unterstützt die Diagnostik-Initiative für lysosomale Speicherkrankheiten von Archimed Life Science GmbH. Daher kann Archimed Ärzten die Trockenblut-Testung kostenfrei anbieten.
ERT can improve regional myocardial function

LV radial function before and after 6 and 12 months of ERT treatment

- Radial function was assessed by peak systolic strain rate (left) and systolic strain (right)

*p < 0.05 vs baseline. LV, left ventricle.

Treatment based reduction of LVM is dependent on level of fibrosis at initiation


B, baseline; LVM, left ventricular mass; y, year.

Effect of ERT over time
Comparison of fibrosis groups
- no fibrosis vs mild fibrosis
- no fibrosis vs severe fibrosis
ERT has a consistent and positive effect on ECG parameters

The value of ECG parameters as markers of treatment response in Fabry cardiomyopathy

- Retrospective analysis of data from 38 patients with Fabry disease receiving ERT
- Median follow-up duration: 6.4 ± 1.2 years

ERT, enzyme replacement therapy.

* p < 0.05 compared with previous follow-up.
**p < 0.005 for males vs females.

Patients with an abnormal baseline ECG are strongly associated with disease progression

Criterion values and coordinates of the ROC curve for age at treatment initiation/diagnostic performance of an abnormal baseline ECG for disease progression

<table>
<thead>
<tr>
<th>Age at treatment initiation (years)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>+LR</th>
<th>95% CI</th>
<th>−LR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 27</td>
<td>100</td>
<td>61.1</td>
<td>2.57</td>
<td>1.4–4.6</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&gt; 28</td>
<td>100</td>
<td>66.7</td>
<td>3.0</td>
<td>1.6–5.8</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>&gt; 29</td>
<td>94.4</td>
<td>72.2</td>
<td>3.4</td>
<td>1.6–7.2</td>
<td>0.08</td>
<td>0.01–0.5</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>94.4</td>
<td>77.8</td>
<td>4.25</td>
<td>1.8–10.2</td>
<td>0.07</td>
<td>0.01–0.5</td>
</tr>
<tr>
<td>&gt; 31</td>
<td>94.4</td>
<td>83.3</td>
<td>5.67</td>
<td>2.0–16.0</td>
<td>0.07</td>
<td>0.01–0.5</td>
</tr>
<tr>
<td>&gt; 35</td>
<td>94.4</td>
<td>88.9</td>
<td>8.5</td>
<td>2.3–31.5</td>
<td>0.06</td>
<td>0.009–0.4</td>
</tr>
<tr>
<td>&gt; 36</td>
<td>94.4</td>
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<td>17</td>
<td>2.4–114.6</td>
<td>0.06</td>
<td>0.009–0.4</td>
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<td>–</td>
<td>–</td>
<td>0.17</td>
<td>0.06–0.5</td>
</tr>
<tr>
<td>Abnormal baseline ECG</td>
<td>94.1</td>
<td>88.9</td>
<td>8.47</td>
<td>2.28–31.46</td>
<td>0.07</td>
<td>0.01–0.45</td>
</tr>
</tbody>
</table>

CI, confidence interval; +LR, positive likelihood ratio; −LR, negative likelihood ratio; ROC, receiver operating characteristic.
## Cox proportional hazards regression analysis assessing the time dependence of risk factors for clinical events

<table>
<thead>
<tr>
<th>Years on agalsidase beta 1mg/kg EOW</th>
<th>Model 1: 0–0.5 years</th>
<th>Model 2: &gt; 0.5–5 years</th>
<th>Model 3: &gt; 0–5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>p value</td>
</tr>
<tr>
<td>Pre-ERT event: yes (vs no)</td>
<td>1.1</td>
<td>0.6–2.0</td>
<td>0.81</td>
</tr>
<tr>
<td>Age ≥ 40 years at first ERT (vs age &lt; 40 years)</td>
<td>4.4</td>
<td>2.2–8.7</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Male (vs female)</td>
<td>1.9</td>
<td>1.1–3.4</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Registry analysis
Clinical events defined as renal failure, cardiac events, stroke, and death.

