Disclosure Information

I hereby declare that I have had business or personal interests in the following industrial enterprises since 1 September 2016:

Name of the enterprise / Nature of the interest

<table>
<thead>
<tr>
<th>Enterprise</th>
<th>Interest</th>
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<tbody>
<tr>
<td>Nothing to declare</td>
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</table>
Clinician, microbiologist and pathologist - joining efforts in diagnosis

Infectious sudden cardiac death in children and adolescents

Marta C Cohen MD FRCPath DMJ(Pathol)
Causes SCD

• Structural anomalies: CHD
• Arteries
• Myocardium
• Conduction system
• Infections
• Metabolic
The SCH experience : 2003-2016
Yearly incidence Cardiac deaths @ SCH: 60 c/921 coroner autopsies

Range: 2%-12%; Average Incidence: 6.5%
Heart condition in 60 cases of sudden death at SCH: 2003-2016

60 cases out of 921 sudden death autopsies: 6.5% total cases.
Heart condition in 60 cases of sudden death at SCH: 2003-2016

60 cases out of 921 sudden death autopsies: 6.5% total cases.
0.8% of 921 SUDI/SUDC 2003-2016
13% of cardiac causes of SUDI/SDUC 2003-2016
WHO defined Myocarditis as:

Inflammatory disease of the heart muscle diagnosed by established histological, immunologic, and immunohistological criteria.
Myocarditis

- Inflammation of the heart
- Usually viral
- Also bacterial and fungal
- Allergic reactions
- Drugs and chemicals
- In South America: T cruzi (Chagas Disease)

- ≥ 14 leukocytes hpf
- Necrosis
- C9
- 22.5% cocksackie B
Diagnosis Myocarditis

- History & clinical features
- **ECG:** > abnormal
- **Non-specific biomarkers** (CRP, WCC, ESR)
- **Echocardiography:** > dilated cardiomyopathy LV dilatation & reduced ejection fraction
- **MR:** assess LV ejection, chamber size, wall thickness, localize tissue injury (oedema, hyperaemia, fibrosis)
- **Endomyocardial biopsy:** not routinely used for dx myocarditis. Clear clinical indications.

**Histology:** DALLAS CRITERIA

- **inflammatory cellular infiltrate +/- myocyte necrosis**
- **Focal / diffuse mononuclear infiltrates (T cells and macrophages) with >14 cells/mm²**
Viral myocarditis

- Coxsackie
- Parvovirus B19
- Adenovirus
- CMV
- Herpes 6
- Hepatitis C
- HIV
- Influenza
- EVB

43%
Clinical history a recent case...

- 13 year old
- Well until the Wednesday of 11.3.2015
- Chest discomfort following a tackle and fall during a rugby match with the other player landing on him
- 12.3.15: nausea, no appetite
- 14.3.15: found unresponsive in bed
- Pronounced life extinct
@ PM: Dilated heart
@ PM

- Pale and floppy heart
- Significant pallor of the ventricular myocardium
- Myocarditis suspected
- Sample taken and sent to virology for PCR
Histology: necrosis and inflammation heart
AV node involved myocarditis
PCR identified Parvovirus B19

- Myocardial endothelial cells (not cardiac myocytes) have been identified as the target for Parvo19.
- High prevalence of parvovirus B19 genomes in 35% cases in chronic dilated cardiomyopathy suggests that this develops from previous parvovirus B19–associated myocarditis

Whereas other viruses infect cardiomyocytes, PVB19 targets coronary endothelium.

For cell entry and replication, PVB19 uses the erythrocyte P-antigen cellular receptors and alpha 5 beta 1 integrin coreceptors located on the coronary endothelium.

In children PVB19 is associated to endothelial dysfunction, myocardial ischemia, and progressive cardiac dysfunction.

