TREATMENT OF DILATED CARDIOMYOPATHY in patient with EMERY-DREIFUSS muscular dystrophy: from ablation to heart transplantation

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October 16-18, 2015, Venice, Italy
Male, 38 years, first visit in the clinic (June, 2012)

**Symptoms**
- moderate general weakness
- presyncope without association with physical activity
  - proximal muscular weakness
- dyspnea at moderate physical activity
  - episodes of palpitation

**Life History**
- father 66 years, history of stroke
- mother 63 years – arterial hypertension, pacemaker implantation in 54 years
- year of birth 1974
- clinically healthy sons 3 и 11 years
- profession: the lawyer
- abuse: smoking
Male, 38 years, first visit in the clinic (June, 2012)

**Medical History**
- since 5 years – progressive muscular weakness, frequent falls
- in 6 years – the diagnosis of muscular dystrophy
- since 2006 (32 years) – palpitations, heart pain, minimal decreasing of LV EF
- 2012: increasing palpitations, presyncope
  - ✓ Echo-CG: LV end-diastolic volume 230 ml, LV EF 40%
  - ✓ Holter monitoring without medication: sinus bradycardia, episodes of atrial flutter/ fibrillation, AV block II degree (Mobitz 1), > 4,000 PVBs, unsustained VT
  - ✓ coronary angiography: normal coronary arteries

**Physical Examination**
- height 180 cm, weight 77 kg
- walking difficulties, moderate knees and elbows contractures
- no edema
- breathing rate 18 per minute
- no wheezing in the lungs
- heart rate 56 beats per minute, premature beats 2-4 per minute
- no cardiac murmur
- blood pressure 110/70 Hg mm
- no ascites and hepatomegaly
### Genetics Consultation

#### Preliminary Diagnosis – Emery-Dreifuss Muscular Dystrophy

<table>
<thead>
<tr>
<th>Clinical Signs</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking, standing up, jumping difficulties, muscular weakness</td>
<td>+, since 5 years</td>
</tr>
<tr>
<td>Progressive contractures</td>
<td></td>
</tr>
<tr>
<td>High level of creatin kinase</td>
<td>+, 576 U/l</td>
</tr>
<tr>
<td>Normal intellect</td>
<td>+</td>
</tr>
<tr>
<td>No pseudohypertrophies</td>
<td>+</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>+</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>+</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EDMD</th>
<th>Gene</th>
<th>Locus</th>
<th>Protein</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDMD1</td>
<td>EDM</td>
<td>Xq28</td>
<td>Emerin</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>EDMD2</td>
<td>LMNA</td>
<td>1q22</td>
<td>Lamin A/C</td>
<td>Dominant</td>
</tr>
<tr>
<td>EDMD3</td>
<td>LMNA</td>
<td>1q22</td>
<td>Lamin A/C</td>
<td>Recessive</td>
</tr>
<tr>
<td>EDMD4</td>
<td>SYNE1</td>
<td>6q25.1</td>
<td>Nesprin 1</td>
<td>Dominant</td>
</tr>
<tr>
<td>EDMD5</td>
<td>SYNE2</td>
<td>14q23.2</td>
<td>Nesprin 2</td>
<td>Dominant</td>
</tr>
<tr>
<td>EDMD6</td>
<td>FHL1</td>
<td>Xq26.3</td>
<td>SLIM1</td>
<td>X-linked recessive</td>
</tr>
<tr>
<td>EDMD7</td>
<td>TMEM43</td>
<td>3p25.1</td>
<td>Transmembrane protein 43</td>
<td>Dominant</td>
</tr>
</tbody>
</table>
Possible therapeutic and diagnostic strategy

- biopsy (of the myocardium, skeletal muscle)?
- RF-ablation (pulmonary veins isolation, cavitricuspid isthmus)?
- pacemaker implantation?
- ICD implantation and administration of amiodarone
Appropriate ICD/CRTD shocks in patients with DCM depending on its aetiology (genetic or inflammatory)

