Congenital atrioventricular block in structurally normal heart.

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CAVB: Congenital atrioventricular block

Introduction

CAVB

Complex CHD
- Heterotaxia
- Corrected TGA
  ...

Normal heart (~80%)
- Autoimmune mediated (~85%)
- Myocarditis
- Myocardial tumor
- Genetic abnormalities
  - LQTS
  - Kearns-Sayre syndrome
Introduction

- CAVB is a rare, potentially lethal disease
- Estimated incidence: 1/15,000 ~ 25,000 live births
- Recent ↑ incidence: 1/25,000 to 1/11,000
  - enhanced neonatal care
  - better diagnostic methods
  - more antenatal diagnosis
  - ↑ No of mothers with connective tissue disease

- Diagnosis can be made *in utero*
  - As early as 16 ~ 28 week of gestation age
Etiology

- Transplacental passage of
  - Maternal anti-SS-A/Ro, anti-SSB/La ribonucleoprotein Ab
  - Damage to fetal myocardium & conduction system cells (Ro Ag)
- Mother
  - completely asymptomatic in presence of auto Ab
  - collagen vascular disease (eg, SLE, Sjögren syndrome etc)

- Unclear
  - **What triggers** the maternal Ab interaction with the fetal Ro in a small percentage of Ab exposed babies
  - Why this affects in particular the mid-gestational fetus
Ro/SS-A and La/SS-B antigens in a small cytoplasmic RNP particle.

- **Ro60 protein**
  - quality control of the intracellular metabolism of newly synthesized mRNA to prevent release of misfolded 5sRNAs

- **Ro52 protein**
  - regulation of cell Growth,
  - apoptosis, down regulates pro-inflammatory cytokine production

- **La/SS-B protein**

Critical role
- prevention of autoimmunity
- Involve in cell survival

RNP= ribonucleoprotein

### Frequency of antibodies in various autoimmune diseases

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<th>Author</th>
<th>SLE (%)</th>
<th>CHB (%)</th>
<th>RA (%)</th>
<th>SS (%)</th>
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SLE = systemic lupus erythematosus; CHB = congenital heart block; RA = rheumatoid arthritis; SS = Sjo¨gren’s syndrome; MCTD = mixed connective tissue disease; PSS = progressive systemic sclerosis.

*European Heart Journal (2001) 22, 813–824*
Histologic Findings

- Myocardial biopsy: not routinely performed
  - various stages of fibrosis of the AV conduction area
    - (depending on the timing of the specimen)
  - Immune deposition
    - Frequent

- The mechanism of cell death and fibrosis: unclear.

- Hypotheses:
  - alloimmune-mediated inflammatory responses
  - immune-triggered apoptosis.
whereby maternal antibodies initiate events that lead to a persistent myofibroblast, a phenotype associated with wounding. We have previously reported that apoptosis of cardiocytes results in the surface expression of SSA/Ro and SSB/La components, subsequent opsonization by cognate antibodies and the secretion of cytokines, such as TGF-β from macrophages, which transdifferentiate fibroblasts into scar-promoting myofibroblasts.
TNF-α mRNA expression in conduction tissue of fetus with CAVB and control.

20-wk fetus with CAVB

23-wk fetus with control

Oligonucleotide in situ hybridization using the sense and antisense TNF-α digoxigenin-labeled probes. mRNA is reported using peroxidase-conjugated anti-digoxigenin.

no detectable expression of TNF-α in the control heart

demonstrated localized to a region near the AV groove at a site enriched in mononuclear cells

The Journal of Immunology, 2003, 171: 3253-3261
Histological evidence of increased fibrosis in conduction tissue and colocalization with TGF- and myofibroblasts in CAVB.

- Picrosirius stain was used to identify collagen (red).
- Enhanced fibrosis is detected from the fetuses with CAVB, but not healthy control. B,
- A section adjacent to that represented in A was double stained with anti-human TGF-(peroxidase) and anti-SMAc (alkaline phosphatase) to demonstrate the proximity of TGF-, myofibroblasts, and fibrosis.
Pathological changes

- Fetal myocarditis, haemorrhage, necrosis, degeneration
- Fibrous replacement of the conducting tissue, myocardium
- Widespread dystrophic calcifications

- Caused by failure of the AV conduction system to connect
  - discontinuity btw atrial musculature & AV node or His bundle

- Exaggerated apoptosis and macrophage infiltrates
  ⇒ progressive scarring.

