Myocarditis and dilated cardiomyopathy

Diagnosis and management

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• Viral myocarditis
• Dilated cardiomyopathy
• Diagnosis
• Treatment
What is viral myocarditis?

“Sleeping” viruses $\rightarrow$ Injury

$\Delta$ Immunogenetic background

$\Delta$ Environment
  • Additional virus
  • Illness

Herpesvirus
What is a viral myocarditis... cough of the heart!

- Herpesvirus
- Parvovirus
- Epstein BV
- Enterovirus

Δ Immunogenetic background

Δ Environment
  - Additional virus
  - Heart failure
Virus persistence 6 months after acute myocarditis relates to heart failure

Figure 1

- Virus elimination (n=64)
- Virus persistence (n=108)

% change in EF

n=28  n=5  n=14  n=8  n=9  n=28  n=9  n=49  n=10  n=12

Follow-up 6.8 months

Kuhl, Circulation 2005
Viral myocarditis

Parvovirus, Enteroviruses, Adenovirus, EBV, HHV6

Asymptomatic

Cough of the heart

Acute myocarditis

Idiopathic (dilated) CMP

Genetic background
Environment

20%
• Viral myocarditis
• **Dilated cardiomyopathy**
• Diagnosis
• Treatment
Idiopathic cardiomyopathies (DCM)
Non-ischemic, non-valvular, non-hypertrophic CMPs

Gene mutations
Metabolic Δ

Structural Δ

Inflammatory Δ

Viruses
Idiopathic cardiomyopathies (DCM)
Non-ischemic, non-valvular, non-hypertrophic CMPs

Gene mutations → Structural Δ

Metabolic Δ → Inflammatory Δ

Viruses

Immunogenetic background
Increased microRNA-155 expression during Coxsackievirus-B3 induced myocarditis

**MicroRNA-array analysis in mice and human**

- C3h=susceptible to inflammation
- B6= resistant to inflammation

**In situ hybridisation of miR-155**

*Infiltrate*

*Healthy myocardium*
LNA-antimiRNA-155 reduces acute cardiac inflammation during viral myocarditis

Locked Nucleic Acid (LNA) anti-miR-155, 25mg/kg iv.

day 0  CVB3

day 1  LNA#1

day 4  LNA#2

day 6  LNA#3

day 7  sacrifice

Cardiac miR-155 levels

40% KD

p=0.0002
LNA-antimiRNA-155 reduces acute cardiac inflammation during viral myocarditis
Idiopathic cardiomyopathies (DCM)
Non-ischemic, non-valvular, non-hypertrophic CMPs

Gene mutations
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DCM
Gene mutations in idiopathic dilated cardiomyopathy

**GENES**

- Lamin A/C
- δ-sarcoglycan
- Dystrophin
- Desmin
- Vinculin
- Titin
- Troponin-T
- α-tropomyosin
- β-myosin heavy chain
- Actin
- Phospholamban
- Mitochondrial DNA mutations

Fatkin, et al. NEJM 1999
The 80 % gap of DCM

- Hypertrophic CMP & gene mutation
  - 80 (-90 %) % with proven mutation
  - 10-20 % gap

- Dilated CMP & gene mutations
  - 20 -(50?) % proven mutations
  - 80 % gap → cause ??
Idiopathic cardiomyopathies (DCM)
Non-ischemic, non-valvular, non-hypertrophic CMPs

Gene mutations
Metabolic Δ
Structural Δ
Inflammatory Δ
Viruses

DCM
Patient, female, 34 years old

- Becker disease: dystrophin abnormality
  - Normal cardiac function 3 months before
- Flue like symptoms, followed by severe dyspnoe
  - Echocardiography:
    - Severe cardiac dysfunction (EF 15 %)
    - Cardiac dilatation (EDD 68 mm)
  - Cardiac biopsies: Epstein Barr virus (820 copies/µg DNA)
Link between hereditary and viral cardiomyopathies

- Viral protease cleaves dystrophin
  - disruption of the dystrophin–glycoprotein complex
  - similar to hereditary abnormalities in dystrophin expression
Patient, male, 34 years old
Cardiac biopsies: EBV↑ + inflammation↑

CD45b (T-lymphocytes)

Dystrophin-1

Dystrophin-2

Dystrophin-3
Viral cardiac infection and genetic predisposition

- Dystrophin abnormality
- Severe cardiac dilatation and failure
- Viral infection in the heart
Idiopathic cardiomyopathies (DCM)