* Three models were run to assess if the incidence of events according to the above factors was time-dependent: Model 1 examined risk factors within the first 6 months; Model 2 examined risk factors within 6 months to 5 years; Model 3 examined risk factors for the entire analysis period of up to 5 years.

CI, confidence interval; EOW, every other week; ERT, enzyme replacement therapy; HR, hazard ratio.

Agalsidase beta 1mg/kg EOW significantly reduced LVM in patients aged < 30 years (vs untreated)


Years during natural history period

Years following initiation of therapy
CORRELATION OF EARLY INFILTRATION WITH MICROFIBROSIS WITH ECG/EGM
Typical ECG signs\textsuperscript{1}

Early diagnosis before LVH develops

P wave very sensitive\textsuperscript{2}

Differentiation vs other LVH and prognosis

novel index\textsuperscript{3}

Detectable Pre-hypertrophic Phenotype in Fabry Disease: Low Native T1 and Structural, Functional, and ECG Changes

Comparison of ECG Abnormalities Between Low Native T1 and Normal Native T1 Fabry Disease Subgroups

<table>
<thead>
<tr>
<th></th>
<th>Low Native T1</th>
<th>Normal Native T1</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG (n=100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>31</td>
<td>10</td>
<td>0.005</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>LGE (n=88)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>14</td>
<td>2</td>
<td>0.01</td>
</tr>
<tr>
<td>Negative</td>
<td>38</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Troponin (n=73)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised</td>
<td>5</td>
<td>2</td>
<td>0.45</td>
</tr>
<tr>
<td>Normal</td>
<td>35</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>NT-proBNP (n=76)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised</td>
<td>7</td>
<td>5</td>
<td>0.89</td>
</tr>
<tr>
<td>Normal</td>
<td>36</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Structure and function (n=100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MWT, mm</td>
<td>9±1.5</td>
<td>8±1.4</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>LVMI, g/m²</td>
<td>63±10</td>
<td>58±9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>73±8</td>
<td>69±7</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

BBB, bundle branch block; ECG, electrocardiogram; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; MWT, maximal wall thickness; NT-proBNP, N-terminal pro B-type natriuretic peptide; VE ventricular ectopics.

