Emerging trends in syncope – cardiac risk & genetics

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What is it?

- Syncope:
  - Transient loss of consciousness
  - Transient global cerebral hypoperfusion
  - Rapid onset
  - Usually brief
  - Spontaneous complete recovery
- Cardiac syncope (10% of all syncope, prevalence increases with age)
  - Arrhythmia as primary cause (brady vs tachy)
  - Structural abnormality
  - 'non-cardiac' cardiovascular

Structural cardiac causes syncope

- Valve abnormalities
  - Most commonly AS (congenital vs bicuspid)
    - Murmur always audible
    - Congenital is 3-6% of all congenital heart defects (8/1000)
    - Often present before first year of life but may be later
    - Bicuspid valve 1-2% of all births (higher in males)
  - Pulmonary stenosis
    - 8-15% of all congenital anomalies
    - Mild – moderate often asymptomatic
  - Mitral and tricuspid stenosis
    - Relatively rare to present in adolescence

Other mechanical causes

- Cardiac masses
  - Atrial myxoma, usually LA
  - Prolapse through A-V valve may cause syncope
- Cardiac tamponade
  - Ruptured sinus of valsalva aneurysm
  - Previous cardiac procedure (eg pacemaker, EP study)
  - Aortic root dissection
- Extracardiac mechanical obstructions
  - Massive pulmonary embolus
  - Thoracic aortic dissection
  - Pulmonary hypertension

Arrhythmic causes syncope

- Structural abnormalities
  - Cardiomyopathy
- Primary electrical disorders
  - Conduction system disease
  - Channelopathies
- Ischaemic syndromes
  - Coronary atheroma (multifactorial vs familial hyperlipidaemia)
  - Anomalous coronary distribution
  - Coronary fibromuscular dysplasia
  - Takayasu's arteritis

Features in History indicating higher risk

- Occurs during exertion (not post-exertion)
- Associated with palpitations
- Family history of SCD or inherited cardiac condition
- Severe heart failure or coronary disease
- ECG abnormal

Features on ECG suggest Cardiac Cause

- LVH – if associated with Q-waves or repolarisation abnormality
  - LVH by voltage alone reasonably common in young ,slim athletic males
- T-wave inversion in 2 or more contiguous leads
  - Over age 12 in females
  - Ischaemia, cardiomyopathy, channelopathy
- Extreme bradycardia (in context of age and athletic endeavours)
- Conduction delay (extreme 1st degree, or Mobitz II, 3rd degree)
- QT prolongation (or abnormal shortening)

Indications for heart rhythm monitoring

- In-hospital telemetry if considered high risk
  - Relatively immobile, so less useful if exercise-induced
- Holter monitoring
  - Episodes daily or > once per week
  - Also useful if suspect LQTS or conduction disorder
- External loop recorder (or event monitor)
  - Episodes occur at least once per month
- Implantable loop recorder
  - Episodes less than monthly (but within 2-3 year battery life)
  - Patient activated for symptom rhythm correlation or automatic memory

Outcomes for heart rhythm monitoring

Typical symptoms occur and good tracing obtained

Diagnostic (arrhythmia confirmed or ruled out)

Institute treatment if appropriate

Pre-syncope but not syncope occur but nothing on tracing

Not good enough,

Repeat, provoke or seek alternative test

No symptoms but significant arrhythmia detected

'Significant' arrhythmias

- Persistent bradycardia despite reasonable activity levels (suggests sinus node disease)
- Pauses > 3 seconds
- Mobitz II or 3rd degree block
- Rapid SVT (> 240 / min)
- NSVT (depending on age and circumstances, triplet)
- Sustained VT (monomorphic or polymorphic)
- QT prolongation (eg during HR acceleration)
- Alternating RBBB and LBBB

Genetic conditions associated with arrhythmia -affecting 3% of general population

Cardiomyopathies

HCM

DCM

ARVC

Channelopathies

Long QT syndrome

Brugada syndrome

Catecholaminergic polymorphic VT

Short QT

Conduction disorders

Congenital heart block

WPW and SVT

Cardiomyopathies

HCM

- Mostly a disease of the sarcomere
- MYH7 and MYBPC3 account for > 50% all cases
- Overlap phenotypes with restrictive cardiomyopathy and LVNC
- Genetic testing identifies cause in approx. 60% of individuals (mostly AD)
- Syncope strong predictor of risk, and possibly imminent recurrence

Arrhythmogenic Cardiomyopathy

- A disease of the desmosome
- Approx 50% of cases have mutation identified
- Variable and age-related penetrance

DCM

- Genetics more heterogenous
  - Cytoskeletal
  - Sarcomeric
  - Desmosomal
  - Nucleoskeletal
  - Mitchondrial
  - Calcium handling
  - Titin up to 25% of cases
  - Lamin A/C up to 8%
  - SCN5a up to 3%
  - Yield of genetics at best 40%