32 patients (19 – ICD, 13 – CRT-D)
in 29 patients (90.6%) as a primary prevention
mean follow-up 18 month

<table>
<thead>
<tr>
<th></th>
<th>appropriate shocks</th>
<th>no appropriate shocks</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>genetic DCM</td>
<td>100%</td>
<td>41.7%</td>
<td>0.013</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.2±0.9</td>
<td>2.9±0.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>31.8±11.5%</td>
<td>22.8±7.9%</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>
Follow-up (June 2012 – January 2013)

Bakoulev Center for Cardiovascular Surgery (June 2012)

Echo-CG: LV EDD 6.7 cm, LV EDV 198 ml, LV ESV 116 ml, LV EF 43%, LA 4.2 cm, mitral and tricuspid regurgitation I degree

30.05.2012
RF ablation of isthmus

01.06.2012
dual-chamber ICD implantation

amiodarone, warfarin

June: less than 1000 PVBs per day, no atrial flutter/ fibrillation
August: decreasing of the amiodarone dose (100 mg/ day)
November: palpitation, progressive dyspnea and edema

Hospital on a residence (January 2013)

ECG: atrial flutter with heart rate 85-110 beats/minute
Echo-CG: LV EDD 6.8 cm, LV EDV 235 ml, LV EF 16%, PA pressure 47 Hg mm, RV 2.7 cm, mitral and tricuspid regurgitation III degree
amiodarone 100 mg/day, warfarin, perindopril 2.5 mg/day, furosemide 20 mg/day
In gene **EMD** - frame-shift deletion c.del619C in EMD gene causing premature stop-codon appearance and protein shortening (p.236X)

In gene **LMNA** – intron replacement c.IVS4-13T>A, the clinical significance is not known

**Results of PCR-based direct Sanger sequencing**

**December 2012**

Both variants were not found in control group of 100 healthy volunteers
Hospitalization in the clinic (February, 8, 2013)

Physical examination

- skin is pale; no edema
- breathing rate 20 per minute, no wheezing in the lungs
- heart rate 120 beats per minute, pulse irregular, deficits 10-15 beats per minute
- blood pressure 110/60 Hg mm
- no ascites; hepatomegaly +5 cm

Blood examination

<table>
<thead>
<tr>
<th>biochemistry</th>
<th>11.02.13</th>
<th>26.02.13</th>
<th>normal level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine, mg/dl</td>
<td>0.96</td>
<td>0.74</td>
<td>0.6-1.2</td>
</tr>
<tr>
<td>Potassium, mmol/l</td>
<td>3.4</td>
<td>3.6</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Uric acid, mkmol/l</td>
<td>752.2</td>
<td>403.7</td>
<td>242-416</td>
</tr>
<tr>
<td>Bilirubin, mkmol/l</td>
<td>28.4</td>
<td>20.5</td>
<td>5.0-21.0</td>
</tr>
<tr>
<td>Creatine kinase, U/l</td>
<td>458</td>
<td>325</td>
<td>0-125</td>
</tr>
</tbody>
</table>

thyroid status

<table>
<thead>
<tr>
<th>T4 (free.) pmol/l</th>
<th>initial</th>
<th>repeatedly</th>
<th>normal level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30.3</td>
<td>28.6</td>
<td>11.5-22.7</td>
</tr>
<tr>
<td>TTH U/l</td>
<td>8.3</td>
<td>4.4</td>
<td>0.35-5.5</td>
</tr>
</tbody>
</table>
## Blood investigation for myocarditis diagnosis