# Predictors of Clinical Evolution in Pre-Hypertrophic Fabry Disease

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Fabry Disease Global Cohort (n=44)</th>
<th>Normal T1 (n=18)</th>
<th>Low T1 (n=26)</th>
<th>Normal T1 vs Low T1 p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular mass, g/m²</td>
<td>75.5±16.5 (75.5, 60.0 to 89.0)</td>
<td>63.2±12.9 (59.0, 55.0 to 73.0)</td>
<td>84.8±12.8 (87.0, 75.0 to 95.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Maximum left ventricular wall thickness, mm</td>
<td>9.2±2.0 (9.0, 7.0 to 11.0)</td>
<td>7.6±1.7 (7.0, 7.0 to 8.0)</td>
<td>10.3±1.3 (11.0, 9.0 to 11.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Native septal T1, ms</td>
<td>906±68 (922, 842 to 967)</td>
<td>970±22 (972, 948 to 986)</td>
<td>857±48 (852, 821 to 892)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Septal T2, ms</td>
<td>40±3 (41.0, 38.0 to 43.0)</td>
<td>40.8±3.4 (41.0, 39.0 to 43.0)</td>
<td>39.7±3.2 (40.0, 37.0 to 43.0)</td>
<td>0.30</td>
</tr>
<tr>
<td>Late gadolinium enhancement, n (%)</td>
<td>4 (9.1)</td>
<td>0 (0)</td>
<td>4 (15.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Mainz Severity Score Index</td>
<td>15.0±8.7 (12.0, 9.0 to 21.5)</td>
<td>11.6±7.1 (10.0, 8.0 to 13.0)</td>
<td>17.5±9.0 (19.0, 9.0 to 25.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Enzyme replacement therapy, n (%)</td>
<td>18 (40.9)</td>
<td>5 (27.8)</td>
<td>13 (50.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Classic mutation, n (%)</td>
<td>30 (68.2)</td>
<td>9 (50.0)</td>
<td>21 (80.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>PR interval, ms</td>
<td>144.8±23.1 (141.0, 131.0 to 157.0)</td>
<td>140.5±15.9 (140.5, 131.0 to 147.0)</td>
<td>147.9±27.0 (141.0, 131.0 to 161.0)</td>
<td>0.57</td>
</tr>
<tr>
<td>QRS interval, ms</td>
<td>96.2±11.2 (95.0, 89.0 to 100.0)</td>
<td>95.2±10.0 (96.5, 88.0 to 100.0)</td>
<td>96.2±11.8 (94.0, 92.0 to 100.0)</td>
<td>0.71</td>
</tr>
<tr>
<td>Sokolow-Lyon Index</td>
<td>29.1±8.2 (28.0, 21.0 to 36.0)</td>
<td>24.9±7.7 (23.5, 21.0 to 26.0)</td>
<td>32.1±7.2 (33.0, 27.0 to 38.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Repolarization abnormalities, n (%)</td>
<td>17 (38.6)</td>
<td>2 (11.1)</td>
<td>15 (57.7)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Data presented as mean±SD (median, interquartile range) or n (%).
ECG ABNORMALITIES IN FABRY

FABRY

NORMAL
RECOGNITION OF EARLY CHANGES

ECG, electrocardiogram; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

PRE-HYPERTROPHIC ECG CHANGES

429 AUTOMATED MEASURES

43 SIGNIFICANT ONES

SELECTION OF MOST DISCRIMINANT ONES

COMBINED SCORE
FRAGMENTED QRS AS INDICATOR FOR EARLY PATHOLOGICAL CONDUCTION

→ Associated with adverse cardiac events (blocks/VT/SCD)

Mmmm, Tastes like a combination of Who Cares? & So What?
MRI vs. ECG...OR: HOW EARLY BECOMES LATE...

ECG, electrocardiogram; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Stages of Cardiac Involvement in Fabry Disease: Electrocardiographic changes in Fabry disease precede left ventricular hypertrophy and sphingolipid storage in cardiovascular magnetic resonance!!

A – healthy control, no left ventricular hypertrophy (LVH), normal T1, MBF (stress myocardial blood flow), GLS (global longitudinal strain), P wave time and T wave ratio.

B – FD with normal T1 and without LVH; MBF and GLS are mildly reduced, P wave is short and T wave ratio reduced.

C – FD with low T1 and without LVH, low MBF and GLS, P wave duration and T wave ratio are no different from control.

D – FD with LVH; T1 is low, MBF and GLS are significantly impaired, P wave is long and T wave ratio increased
Thus, it seems reasonable to state that...

ECG changes not only precede LVH, but also detect very early atrial and ventricular remodeling processes when imaging seems normal...even normal T1...change of paradigms?

The ECG changes we see make sense and are in line with MRI findings...

A really normal ECG is quite reassuring...excellent negative predictive value...

Automated ECG measures and combination thereof may be helpful for detection of very early cardiac involvement...

One day perhaps we screen based on ECG and combined indices...

It is worth investing in more ECG studies...we don’t know enough...probably never will...

Presenter’s own opinion
THANKS TO...

- Automated ECG core-lab in Glasgow Peter MacFarlane
- Iacopo Olivotto, Peter Nordbeck, Philippe Richardot
- Stephan Rohr Cellular EP Bern
- Christian Lovis Medical IT, Campus Biotech Geneva
- James Moon and his group in London...

- ...and many others who will send us thousands of ECGs to feed the machine...