Channelopathies

- LQTS
  - Mutations identified in 70-80% individuals (16+ gene panels)
  - LQT1 is KCNQ1, potassium channel, exercise trigger for events
    - Most likely of all subtypes to be symptomatic
    - Symptomatic episodes more likely to be self-limiting
    - Good protection afforded by B-blockers (+/- LSCS)

Location of KCNQ1 mutations Japanese registry

Shimizu et al, JACC 2004;1:117-125

Location	Transmembrane (n=66)	C-terminus (n=29)
ECG diagnostic criteria (%)	82	24
All cardiac events (%)	55	21
Syncope (%)	55	21
Aborted SCA / SCD (%)	15	0
ECG parameters	? ? ?	±
Risk events at young age (HR)	3.4	1

LQT2

- LQT2 is KCNH2, potassium channel
  - Sudden noises and post-partum period
  - Probably only subtype where females higher risk
  - Characteristic notching of T-waves precordial leads (and others)
  - Good protection afforded by B-blockers (especially Nadolol) +/- LSCS

Location of KCNH2 (Herg) mutations

- 6 transmembrane spanning components, N-terminus and C-terminus
  - PORE region spans S5-S6 transmembrane segments
- 201 individuals from 51 families in International LQT registry (Moss et al, Circulation. 2002;105:794-799.)
  - 35 pore, 166 non-pore
  - Individuals with PORE mutations had:
    - Longer QTc, more notching of T-waves
    - Higher risk of events
    - Higher risk malignant arrhythmia
    - Younger age at first event
    - More likely to be probands

Other channelopathies

- LQT3 is SCN5a, a sodium channel, events more likely at rest
- Variable phenotypes in SCN5a
  - LQT3 – a gain of function mutation
  - Brugada syndrome – a loss of function mutation
  - Cardiac conduction disorders – loss of function mutations
  - Dilated cardiomyopathy (with prominent arrhythmia) – loss or gain mutns
  - Atrial fibrillation – loss or gain mutations
  - Overlap phenotype (mutation with both loss and gain of function effects)
- CPVT
  - Mutations identified in 60-70% individuals

Efficacy of B-blockers in LQTS

Study name	Citation Type Authors (first and last) Institution N subjects (types of LQTS)	B-blockers studied	Results/ Conclusions
Efficacy different B-blockers in treatment of LQTS	JACC 2014; 64(13):1352-1358 Registry (?single centre) Abu-Zeitone...... Moss Rochester, NY based registry 1530 (LQT1 379, LQT2 406),	Atenolol (441) Metoprolol (151) Nadolol (259) Propanolol (679)	All 4 BBs similarly effective in preventing 1st events In LQT2 Nadolol signif reduced events (HR 0.4) In patients with previous BCE on BBs, highest risk of recurrence with Propanolol
Not all BBs equal in management of LQT1 and LQT2	JACC 2012; 60(20): 2092-2099 Registry Chockalingam..........Wilde 12 institutions in USA, Europe and SA 382 (LQT1 207, LQT2 175), probands and relatives (27% symptomatic)	Metoprolol (147) Nadolol (101) Propanolol (134)	Propanolol shortened QTc, espec if baseline >480 Symptomatic patients on Metoprolol had more BCE Event-free survival 91% for Propanolol/Nadolol vs 60% for Metoprolol
BB efficacy high-risk patients with LQT1 and LQT2	J Card EP 2010; 21(8): 893-901 Registry Goldenberg......Zareba International LQTS registry (all the big names) 971 (LQT1 549, LQT2 422)	Atenolol (139) Metoprolol (36) Nadolol (121) Propanolol (143)	0-14 age highest risk males and LQT1 15-40 age highest risk females and LQT2 39% LQT1 and 46% LQT2 had an event Atenolol signif reduced events in LQT1 Nadolol signif reduced events in LQT2
BB therapy failures symptomatic probands with genotyped LQTS	Paediatric Cardiology 2004; 25: 459-465 Restrospective Chatrath.......... Ackerman Mayo Clinic 28 (18 LQT1, 7 LQT2, 3 LQT3) Probands	Atenolol (12) Propanolol (10) Metoprolol (4) Nadolol (2)	7 patients had 15 BCE (6 LQT1, 1 LQT2) 13 events while compliant, 10 of which Atenolol, 3 Propanolol

B-blockers and LQT 3

- Previous fears of bradycardia complications in LQT3 and lack of efficacy led to low B-blocker usage and higher ICD implant rate
- 391 LQT3 patients with 51 mutations, 7 registries
- 174 males
- 82 probands, 309 relatives, age range 1-40
- 30% of patients experienced one event
- E1784K and D1790G, were relatively benign
- 28.3 % were started on B-blockers
  - 11/60 females had an event, signif 83% reduction
  - 12/51 males had an event, non-signif ? Due to low numbers