<table>
<thead>
<tr>
<th>Viral DNA</th>
<th>30.11.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus (CMV)</td>
<td>no</td>
</tr>
<tr>
<td><em>Herpes Simplex</em> Virus Type 1 (HSV-1)</td>
<td>no</td>
</tr>
<tr>
<td><em>Herpes Simplex</em> Virus Type 2 (HSV-2)</td>
<td>no</td>
</tr>
<tr>
<td><em>Human</em> Herpes Virus (HHV-6)</td>
<td>no</td>
</tr>
<tr>
<td>Epstein Barr virus (EBV)</td>
<td>no</td>
</tr>
<tr>
<td>Varicella zoster virus (V2V)</td>
<td>no</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>no</td>
</tr>
</tbody>
</table>

### Anti-heart antibodies

<table>
<thead>
<tr>
<th>Type of antibody</th>
<th>28.02.2013</th>
<th>normal level</th>
</tr>
</thead>
<tbody>
<tr>
<td>heart-specific anti-nuclear antibodies</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>IgG to the endothelial antigens</td>
<td>1:160</td>
<td>1:40</td>
</tr>
<tr>
<td>IgG to antigens of cardiomyocytes</td>
<td>1:80</td>
<td>1:40</td>
</tr>
<tr>
<td>IgG to antigens of smooth muscle</td>
<td>1:80</td>
<td>1:40</td>
</tr>
<tr>
<td>IgG to antigens of conductive system</td>
<td>1:160</td>
<td>1:80</td>
</tr>
</tbody>
</table>
Initial ECG

- atrial flutter (2:1, 3:1, 4:1)
- ICD pacing VVI (20% of QRS)
  75 beats/minute
- Heart rate:
  day - 74-126/minute (mean 85/minute)
  night - 67-88/minute (mean 76/minute)
- PVBs, total 787 (maximal 85/minute),
  18 couplets, 1 triplet
- ST-T: no changes

Holter (amiodarone 400 mg/day)

- atrial flutter (2:1, 3:1, 4:1)
- ICD pacing VVI (20% of QRS)
  75 beats/minute
- Heart rate:
  day - 74-126/minute (mean 85/minute)
  night - 67-88/minute (mean 76/minute)
- PVBs, total 787 (maximal 85/minute),
  18 couplets, 1 triplet
- ST-T: no changes

Echo-CG

- LV: end-diastolic diameter 7,0 cm; EDV 305 ml; ESV 188 ml, EF 33%
- RV: 2,8 cm. LA: 187 ml. RA: 148 ml
- Mitral regurgitation I degree. Tricuspid regurgitation II degree
- PA systolic pressure 40-46 Hg mm

Multi-slice computed tomography

- normal coronary arteries
- dilatation of the all heart chambers, LV end-diastolic diameter 80 mm
- homogenous thinning of right ventricle
- no intracardiac thrombosis
Causes of deterioration and the potential therapeutic and diagnostic tactics

- the accession of the myocarditis?
- increasing of tricuspid regurgitation and asynchrony due to ICD implantation?
- relapse of sustained tachyarrhythmia?
- natural follow-up of disease?

- perindopril 2.5 mg/day
- amiodarone 400 mg/day
- warfarin 2.5-3.75 mg/day
- furosemide 40-60 mg/day
- CRT-D reimplantation?
- electrical cardioversion
- heart transplantation?

ECG after cardioversion

ECG after ICD shocks
Urgency heart transplantation due to electrical storm

- 19.03.2013 – syncope, ICD shocks; emergency hospitalization in ICU
- 19.03.2013 – implantation of veno-arterial ECMO system
- 21.03.2013 - orthotopic heart transplantation; induction immunosuppression - bazoliximab
- 22.03.2013 - explantation of ECMO; tacrolimus + mycophenolic acid + methylprednisone
- 21.03.2013 – 17.04.2013: temporary pacing 90-100/minute; rejection 0-I degree

Macrosopy: weight 470 g, sizes 11x9x4.5 cm; normal coronary arteries myocardium flabby, homogeneous, pink-brown

Microscopy

Polymorphism of cardiomyocytes: there are atrophic, hypertrophic and normal cells with a tendency to atrophy; their relationship unequal.