Non-ischemic, non-valvular, non-hypertrophic CMPs

Viruses → Structural Δ → Gene mutations → Metabolic Δ → Inflammatory Δ → DCM
Autoimmune diseases

• Cardiac involvement in systemic diseases:
  – Churg-Strauss: 30–60 %
  – Sarcoidosis: 5–30 %
  – Other systemic diseases: 2–20 %

• History: systemic complaints

• Blood: inflammation & T-cell activation
  – Neopterine
  – Soluble-IL2 receptor
  – ANF and CRP
Female 32 yr

• Prior medical history: none

• Presented to the first heart aid with chest pains
  – Flu-like symptoms 2 weeks prior to admission
  – Progressive position dependant chest pain
Female, 32 y

- Physical: no fever, HD stable
- Biochemistry:
  - TnT 0.67µg/L,
  - CRP 136 mg/L, WBC 19.10^9/L, soluble IL2-rec↑↑
- Echocardiogram:
  - slightly depressed LV function (EF 51%),
  - no pericardial effusion,
  - normal left ventricular dimensions
• T2-weighted: increased signal intensity anteriorly and laterally of the left ventricle
• Late enhancement: focal transmural hyperenhancement basal-lateral of the left ventricle
Female, 32y

- LV dysfunction deteriorated
- Endomyocardial biopsies:
  - Viral PCR:
    - Parvovirus B19 pos (2184 copies mcg/DNA)
    - EBV, HHV6, ADV and EV negative
  - Histology
    - Increased CD3/CD45 positive lymphocytes
Female, 32 years

- Despite aggressive immunomodulatory (IVIG 2gr/kg) and immunosuppressive (prednisone 50mg/day iv) therapy
- Cardiac function declined
- Ultimately requiring a left ventricular assist device → cardiac transplantation
Cardiac biopsies at LVAD
Cardiac biopsies at LVAD

- Extensive infiltration (lymphocytes and eosinophiles)
- Damaged myocytes (myocyte necroses)
- Giant cells
Idiopathic cardiomyopathies (DCM)
Non-ischemic, non-valvular, non-hypertrophic CMPs

Gene mutations
Metabolic $\Delta$

Structural $\Delta$

DCM

Viruses
Inflammatory $\Delta$
Metabolic and toxic causes

• Metabolic triggers
  – Metabolic syndrome: obesity /diabetes/ hypertension
  – Fabry disease

• Toxic triggers:
  – Ethyl (reversible)
  – Drugs (cocaine)
  – Chemotherapy (anthracyclines)
Male, 45 years

- Idiopathic CMP
  - Slight hypertrophy
  - EF 35%
  - EDD 58 mm
- Non-sustained VT
- Cardiac oedema
- Minor renal dysfunction

CMR: T2 and LE
Male, 45 years

- Idiopathic CMP
  - Slight hypertrophy
  - EF 35 %
  - EDD 58 mm
- Non-sustained VT
- Oedema at MRI
- Cardiac biopsies:
  - Motten eaten myocytes
  - Sfingolipid accumulation
- \( \alpha \)-galactosidase deficiency

CMR: T2 and LE

Cardiac biopsies
• Viral myocarditis
• Dilated cardiomyopathy
• **Diagnosis**
• Treatment
How to diagnose...

- History
- Signs and symptoms
- Blood studies
  - ECG
  - Echo
  - CMR
- Biopsies
Myocarditis

• History
  – Often flu-like symptoms days-weeks prior to cardiac symptoms

• Signs and symptoms
  – Diverse: from malaise, atypical chest discomfort, heart failure to idiopathic ventricular arrhythmias.
History in DCM

- **Systemic symptoms (inflammation/metabolic)**
  - Joints, skin, gastro-intestinal, fatigue
- **Familial history (genetic?)**
  - Premature heart disease, sudden death, neurological diseases
- **Toxic causes**
  - Drugs, alcohol, chemotherapy
- **Metabolic**
  - Diabetes, hypertension, obesity
How to diagnose…

- History
- Signs and symptoms
- ECG
- Blood studies
- Echo
- CMR
- Biopsies
How to diagnose...

