Fibrodysplasia Ossificans Progressiva (FOP)

Pre-Symposium Course on Rare Bone Diseases
Organised by the KBVR / SRBR Osteoporosis and Fracture Prevention Group

Hotel Dolce La Hulpe, Brussels
Friday, 10 March 2017

Em. prof. dr J. Coen Netelenbos (FOP Expert Center VUmc, Amsterdam)

Clinical picture
Pathophysiology
New treatment possibilities

Heterotopic Ossification (HO)

1. Genetic HO = myositis ossificans or FOP
2. Traumatic HO
3. Neurogenic HO
Live with FOP

Harry Raymond Eastlack (1933-1977) from Philadelphia

Frederick S. Kaplan, MD, The University of Pennsylvania

Coen Netelenbos, VU University Medical Center Amsterdam, NL
Second skeleton
second skeleton
John en Sandra
25 juni 1999 te Venhuizen
Dancing with FOP
Fibrodysplasia Ossificans Progressiva (FOP)

Hallmark

Coen Netelenbos, VU University Medical Center Amsterdam, NL
Hallux valgus on the prenatal feet ultrasound of the characteristic bone malformation in fibrodysplasia ossificans progressiva at birth

Catalina Maftei et al. Prenatal Diagnosis online 19 NOV 2014 DOI:10.1002/pd.4518
Fibrodysplasia Ossificans Progressiva (FOP)

- ultra rare genetic disease characterized by:
- progressive bone formation in muscle, tendon, ligaments
- hallmark: congenital malformation big toes
- intermittent disease flare-ups with variable presentation & outcome
- severe flare-up after surgical treatment / trauma/ IM injection
- no treatment - early mortality cardio-respiratory insufficiency
  = terrible nightmare
1: 2,000,000

NUMBER FOP PATIENTS
As a result of the efforts of IPC members in their search of FOP patients, the number of identified individuals with FOP is increasing. In October 2014 the numbers are:

<table>
<thead>
<tr>
<th>IPC Countries**</th>
<th>Number of FOP patients</th>
<th>Country</th>
<th>Number of FOP patients</th>
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<tbody>
<tr>
<td>Argentina</td>
<td>24</td>
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<td><strong>Total</strong></td>
<td></td>
<td><strong>Total</strong></td>
<td><strong>746</strong></td>
</tr>
</tbody>
</table>

Coen Netelenbos, VU University Medical Center Amsterdam, NL
Mutation in BMP type I receptor ACVR1 or ALK2 (R206H)

Shoore EM et al. Nature Genetics 2006;38:525 - 527

1 misspelled letter with gigantic consequences:

dr Jan-jan Liu

Coen Netelenbos, VU University Medical Center Amsterdam, NL
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Catastrophic Misdiagnosis In FOP

Before you do a biopsy or operate: examine the big toes!

Coen Netelenbos, VU University Medical Center Amsterdam, NL
\(^{18}\text{F-NaF PET/CT scan}\)

Young woman during and after a flare-up

Resulting in serious
Contractures of right
Hip and Knee
Descending and slowing down $^{18}$F-NaF activity PET scan, later followed by ossification on CT scan.

Coen Netelenbos, VU University Medical Center Amsterdam, NL
Case History Jaw Operation

25 yr old woman with FOP mutation
since 8 years total ankylosis of the jaw
caused by zygomatico-mandibular heterotopic ossification (HO)
after a fall from the stairs at the age of 10 years
Spect / CT $^{99m}$Technetium Bone Scan
21 days before operation 2014
Coen Netelenbos, VU University Medical Center Amsterdam, NL
$^{18}$F-NaF PET/CT scans post-operatively

Figure 1.

Coen Netelenbos, VU University Medical Center Amsterdam, NL
Now almost 2.5 years later:

- Inability to move the jaw
- Now stable 5-6 mm inter-incisal distance (was -3 mm by overbite)
- Better Quality of Life:

Absolutely no regrets
In a FOP patient, the “gain of function” mutation of the AVCR1 receptor makes it able to bind BMP molecules.
Heterotopic ossifications found in FOP patients are similar to those observed in a new mouse FOP model.

A. "Stenen" Dorus from Leiden Anatomical Museum

B. Genetically humanized conditional-on knock-in model for Acvr1[R206H] mutation

Contrary to the wildtype ACVR1 receptor, the FOP R206H mutation responds to activin receptor in mice.

Sarah Hatsell, Vincent Idone et al. Sci Transl Med. 2015 Sep 2;7(303):303ra137
Human monoclonal activin-antibody prevents ossification in human FOP mouse model

• Specific anti-activin antibodies under investigation (Regeneron Pharma)
• 2016 Phase 1 clinical trial
• 2017 Phase 2 clinical trial
Palovarotene

- Retinoic acid receptor gamma (RARγ) agonist
  - Trial in COPD patients no benefit
  - Vitamin A blocks cartilage formation
  - Blocked HO in FOP mouse models

- Palovarotene currently under investigation (Clementia Pharma)
  - 2016 Phase 2 clinical trial FOP patients
    - 2017 Phase 3 trial
Towards a cure for Fibrodysplasia Ossificans Progressiva


Coen Netelenbos, VU University Medical Center Amsterdam, NL
2017 Symposium KBVR / SRBR Osteoporosis and Fracture Prevention Group
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FOP Expert Center VUmc
Patient care and clinical and basic research

- Internist-Endocrinologists
- Cardiologist
- Pneumonologist
- Audiologist
- Radiologists
- Nuclear specialists
- Anesthesist
- Pediatrician
- Specialist in rehabilitation
- Jaw surgeons
- Orthopedic surgeon
- Genetecists
- Biologists (bone lab., dental lab, vascular lab)

Coen Netelenbos, VU University Medical Center Amsterdam, NL
Thanks