Nucleus In cardiomyocytes: ugly shape with perinuclear edema; decaying nuclei (apoptosis).

Fibrosis: diffuse focal (most pronounced in the interventricular septum and the left ventricle), periarterial.

Interstitial edema.
Problems of heart transplantation in myopathies

- generally high perioperative risk (serious medical condition of the patients)
- difficulty of anesthesia due to:
  - damage of respiratory muscles (long period of intubation, etc.)
  - involving the back of the neck muscles (difficulty in intubation)
- increased risk of aspiration (gastric reflux)
- rhabdomyolysis
- the risk of malignant hyperthermia (disturbances of Ca ++ metabolism in skeletal muscle with the development of severe contractures)
  - trigger are anesthetics, antidote is dantrolene
  - optimal are total IV anesthesia and the use of non-depolarizing muscle relaxants
- worsening peripheral myopathy by the action steroids (atrophy of proximal muscle without necrosis, CK levels are normal):
  - stimulation of catabolic path AKT1 / FOXO1
  - decrease in protein synthesis
  - hypokalemia
- increased risk of cardiomyopathy in the transplanted heart?
## Heart transplantation in the Emery-Dreifuss muscular dystrophy and other genetic myopathies

<table>
<thead>
<tr>
<th>Cases report in Medline (EDMD)</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>First case report in EDMD</td>
<td>1987 г.</td>
</tr>
<tr>
<td>Immediate success of heart transplantation in EDMD</td>
<td>12 (4?)</td>
</tr>
<tr>
<td>Male/ Female</td>
<td>4/2 (10?)</td>
</tr>
</tbody>
</table>

**Italian register of LMNA-associated myopathies:** of the 78 patients, 17 (22%) had autosomal dominant Emery-Dreifuss muscular dystrophy 2 (EDMD2), ICD or pacemaker was implanted in 41 (53%) myopathic patients, heart transplantation was performed in 8 (10.3%) myopathic patients

**Maggi L et al. Neurology. 2014 Oct 28;83(18):1634-44.**

**Berlin:** of 582 heart transplant recipients, six patients (1%) had muscular dystrophy associated with cardiomyopathy, all patients had an uneventful postoperative course; one patient died suddenly 27 months after operation


**Madrid:** among 311 patients who underwent heart transplantation, five (2%) had end-stage cardiomyopathies related to inherited myopathies; mean age at the time of transplantation was 38.6 years (range from 24 to 55); all of them are alive with a good performance status

Examination of the mother of patient (63 years)
deletion c.del619C EMD in the heterozygous state

Diagnosis: dilated cardiomyopathy (mild form of X-linked Emery-Dreifuss muscular dystrophy).

- Pacemaker in 54 years due to SSS, AV block with syncope; moderate dyspnea
- Previous diagnoses – arterial hypertension, coronary heart disease
- Echo-CG: LV EDD 6.4 cm, LV EF 50%, LA 164 ml, RA 150 ml, PA pressure 50 Hg mm
- MSCT: normal coronary arteries
Conclusions

- Cardiomyopathy in patients with primary myopathy (Emery-Dreifuss muscular dystrophy, EDMD) may progress rapidly despite earlier stable course and requires regular monitoring by a cardiologist.

- The presence of mutations in two genes can explain unusually severe cardiomyopathy in our patient with Emery-Dreifuss muscular dystrophy.

- In all cases of «unexplained» decompensation in EDMD patients, myocarditis should be excluded.

- Verification of a specific genetic variant of myopathy with cardiac involvement is essential to determine the treatment, including surgery.

- Indications to RF ablation and ICD implantation in EDMD patients should be determined considering immediate and long-term prognosis.

- Despite peripheral myopathy and limitations in the use of anesthetics, heart transplantation can be successfully performed in patients with EDMD using modern regimens of immunosuppression.

- X-linked EDMD in women occurs in a mild form behind the masks of more frequent heart disease and may not be recognized for a long time.