Other medications and LQT3

- Mexiletine (and B-blockers)
  - Priori et al JACC March 2016
  - 34 LQTS patients
  - Significant QTc reduction (63 msec +/- 6)
  - Significant reduction in events (annual rate reduced from 10.3% to 0.7%)
  - ? All mutations respond equally
  - Peter Schwartz recommends:
    - efficacy of mexiletine should be tested in all LQT3 patients
    - continuous ECG monitoring by the acute oral drug test technique (1/2 daily dose)
    - < 90 minutes peak plasma concentration is reached
    - If QTc is shortened > 40 ms, **NO** PR prolongation, **NO** QRS widening **NO** Brugada ECG pattern mexiletine could/should be added to ß-blocker therapy

Other meds

- Ranolazine (and B-blockers)
  - Na channel blocker
  - Appears to have more sensitivity for late sodium current (INaL) than for peak sodium current
  - Known to cause QT prolongation in some, but is not pro-arrhythmic
  - Shortens QT interval in (selected) LQT3 patients
  - 2 x studies on D1790G, N1325S mis-sense and the ? KPQ deletion mutation in the SCN5A gene
    - 1 in 2008 demonstrated short-term (modest) QTc shortening
    - Second, an outcome study ? Still recruiting

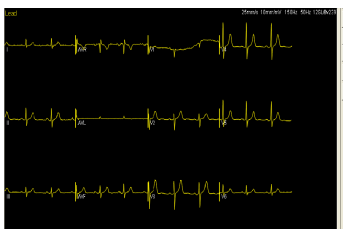
Future directions

- Stem cell therapy
  - REMEDI Ireland currently recruiting LQT genotyped patients for stem cell study
- 'personalised medicine'
  - Mutation specific treatment
    - Depends on robust clinical genetics and detailed bio-informatics
- Standardised treatment for all?
  - Propanolol (? LA in adults) for low-risk, non-LQT2
  - Nadolol for LQT2, 'high-risk' with BCE on B-blocker (and CPVT)
  - Additional meds for LQT3

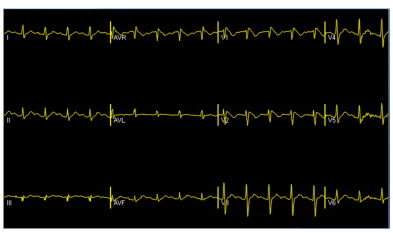
Brugada syndrome

- True prevalence unknown
- Ventricular arrhythmia (polymorphic VT) + ST elevation V1-V3
- South-East Asian males
- Events usually at rest/during sleep
- Sodium channel mutation found in 20%
- 4 other genes recently discovered
- Characteristic ECG not always present at rest
  - May be unmasked by infusion of Na-channel inhibitors (Flecainide / Ajmalin)
- Highest risk of arrhythmia if 'Type 1' resting ECG and/or syncope
- Management
  - VT stim
  - ICD

Patient pre - Ajmalin



Patient during Ajmalin



But…

- Ajmaline test may have a false positive rate of 5-25%
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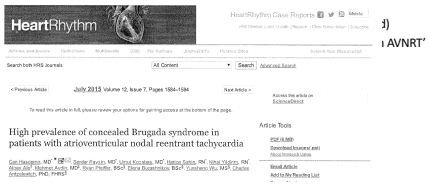


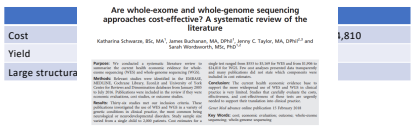
…) …AVNRT'

General trends genetic testing

- Next Gen sequencing emerged approx. 2005
  - Has improved speed, depth of screening and sensitivity, and reduced costs
  - Yield from broader panels not hugely improved c/w restricted old panels
  - Still misses large deletions and copy number variants
- Whole exome sequencing (WES) and Whole Genome Sequencing
  - 1st human genome completed 2003 – cost 0.5 to 1 billion
  - Addition of NGS subsequently has significantly improved process
  - Consider for individual or family where standard panel test not helpful
  - Most helpful in trios (affected child with unaffected parents, ? De novo mutation or recessive condition) or small nuclear families well phenotyped

WES and WGS

- Review of cost-effectiveness in Nature – scant information
  - May improve patient outcomes, reduce delay to diagnosis and enable more efficient use of healthcare resources
- Significant challenge to prioritise and identify actionable variants from 1000s of ra



In summary

- Cardiac causes of syncope uncommon but potentially fatal
- Recognition of risk and initiation of appropriate investigation and management pathways critical to good outcome
- Individuals at risk (especially younger age group) may be perfectly well in between arrhythmic episodes
- Careful family history may be an indicator of underlying cause
- Genetic testing may occupy a more central role in future
  - Reducing delay to diagnosis in rare conditions (eg pt OW)
  - Selecting appropriate therapy
  - Gene based treatment (??cure)
  - Beware of variant reclassification