Brugada syndrome: An old disease with a new name?

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To die in one’s sleep……..
To die in one’s sleep …… basic to human fears

Fodder for mythology, folklore and superstitions for time immemorial

MythS and Legends
Science has not done any better; motley string of acronyms:

- **SIDS** (Sudden Infant Death Syndrome)
- **SUNDS/SUDS** (Sudden Unexpected Nocturnal Death Syndrome)

**ALL SUDDEN, ALL DEAD!**

MythS and Legends
Male
Young (20’s to 40’s)
Apparenetly healthy, with no prior history of heart problems
Southeast Asian, Pacific Rim countries and Polynesians

Who be the damned?
SUNDS in the Hmong people were attributed to diet and lifestyle changes in a new country.

War trauma contributed to “nervous breakdowns”: Nightmares of attacks by ghosts and even deaths.

Tsog Tsuam: a malevolent spirit that holds down victims during sleep, leaving them conscious by paralyzed.

Hmong SUNDS in the US

Bliatout, Bruce (1982)
Goh KT et al Lancet 1990;335:1154
Yap EH et al Lancet 1990;336:376-377
Linked to eating rice cakes

Young, apparently healthy males in their prime

**Phi Am**: Widow ghost, foraging for young men

- Victims experience nightmares, an overwhelming fear, and inability to move or scream
- Female widow ghost that only hunts men
- Kills by sleeping on one’s chest
- Nadamanee et al, 27 Thai men with Lai Tai, 16 had Brugada pattern ECG (Circ 1997;96:2595-600)

**Thailand: Lai Tai**
Tagalog root word for:
“Bangon” to rise, and “Ungol” to moan

- Healthy young males, after a heavy meal and alcohol
- Anecdotal reports of moaning, groaning, gasping, choking, frothing and labored breathing
- Victims are found dead, usually in peaceful slumber with no terminal struggle

- Reported in literature as early as 1917

Philippines: **Bangungot**
**Batibat**: A vengeful demon in Ilocano folklore

- Takes the form of a huge, old and fat lady who resides in trees
- If felled as used for the support post in a house, becomes vengeful
- Sleeps on the victim till he suffocates!!

**Bangungot**
Pokkuri: dying suddenly and unexpectedly without prolonged suffering, reported as early as 1959

Pokkuri-dera:
- temples where prayers for an easy death are granted
- Buddhist temples
- Anichi-ji in Nara prefecture, Japan (Genshin, a Pure Land Buddhist saint)
- Legend has it that when Genshin’s mother was near death, he clothed her in clean white clothing and prayed for relief from suffering for her
- She died shortly and peacefully, and with a smile on her face

Japan: Pokkuri, not a bad thing?
Remedies for SCD

- Wiggling your toes or fingers with drive a *Batibat* away
- Drinking water before bed
- Lying on the left side
- Avoid big meals before bed
- Avoid *Balut* when drinking beer
- Pray hard!
- Pay a visit to *Laureal* and *La Senza*: Lipstick, nail painting and sexy lingerie!

Quack Doctors and *Bomohs*
Brugada brothers: Josep, Ramon and Pedro
The first patient with this syndrome presented to the brothers, Pedro and Josep Brugada in 1986
- 3 year old Polish boy
- Multiple resus by his father
- Always during a febrile illness
- Sister had died suddenly at the age of 2 after multiple episodes of aborted sudden death
- Both had very similar ECGs

A historical perspective
Subsequent addition of 2 more patients allowed preliminary data to be presented at the 1991 North American Society of Pacing and Electrophysiology (NASPE).

The first paper including 8 patients was published in 1992.

Yan GX, Antzelevitch C. (Circulation 1996, 93:372-379) in an article related to cellular basis of the J wave in ECG, was the first the use the eponym Brugada syndrome.

A historical perspective
3 types:

- **Type 1** is diagnostic of Brugada syndrome
- Coved ST segment elevation > 2mm, followed by a negative T wave
- >1 right precordial leads (V1 to V3)
- In the presence or absence of a sodium channel blocking agent

**ECG Manifestations**
Type 1 ECG changes must be in conjunction with one of the following before a definitive diagnosis of BS can be made:

- Documented VF
- Polymorphic VT
- FH of SCD <45
- Inducible VT with PES
- Syncope
- Nocturnal agonal breathing
Type 2:
- Saddleback appearance ST elevation
- >2mm J point elevation
- Trough displaying >1mm ST elevation
- Either a positive or biphasic T wave
- Not diagnostic of Brugada syndrome unless converts to the diagnostic type 1 pattern with sodium channel blockers

ECG manifestation
Type 3:

- Has either a saddleback or coved appearance
- ST segment elevation < 1 mm
- Not diagnostic of Brugada syndrome, unless converts to a type 1 pattern after sodium channel blockers

ECG manifestations
ETIOLOGY AND GENETICS
Usually identified as a sporadic case

50% have a family history of the disease

Genetic abnormalities linked to mutations in ion channels gene SCN5A (Chromosome 3p21-24), which encodes for the cardiac sodium channel

First link was made by Chen et al (Nature 1998; 392:293-6)

Different effect of the same gene are also responsible for Long-QT variant 3

Etiology and Genetics
\( I_{to} \) mediated spike and dome morphology in the epicardium, but NOT endocardium creates a transmural voltage responsible for the ECG J wave.

Cellular mechanism
Loss of action potential dome at some sites but not in others results in transmembrane dispersion of repolarisation and refractoriness.