Frequently lead to severe sequelae such as transplantation and death.
In our case extensive necrosis: C9 +
Parvovirus B19 Myocarditis Causes Significant Morbidity and Mortality in Children

19 Patients PVB19 PCR+

- Mechanical support (n=9)
  - Deaths (n=2)
  - Survivors with normal function (n=2)
- Early death (n=3)
- Survivors (n=4)
  - Normal function (n=3)
- Transplants (n=3)
  - Persistent dysfunction (n=1)
  - Bridged to transplant (n=5)
SUDDEN DEATH in myocarditis

- Median age: 10 months (r: 10 d–16 yrs)
- ≈9% of sudden deaths in young athletes USA in whom a confirmed cv event was documented, *Circulation.* 2009;119:1085–1092
Phase 1:
Myocardial injury due to viral replication

Phase 2:
Activation of antigen specific T & B cells → Antibody production. Chemokines: contain inflam response but may cause injury

Phase 3:
Autoantibodies & persistent T cell activation can be induced by myocardial antigens that cross react with viral peptides. Different outcomes
CASE

• 17-year-old teenager with no known health problems
• Found dead on his bed
• Vascular congestion of lungs, stomach, bowel, liver and spleen. An enlarged lymph node was also present near the caecum.
• Inflammation & necrosis in the heart, predominantly affecting LV and LVS
• ? myocarditis
Viral studies were negative
Pericarditis
DD of infectious myocarditis

Clue: eosinophils were the predominant inflammatory cells

Conclusion:
Hypersensitivity myocarditis

This can occur days or weeks after exposure to a variety of drugs and usually subsides after withdrawal of the offending substance. Toxicology negative.
2 similar clinical cases

2011
- 7 days old male. NVD
- Sleepy, not feeding well
- Arrested at home

2013
- 9 days old female NVD. Discharged
- Day 4: pyrexial and sleepy
- ? Meningitis. Admitted to NICU.
- Day 8th Resp arrest
- Day 9th ECG ischaemic pattern
- Care withdraw
At post mortem

- Evidence of heart failure
- Bilateral pleural effusion
- Ascites
- Bilateral adrenal haemorrhage

- Severe myocarditis with numerous lymphoid cells and early myolysis
Enterovirus encephalomyocarditis

- IS had another 3 cases: 5 cases
- All were 5-11 days post birth
- Virology confirmed enterovirus RNA by PCR in all cases with four of the five known cases the type detected was coxsackie virus B, subtypes 1,2,3 and 4 respectively
- Mothers of all neonates were asymptomatic and enterovirus infection was not suspected in any of the neonates prior to their deaths.
Heart: pale, floppy
Histology: chronic type inflammation (A); myolysis (B); CD3 positive T-lymphocytes (C), CD68 positive macrophages within the myocardium
CD3 and CD4 in heart
CD68
Myocarditis

Myocarditis

Encephalitis
Brain
Encephalitis

A: Cerebral white matter parenchyma showing multifocal necrosis with mixed inflammatory cells, microgliosis and perivascular lymphocytic infiltrate

B: Inflammation of the pons with variable neuronal damage

C: Inflammation of the dentate nucleus with occasional neurons showing eosinophilic degeneration but without definite evidence of established hypoxic injury

D: Section of the spinal cord with foci of inflammation
Spinal cord
Spinal cord
Other organs

- A&B: inflammation in the dura and tentorium
- C: thymus with acute involution
- D: Liver with microabscesses
DIAGNOSIS: non-polio Enterovirus encephalomyocarditis

- Case 1: Enterovirus was detected from the cerebrospinal fluid. VP1 genotype, corresponding to Coxsackie B virus type 3. The nasal swab obtained respiratory syncytial virus, enterovirus and rhinovirus.
- Case 2: PCR Conducted using paraffin-embedded myocardial tissue confirmed the presence of Enterovirus RNA.
Table 1. Summary of the clinical details, autopsy findings, histology and type of enterovirus identified in our five neonatal autopsy cases.