- Mechanisms by which maternal antibodies initiate and finally eventuate the fibrotic transformation are not clear
Antibodies against the human AV node & corresponding negative controls

- Immunofluorescent staining with FITC-labelled monoclonal antihuman mouse Ab; F(ab)2-IgG fragment staining=white arrows X800.
- F(ab)2-IgG fragment staining avoids non-specific IgG-binding.

- A: Absence of the AV node
- Note the pocket in the central fibrous body in A in which the AV node was most likely located earlier in his life. Also note the normally patent AV node artery in A.
Apoptotic cells from both the sinus node (SN) and AV node (AVN)

Round or ovoid nuclei are typical of P cells normally present in both the sinus node and AV node of human hearts.
Both apoptotic (black arrows) and nonapoptotic (open arrows) cells are indicated in both the sinus node and AV node.
Mothers who have SLE/ Sjögren's synd(SS)/undifferentiated connective tissue disease

In utero heart block with normal heart
- > 85%: maternal autoAb to SSA/Ro or SSB/La Ribonucleoproteins regardless maternal Sx

Cardiac injury (CAVB/ myocarditis/endocarditis)
- MC IUP 16~ 28 weeks of gestation
- 3rd-degree heart block: irreversible.
- substantial mortality rate (20%)
- morbidity \( \Rightarrow \) need permanent pacing
Neonatal Lupus syndrome

- Other manifestations of Neonatal SLE (hematologic/ skin...)
  - Transient
  - Parallel with maternal Ab titer in the fetal and neonatal circulation
  - Disappear with the clearance of the maternal Ab by 6~8 Mo of age
  - Continual regeneration
Fetal SVC/aorta Doppler tracing of complete AV block
complete AV block of atrial & ventricular contraction
(ventricular rate = 60 bpm)
Sex & Age

- **Sex**
  - females > males.

- **Age**
  - Fetuses or newborn
    - more serious course require earlier pacing
  - Later in childhood.
Clinical Manifestations

- **Fetus**
  - hydrops fetalis - high mortality rate.
  - Bradycardia / fetal distress
  - history of recurrent fetal loss
  - recurrence for heart block in subsequent siblings is 17-22%.

- **Newborn**
  - Low C.O
  - Asymptomatic - not likely to be identified
  - Associated discoid skin lesions.

- **Older infants or children**
  - Asymptomatic
  - Low C.O.
    - pallor, mottling, lethargy, exercise intolerance, palpitations, dizziness, or syncope, sudden death
    - night terrors, tiredness with frequent naps, and irritability
Physical examinations

- Low heart rate for age
- Junctional escape rhythm - regular at 60-80/min
- Variable S₁ (AV asynchrony)
- Cool skin, mottling, or cyanosis.
- Tachypnea and hepatomegaly (CHF)
- Complex of hydrops fetalis.
Lab Studies

- anti-Ro and anti-La antibody levels (ELISA)
  - Baby
  - Mother

- Assessment for other organ and/or tissue damage
  - Platelet (R/O thrombocytopenia)
  - Liver enzymes (R/O alloimmune hepatitis)
Clinical considerations

Pregnancy in women with anti-Ro/La antibodies

- All women with autoimmune Sx
  - Early first \( \Delta \) screening: reactivity to Ro and La
  - F/U immunoblot fine specificity of anti-Ro reactivity
    (anti–52 kD, 60-kD Ro)

- If anti-La (+), anti-Ro52 or Ro60 (+)
  - High risk for development of CAVB in the fetus.
    - Monitor the fetal PR interval (by Echo)
      - weekly (16 ~ 26 weeks’ GA)
      - biweekly (26 ~ 32 weeks’ GA)
Imaging Studies

- **Echocardiography**
  - Assess ventricular function and size
  - R/O congenital or acquired cardiac malformations
  - Valve dysfunction.