Conduction of action potential from sites where it is maintained to sites where it is lost causes local re-excitation, development of closely coupled extrasystole via a phase 2 mechanism.

Cellular mechanism
Syncope in a 11 year old
3 am shock!
INCIDENCE AND DISTRIBUTION
Brugada syndrome is responsible for 4 to 12% of SCD, and up to 50% of all sudden deaths in patients with apparently normal hearts.

A prospective study of 22,027 subjects in Japan showed an incidence of 0.05% of ECG's compatible with BS (Tohyou Y et al Jpn J Electrocardio 1995;15:223-6).

In another study in Awa (Japan) the incidence was 0.6% (Namiki T et al Circulation 1995;93:334).

In Children, the incidence can be as low as 0.0006% (Hata Y Circulation 1997;20:2310).

Incidence and distribution
However, ECG changes in BS may show temporal normalization, resulting in underestimation of incidence.

Masao S et al (Eur Heart J 2003; 24:1488-93) the average proportion of Brugada like ECG during 10 years was 1.22+ 0.23%, 29 of the 69 subjects had temporal normalization.

In symptomatic patients, transient normalization of ECG patients were at similar risk for VF and SCD compared to those with persistent ST elevation.

Incidence and distribution
Temperature 39 degrees C
Temperature 37 degrees C
On discharge
Fig. 1  Annual changes of ECG of a 59-year-old man without any episode of ventricular arrhythmias during follow-up period. Pattern of ST segment elevation during follow up period changed. In 1995 typical coved type of ST elevation was seen.
Figure 4. Risk stratification scheme in patients with Brugada syndrome according to clinical presentation. Reprinted with permission from Circulation. Copyright 2002, American Heart Association.
SCD: HR 12.4; CI 5.6 to 27.3; P=0.002

Syncope: HR 3.4; CI 1.6 to 7.4; P=0.002

Spontaneous Type 1 ECG: HR 2.1; CI 1.2 to 3.6; P=0.01

Event rate /year: SCD 7.7%, syncope 1.9%, asymptomatic 0.5%.

Probst V et al Circ. 2010;121:635-643
Therapeutic options: Not so Quack after all......
Sympathetic stimulation with Isuprotoreanol infusion can normalize Brugada pattern

Parasympathetic activity could be arrhythmogenic

Hypokalemia and circadian rhythm could also be pro-arrhythmic

**Autonomic nervous system**

*Figure 6. Circadian pattern of VF episodes in patients with Brugada syndrome. A nocturnal increase of VF episodes was found in 19 Thai-SUNDS patients with Brugada syndrome who received an ICD. All VF episodes were detected and documented by ICD interrogation. Interestingly, a significant number of VF episodes were asymptomatic because these episodes occurred while the patients were asleep (between 10 PM and early-morning hours) and they did not experience ICD discharges.*
Autosomal dominant

Male predominance (8:1 ratio)

Male patients have a higher risk of SCD

Kv4.3 down regulated in pregnancy likely secondary to oestrogen

Male predominance

High level of blood glucose raises Insulin production
Activates Na+/K+ pump and cause hyperpolarization
Also depletes extracellular K+
Increases vagal tone

Heavy meals and glucose load

SCN5A p.T1620M cause accelerated deactivation of Na+ channel only at body temp, not at room temp

Dumaine R et al Circ Res 1999;85:803-809
Implantable technology development

Dr. Beck’s defibrillator 1947
Class IA Vaughan-Williams class
Sodium channel blocker with strong $I_{to}$ blockade
Anticholinergic activity may also play a role

Belhassen et al *Pacing Clin Electrophysiol* 2002;25:1634-40
The cause of death in one’s sleep can be many.

Our understanding of Brugada syndrome is far from complete.

Genetic testing for SCN5A can be helpful.


*Circulation* 2005;111;659-670; originally published online Jan 17, 2005;

DOI: 10.1161/01.CIR.0000152479.54298.51

Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514

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Spontaneous Type 1 ECG

Symptomatic

- Aborted SCD
- Syncope
  - Seizure
  - NAR
  - Evaluate for clear extracardiac cause
    - ICD (class I)
    - EPS recommended for assessment of supraventricular arrhythmias

Asymptomatic

- Family History of SCD suspected to be due to BS
  - EPS (class IIa)
    - +: ICD (class IIa)
    - -: Close Follow-up

- No Family History
  - EPS justified (class IIa)
    - +: ICD
    - -: Close Follow-up
Flecainide, ajmaline, procainamide, disopyramide, propafenone and pilsicainide

Should be monitored during test

End point:
- Diagnostic type 1 Brugada ECG obtained
- ST segment type 2 ECG increases by >2mm
- VPC/arrhythmias
- QRS widens >130% of baseline

Sodium channel blocker test
Fig 2.
Les effets de l'ajmaline en intraveineuse sur l'ECG.
Fig. 2 – Effects of the intravenous administration of ajmaline on the ECG.
Sodium Channel Block-induced Type 1 ECG

**Symptomatic**
- Aborted SCD
  - Syncope NAR
    - Evaluate for clear extracardiac cause
      - ICD (class I)
      - ICD (class IIa) Follow-up
- Close

**Asymptomatic**
- Family History of SCD suspected to be due to BS
  - EPS justified (class IIb)
    - +
    - -
      - ICD (class IIb)
      - Close Follow-up
- No Family History
  - Close Follow-up

EPS recommended for assessment of supraventricular arrhythmias