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age and Gender</th>
<th>Clinical features</th>
<th>Gross autopsy findings</th>
<th>Histology of heart and CNS</th>
<th>Other abnormal histology*</th>
<th>Virology for enterovirus (PCR)</th>
<th>Enterovirus type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9 days, female</td>
<td>Fever, Diarrhea, Jaundice, Skin rash, Seizures</td>
<td>Petechial skin hemorrhages on scalp and shoulder</td>
<td>Myocarditis, Encephalitis, Meningitis, Myelitis</td>
<td>None</td>
<td>+ nasal swab, heart, lung, rectum and CSF.</td>
<td>Coxsackie virus B, type 2</td>
</tr>
<tr>
<td>2</td>
<td>5 days, female</td>
<td>Reduced feeding, Increased sleepiness</td>
<td>Unremarkable</td>
<td>Myocarditis, Encephalitis, Myelitis</td>
<td>Lungs, Liver</td>
<td>+ nasal swab, lung, heart and stool sample</td>
<td>Enterovirus RNA (unknown Type)</td>
</tr>
<tr>
<td>3</td>
<td>11 days, female</td>
<td>Breathing problems, Skin rash</td>
<td>Pericardial effusion</td>
<td>Myocarditis, Encephalitis</td>
<td>Lungs, Spleen, Pancreas, Small intestine</td>
<td>+ CSF and heart tissue.</td>
<td>Coxsackie virus B, type 1</td>
</tr>
<tr>
<td>4</td>
<td>7 days, male</td>
<td>Reduced feeding, Increased sleepiness, Jaundice</td>
<td>Unremarkable</td>
<td>Myocarditis, Encephalitis (Spinal cord was not examined)</td>
<td>None</td>
<td>+ CSF, faeces sample and heart tissue.</td>
<td>Coxsackie virus B, type 4</td>
</tr>
<tr>
<td>5</td>
<td>9 days, female</td>
<td>Fever, Increased sleepiness</td>
<td>Ascites, Pleural and pericardial effusion</td>
<td>Myocarditis, Encephalitis, Meningitis, Myelitis</td>
<td>Lungs, Liver, Stomach, Ribs</td>
<td>+ CSF and nasal swab.</td>
<td>Coxsackie virus B, type 3</td>
</tr>
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*All cases showed stress related changes within the thymus and/or adrenal glands.
Infective endocarditis

- US: 0.05 and 0.12 cases per 1000 paediatric admissions from 2003 to 2010
- IE in children with previous surgery for CHD
- 50% of children with IE complicating CHD have had previous cardiac surgery, > palliative shunt procedures or complex intracardiac repairs.

Circulation 2015
Recently

12 years old Female with repaired complex cyanotic heart disease

Developed endocarditis extending up from the Hancock xenograft in the outflow tract of the pulmonary artery into both thrombosed pulmonary arteries

Nature Reviews Cardiology 2016
Histopathology findings

1. Damaged endothelium necessary or initial pathogen colonization of a cardiac nidus

2. Gram-positive cocci (> pathogens) express multiple adhesins that serve as virulence factors through their ability to enhance host cell/substrate attachments that are important in both the initiation and propagation of endocardial infection.

- The “big 3” pathogens are: viridans group streptococci [VGS], S aureus, and Enterococcus species

IE Mitral valve
S viridans

http://pocketdentistry.com/2-infective-endocarditis/
Endocarditis

• 47 patients (24 males)
• Mean ± SD age at diagnosis, 12.3±5.5 years
• 53 episodes of IE
• Viridans streptococci (17 of 53 episodes [32%]) and S aureus (12 of 53 episodes [23%]).

36/47 patients (77%) had CHD, 24 of whom had cardiac surgery before their first episode of IE
14 c (30%) required valve replacement
16 c (34%) had complications, including mycotic aneurysm, myocardial abscess, or emboli.
In summary

• At SCH a small percentage of SUDI/SUDC are due to myocarditis (0.8%), IE (0.1%) or pericarditis (0.1%)
• Myocarditis range: 1 week-13 years
• Pericarditis: 1 month old with bilateral polycystic kidneys. Recurrent pericardial effusions
• IE: 12 years old in previous repaired cyanotic CHD
• In all these cases the diagnosis was not suspected
• The PM not only provides the cause of death, but also provides tissue to conduct culture and/or PCR to identify causative organisms
• Pathologist, specialists in infectious diseases and forensic microbiologist should work together to maximise outcomes.
Thank you.....

questions?