- **ECG (confirm)**
  - P waves and QRS complexes have no constant relationship
  - Prolonged QRS duration or normal

- **Holter ambulatory ECG monitoring**

- **Exercise testing (>7 yrs)**

- **Electrophysiologic test:**
  - Not routinely performed
  - But provide information regarding pathophysiology & prognosis
Complete AV Block

- **P** waves: at 60 bpm
- **QRS** complexes (junctional escape rhythm): 45 bpm
- Atrial and ventricular activity are completely *unrelated*
- Junctional escape rhythm suggests AV *nodal* site of block
Complete AV Block

- P waves at 50-60 bpm
- QRS complexes (ventricular escape rhythm): 35 bpm
- Atrial and ventricular activity are completely unrelated
- Ventricular escape rhythm suggests His-Purkinje site of block
Treatment
Prenatal management approach still very much unresolved

- Anti-inflammatory fluorinated steroids
- Intravenous immune-globulins (IVIG)
- Plasmapheresis
- Augmentation in the fetal heart rate
  - direct fetal pacing
  - β-inotropic agent
Maternal oral fluorinated steroid (dexamethasone or betamethasone) Tx

- Efficacy and risks are questionable.
- No differences
  - in mortality, prematurity, degree of final block, or need for pacemaker between fetuses treated or not.
- Benefit: pericardial or pleural effusions, ascites, hydrops
- Suggestion: reversal of less-advanced block
- Potential risks
  - Fetal neurological development, growth retardation, oligohydramnios
  - Potential maternal side effects
- Dose
  - daily fetal dexamethasone exposure: does not exceed 0.05 mg/kg BW (based on a maximal 8 mg/kg/day maternal dose and a cord-to-maternal drug ratio of 30%).
β₁-adrenergic actions of the bronchodilators
- ↑ heart rate, ↓ systemic vascular resistance

Recommendation
- fetal heart rates < 50–55 bpm
- significantly reduced cardiac contractility.

Dose (orally to the mother)
- Salbutamol (10 mg q 8 h; maximal: 40 mg/day)
- Terbutaline (2.5–7.5 mg q 4–6 h; maximal 30 mg/day)
- 🚫 ↑ ventricular rate by 5–10 bpm.

Possible maternal side effect
The Hospital for Sick Children, Toronto

Treatment Guideline

**Dexamethasone**
- 8mg/kg/d
- 4mg/kg/d
- 2mg/kg/d

**Fetal life**  **28wk**

If significant ventricular Endocardial fibroelastosis.

**Maternal IVIG**
70g  q 2~3wk

If HR<50–55 bpm or cardiac dysfunction .

**salbutamol**

If uncomplicated case: **No Tx**

overall survival rate to birth of >95% !!

Scandinavian J of Immun 2010; 72, 235–241
Toronto, Texas
Treatment Protocol

At Dx of Fetal isolated AV Block
• HR>55 bmp + Normal ventricular function: **Dexa**
  or
• HR<55 bmp + Abnormal ventricular function: **Dexa +β -inotropic**

Pregnant F/U
Weekly-biweekly: Obstetric assessment
Weekly-biweekly: Fetal Echocardiogram

Delivery at tertiary center
• Uneventful course: c/sec (or vaginal del) at about **37 week**
• **Progressive hydrops**: (paracenthesis)+c/sec+immediate pacing

Neonatal critical care Management
• **Low C.O:** isoprenaline, pacing etc
• **Neonatal lupus:** oral prednrosolone
• **Endocardial fibroelastosis:** IVIG

*(Circulation. 2004;110:1542-1548.)*
Era of diagnosis of fetal isolated CAVB and freedom from death.