- History
- Signs and symptoms
- ECG
- Blood studies
- Echo
- CMR
- Biopsies
CMR in acute myocarditis

- **Acuut**
  - T2W: (+) oedema
  - LE: (+) injury
    - Focal, subbepicardiaal
    - posterolateraal

- **Follow-up**
  - T2W: (-)
  - LE: (+) injury/fibrosis

De Cobelli et al. *JACC* 2006;47: 1649-54
CMR in DCM

• Ischemic
  - Subendocardial/transmural LE

• DCM, non-ischemic/valvular
  - Midwall or subepicardial LE
How to diagnose…

• History
• Signs and symptoms
• ECG
• Blood studies
• Echo
• CMR
• Biopsies
Biopsies

Death of Dallas criteria

(Baughman et al, Circulation, Jan 2006: p593)

- Pro: standardised
- Contra:
  - Poor sensitivity
  - Poor specificity

Virus: diffuse
Inflammation: focal
Biopsies
Quantitative RNA/DNA

- **Viral rt-PCR in biopsies**
  - **Pro:**
    - High sensitivity
    - High specificity
  - **Contra:**
    - Invasive (biopsies)

Enterovirus (coxsackie, echovirus), Parvovirus B19, Adenovirus, EBV, HHV6

**Virus:** diffuse
**Inflammation:** focal
Virus presence in myocarditis vs. idiopathic cardiomyopathy

**Myocarditis**
(n=20/35)

- Virus negatief
- PVB19
- PVB19 + HHV6
- PVB19 + EBV
- PVB19 + EV + EBV
- PVB19 + HHV6 + EV

**Idiopathic CMP**
(n=315)

- Virus negatief
- PVB19
- PVB19 + HHV6
- PVB19 + EBV
- EV + EBV
- HH6 + EBV
- PVB19 + EV + EBV
Inflammatory cell staining in biopsies

- Increased inflammation?
  - Systemic disease (history ?, blood ?)
  - Virus presence?

CD45-leukocytes > 12/mm²
CD3-lymphocytes > 7/mm²
• Viral myocarditis
• Dilated cardiomyopathy
• Diagnosis
• Treatment
**Treatment: idiopathic cardiomyopathy/myocarditis?**

**Cardiac biopsies**

- **Virus positive (60%)**
  - Treat the virus?
    - IV IgG
    - Other
  - Inflammation (T-lymph.)
  - Systemic disease

- **Virus negative (40%)**
  - Anti-inflammatory therapy?
    - Cortisol/Azathioprine
    - Endoxan/tacrolimus
    - Other
  - No inflammation
    - No evidence based therapy
Intravenous immunoglobulins for the treatment of PVB19-related CMP

- Randomized single centre clinical trial since 2010 (n=54)
- Based upon pilot data:
  - 2g/kg iv immunoglobulins
  - DCM, EF<45 %
  - > 6 months duration/standard HF therapy
  - PVB19> 250 copies/µg DNA

Dennert et al. AVT 2010
Urgent need for refined diagnosis/treatment!

- International diagnostic protocols & databases
- New clinical trials

Gene mutations

Structural Δ

Metabolic Δ

Viruses

Inflammatory Δ
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2005 B082
2007 B036
2008 B012
2009 B037
2008046
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Gezond bindweefsel belet ontsteking!

- Functie van het hart
- Cement in het hart
- Belet ontsteking!!
  - Mechanische barrière
  - Cytokines
Afweersysteem in hart: bindweefsel!!

**AFBRAAK**
Metalloproteïnasen

- Afbraak van bindweefsel
- Verhoogde ontsteking

**OPBOUW**
Thrombospondins/SPARC

- Verstevigt het bindweefsel
- Verminderde ontsteking

Heymans, Circulation. 2006;114:565
Schellings J. Exp. Med. 2009
MMP-inhibition

- **Myocardial infarction**
  - Inflammation blunted
  - Hypertrophy reduced
  - Cardiac rupture prevented
  - Cardiac dilatation reduced

- **Hypertension**
  - LV dilatation reduced
  - LV function preserved

Heymans S., *Circulation*, 2005
Inhibite van collageen afbreek voorkomt virale schade door ontsteking


Number of inflammatory foci per grid
Control: 10 ± 1.2
MMP-inhibition: 3.9 ± 1.3
Bench to bedside:
Toegenomen MMP-9 in een patiënt met virale myocarditis

- Male, 20 years, acute fulminant myocarditis
- Echo: EF 20 %, EDD 64 mm
- Cardiac biopsies: Epstein-Barr virus: 1750 copies/µg