Progressive Cardiac Dysfunction in Bethlem Myopathy during Pregnancy

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Bethlem Myopathy:

- first described by Bethlem and Wijngaarden 1976
- OMIM #156610 (Online Mendelian Inheritance in man, www.omim.org)
- about 100 cases described
- age of onset mostly in early childhood with slow progression
- generalized predominantly proximal muscle weakness, joint laxity or contractures
- prognosis: many patients with Bethlem myopathy need a wheelchair after the age of 50 years  Haq et al., 1999
Bethlem Myopathy and genetics:

- autosomal-dominantly inherited congenital myopathy
- associated with mutations in genes encoding collagen VI subunits
- collagen VI protein is associated with extracellular matrix of skeletal muscle
- COL 6 is also expressed in myocardial tissue
- cardiac involvement is frequent in inherited myopathies (i.e. DCM in Becker-Duchenne-mypathy), but cardiomyopathies have not been described in Bethlem Myopathy

Case:

- 30-year-old primigravid woman with Bethlem Myopathy
- Heterozygous pathogenic mutation in COL6A3, exon 17 (p.Gly2080Asp) (c.6239G>A)
- BMI before pregnancy 23.9
- First time presenting at 21 2/7 weeks of gestation
- Fetal ultrasound examination without anomalies
Case:

- **Family history:**
  - mother and sister carry the same mutation with less pronounced phenotype

- **Medical history:**
  - hip dislocations secondary to dysplasia, degenerative osteoarthritis of the right hip joint with arthroplasty 9 years ago
Case:

Neurological examination:

- moderate to severe muscle weakness, accentuated in lower limbs and proximal muscle groups
- gait instability, difficulties in walking on heels
- severe weakness of thigh muscles and hip abductors
- positive Gowers sign and Trendelenburg gait pattern
- lumbar hyperlordosis, distal joint hyperlaxity, finger contractures
- Follicular hyperkeratosis, multiple keloid scars
Gowers sign
Case:

Physical examination:

- Patient reported dyspnea during normal daily activities (NYHA II), irregular heart beats since beginning of pregnancy
- Pulmonary function tests showed mildly restricted lung function
- transthoracic echocardiography (TTE) normal
- Holter electrocardiogram (ECG) with intermittent sinustachycardia
- no physical exercise testing, based on restricted testing due to the muscle weakness
Case:

» 31 0/7:
• TTE with moderate global restricted left ventricular systolic function
• Holter ECG with mild tachycardia (mean 104 bpm, range 79-148 bpm)
• pulmonary function test showed moderate restrictive lung function
• oral treatment with metoprolol 47.5 mg/d was started

➢ 33 1/7:
• deterioration to NYHA III, auscultation and Holter ECG stable
• TTE with myocardial hypokinesia accentuated in interventricular septum, stable EF

➢ 36 0/7:
• shortness of breath at rest
• TTE with beginning left ventricular dilatation, stable EF
• laboratory tests normal (AST, ALT, troponin, NT pro BNP)
Case:

- delivery at 36 2/7:
  - progressive clinical deterioration
  - cesarean section because of decreased motion in hip joints, muscle weakness and shortness of breath
  - healthy boy
  - 2570g
  - APGAR 9-10-10
  - umbilical artery pH 7.30
Case:

- early postpartum clinical course
  - dyspnea and tachycardia improved during 4 days
  - TTE on 4th day showed normal left ventricular dimensions with unchanged EF
  - discharge on 5th postoperative day with metoprolol

- follow up at 2 months:
  patient asymptomatic, no abnormal echocardiographic findings
Case:

Left ventricular volumes and function antepartum and postpartum
Transthoracic echocardiography measurements in pregnancy and postpartum

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Weeks of gestation</th>
<th>Postpartum</th>
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<tbody>
<tr>
<td>Measurement</td>
<td></td>
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<tr>
<td>Ejection fraction, % (normal range)</td>
<td>31 0/7</td>
<td>33 1/7</td>
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<tr>
<td></td>
<td>45 (-)</td>
<td>50 (62±4)</td>
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<tr>
<td>Left ventricular end-diastolic volume (LVEDV), ml (normal range)</td>
<td>131 (-)</td>
<td>138 (92±14)</td>
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Normal third-trimester ejection fraction (%) is 62±4, and normal 4-month postpartum ejection fraction (%) is 64±4. Normal third-trimester left ventricular volume (mL) is 92±14, and normal 4-month postpartum left ventricular volume (mL) is 70±15.

Savu O et al., Circ Cardiovasc Imaging 2012
Bethlem Myopathy and pregnancy

- 38 year old primigravid woman
- gestational diabetes, bicuspid aortic valve and mild pulmonary hypertension diagnosed in 2nd trimester.
- progression of locomotor disability occurred, at 35 weeks of gestation, wheelchair was needed
- labor started spontaneously at 38 weeks of gestation, a vacuum extraction was performed because of the patient’s difficulty in performing expulsive efforts.
Discussion:

» cardiac abnormalities in patients with Bethlem Myopathy have been reported in about 10%, but could be attributed to other predisposing conditions

van der Koi AJ et al., Arch Neurol 2006; Finsterer J and Stöllberger C., Arch Neurol 2007; Pepe G et al. Neuromuscul Disord 2002

➢ diagnostic criteria for peripartum cardiomyopathy and viral myocarditis were not fulfilled


➢ respiratory muscle involvement may have contributed to clinical presentation
Conclusion:

- we report progressive and transient cardiac dysfunction in a patient with Bethlem Myopathy during pregnancy
- we assume this finding to be related to the underlying myopathy rather than viral or obstetric causes
- we recommend **close monitoring** of these patients because of increased myocardial preload during pregnancy
- **mode of delivery should be an individual decision** based on the physical condition of the patient
- decision for cesarean section needs to consider prediposition to increased risk of heart failure because of volume shift during the surgery
Thank you!