Toronto, Texas
Treatment Protocol

(Circulation. 2004;110:1542-1548.)
Transplacental fetal treatment & freedom from death

Toronto, Texas
Treatment Protocol

![Graph showing survival rates with different protocols](image)

(Circulation. 2004;110:1542-1548.)
Postnatal Treatment

Medical

- Medications are not necessary
- Chronotropic / inotropics: temporal until pacemaker
  - Isoproterenol, atropine, or epinephrine
  - May be helpful in fetuses and newborns
    - hydrops fetalis
    - congestive heart failure
    - low cardiac output.
- Immunosuppressive agents in fetuses and newborns
  - potentially slow or halt progressive in utero AV block.
- Steroid: little evidence

- Currently focused on identifying the optimal timing of pacemaker!!
Major criteria for pacing based on ECG or Holter
- Severe symptoms (eg, syncope)
- Average HR < 50 bpm. Sleeping HR < 45 bpm
- Pauses 2’ heart block > 3 seconds.

Borderline major criteria
- Cardiomegaly (dCMP)
- High atrial rate
- Junctional instability (eg, junctional exit block)
- Broad complex escape rhythm
- ↓ ventricular response to exercise
- QT prolongation :(mortality 7~22%)
- Complex ventricular ectopy.

Pacemaker

- Transthoracic epicardial leads
  - neonates, prematures
  - especially steroid-eluting epicardial leads
    - longevity and a better threshold.

- Transvenous approach
  - safe in children (>4-5 Yr) with weight >10-20kg
Prognosis
Fetal CAVB
Risk factors for worse outcome

- Fetal diagnosis
- Presence of hydrops fetalis
- Delivery at < 32 weeks gestation
- Ventricular rate < 55 bpm in early pregnancy
- Hydrops fetalis
- Endocardial fibroelastosis (strong predictor)
- Prolonged QTc

Heart International / Vol. 2 no. 1, 2006 / pp. 1-5
No of new cases with isolated CAVB - different time periods.

A Single Institution’s Experience of 30 Years

Number of cases in different time periods:
- 1965~79: N=11
- 1980~89: N=46
- 1990~98: N=45

Legend:
- Yellow: fetal
- Cyan: Neonatal
- Pink: adult

Hospital for Sick Children, Toronto  
(J Am Coll Cardiol 2002;39:130–7)
Survival
- Fetal: 70%
- Neonatal: 94%
- Childhood: 100%

Kaplan-Meier survival of CAVB diagnosed comparing age group
A Single Institution’s Experience of 30 Years

p = 0.0002
Kaplan-Meier freedom of pacemaker implantation comparing age group of CAVB.
A Single Institution’s Experience of 30 Years

Hospital for Sick Children, Toronto  (J Am Coll Cardiol 2002;39:130–7)
Mortality/Morbidity

- Early infancy: greatest risk of death
- Beyond the neonatal period: significantly lower
- Children: 8 ~ 16%
- Adults: 4 ~ 8% in
- Overall morbidity: 17%
- Dilated CMP: 75%
Free from intervention (solid line) and age at time of diagnosis (dotted line) expressed as survival curves (Kaplan Meier);

\[ n=32; \text{6 censored data in the free from intervention-curve}. \]

Prognosis:

- Usually favorable
- Progressive symptomatic
- Should consider pacemaker implantation
  - Exercise intolerance/Dizziness
  - Syncope (Stokes-Adams attacks)
  - Progressive cardiac enlargement (dCMP)
  - Prolonged pauses
  - Frequent episodes of junctional exit block
  - Flat junctional response
  - Tachyarrhythmias
  - Awake HR<50 beats/min (syncope, sudden death risk).
Unreliability of Ventricular Escape Rhythm in CAVB

No QRS complexes!

15 s
Consultations

- To Rheumatologist
  - Mother: monitoring for possible autoimmunedisease.
  - Infant: particularly if other manifestations of neonatal SLE

- Activity restriction
  - Patients with permanent pacing systems should be restricted
    - Avoid repeated intentional trauma to the pacemaker area
    - Exposure to high magnetic fields, such as direct MRI
Conclusions

- Overall prognosis in CAVB is relatively good but may be influenced by the patient’s age at presentation.

- CAVB diagnosed after the newborn period carries relatively lower mortality and morbidity.

- Possibility of progressive dilated CMP should be taken into consideration when evaluating patients.

- Regular echocardiographic monitoring is indicated in all children and young adults with CAVB.
- Thank you for your attention!