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Masquerade of a Silent Killer

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Congenital long QT syndrome (LQTS), referred to as a ticking time-bomb is a cause of sudden death in young infants, children and adults.[1] Its prevalence is estimated to be 1 in 2500 to 1 in 10,000 individuals internationally, with no racial predilection.[2] It should be viewed as an unrecognized rather than a rare condition.[1] This is a descriptive report of eight children diagnosed to have congenital LQTS from 2000 to 2007 (Table 1), in Sarawak General Hospital, Kuching, Sarawak, Malaysia, the main tertiary referral hospital for Sarawak. The population of Sarawak (2006 Census) was 2,357,500 and that of Kuching, 435,000.

The eight index patients were not related to each other. Three were girls and five were boys. Four were Bidayuh, one Chinese, one Chinese-Iban, one Sea-Dayak and one was Malay. The presenting age ranged from six weeks to 12 years. The presentation in three children was intermittent cyanosis of lips, recurrent febrile seizures, and chest pain with a warm sensation in the chest, respectively. Five children masqueraded as epilepsy and one was on two anticonvulsants, while two children had history of syncope, giddiness and palpitation. However, none of the children were on any of the offending drugs.[3] None of the children had family history of deafness or sudden infant death syndrome.[2] Case 5 had family history of drowning and unexplained accidents, and syndactyly, while Cases 1 and 4 had family history of unexplained death of infants. Cases 3 and 8 had a spontaneously closed ventricular septal defect and a small ostium secundum atrial septal defect, respectively.

The physical examination was unremarkable in all of the patients. None had dysmorphic features, deafness, syndactyly, bradycardia or underlying medical conditions, and no electrolyte abnormalities were detected. The initial corrected QT interval (QT-c) in ECG ranged from 0.443-0.506 sec. and in the continuous 24-hour ECG, it ranged from 0.510 sec. to 0.593 sec. All patients had T wave abnormalities. Cases 1 to 4 and 7 had prolonged QT-c in asymptomatic family members. Case 5 was not available for follow up and hence could not be started on treatment. Seven patients were started on oral propranolol 0.5 mg/kg/day, which was slowly increased weekly,[4] until the patients had relief of symptoms. All the 7 patients who were on propranolol exhibited good response to treatment. Unfortunately, genetic testing was not available, and the current case series is too small to construe any generalizations. Therefore, further studies in the community and hospital are recommended.

In USA, congenital LQTS accounts for 3000 to 4000 sudden deaths in children annually.[4] LQTS is a channelopathy causing delayed ventricular repolarization, with prolongation of QT-c and increased risk of a polymorphic ventricular tachycardia known as "torsades de pointes" (TdP).[5] TdP may be asymptomatic and self-limited or briefly symptomatic with spontaneous resolution. If TdP is sustained beyond several seconds, it may progress to ventricular fibrillation and sudden death.

Hundreds of mutations have been identified in more than 10 LQTS-susceptible genes coding for sodium, potassium or calcium channels.[6] Among the genetic phenotypes designated LQT1 to LQT10, there are six variants of the autosomal dominant form of LQTS known as Romano Ward syndrome (LQT 1-6) and two rare syndromes; Andersen Tawil syndrome and Timothy syndrome (LQT 7 and 8). Jervell and Lang-Nielsen syndrome, (JLN1 and JLN2) are rare malignant autosomal recessive genotypes associated with sensorineural deafness.[6] Recently, five more genotypes LQT9 to LQT13 have been identified.[7] Patients with compound mutations present early with clinical disease.[6]

Mutations in the K^+ channel genes KVLQT1 or KCNQ1, on chromosome 11 result in LQT1 (about 40-55% of cases).[6] While mutation in a K^+ channel gene HERG or KCNQ2 on chromosome 7 results in LQT2 (about 35-45% of cases).[6] Mutation in the Na^+ channel gene SCN5A, on chromosome 3 results in LQT3 (about 8-10% of cases).[6] Furthermore, LQT4 to LQT8 are rarer forms, the involved genes being ANK2, KCNE1, KCNE2, KCNJ2 and CACNA1C respectively.[6,7] Mutations in the K^+ channel genes KVLQT1 and KCNE1 result in JLN1 and JLN2, respectively.[6] The genes involved in the recent phenotypes LQT9 to LQT13 are; CAV3, SCN4B, AKAP9, SNTA1 and KCNJ5, respectively.[7] Approximately 10% may have a second mutation in the same gene or in another ion channel gene.[7]

In one third of patients, sudden death may be the only presentation.[8] The majority (75%) of asymptomatic patients may be diagnosed during family screening.[1] There may be family history of epilepsy, sudden infant death syndrome, recurrent syncope, unexplained fatal accidents, drowning, sudden death, aborted cardiac arrest or deafness.[1] Thus, a detailed drug history is essential as several drugs prolong the QT-c.[3]

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Table 1: Profile of the LQTS Patients.

Parameters	Case No.							
	1	2	3	4	5	6	7	8
Sex	F	F	M	F	M	M	M	M
Race / ethnic group	Bidayuh	Malay	C / Iban	Bid	C	Bidayuh	Bidayuh	Sea Dayak
Age at diagnosis	6wk	12y	16mo	1 y 9mo	4y	7y 7mo	6y 7mo	7y, 2mo
Presentation	Episodic cyanosis of lips	GTCS head aches 1 yr	Recurrent febrile fit	fits	fits	GTCS	Rec fits	Chest pain
Syncope	-	Y	N	N	N	Y	N	N
Giddiness	-	Y	N	Y	N	N	N	N
Seizures	N	Y	Y	Y	Y	Y	Y	N
Palpitations	-	N	-	N	N	Y	N	Y
Cyanosis	Y	N	N	N	Y	Y	N	Y
Warm sensation in the chest	-	N	-	N	N	Y	N	N
Chest pain	-	N	-	N	N	N	N	Y
Easy fatigability	N	N	N	N	N	N	N	Y
Syndactyly	N	N	N	N	N	N	N	N
Structural cardiac abnormality	N	N	Small ASD sec	N	N	N	N	VSD closed spont at 5/12
Deafness	N	N	N	N	N	N	N	N
FH/O unexplained deaths of infants	Y-6 siblings	N	N	Y	N	N	N	NK
FH/O unexplained accidents	N	N	N	N	Y	N	N	NK
FH/O drowning accidents	N	N	N	N	Y	N	N	NK
Drug history	N	N	N	cbz	Lamo valp	valp	valp	Hematenics
Initial Q-Tc in ECG in sec	0.452 - 0.506	0.454	0.454	0.444	0.443	0.454	0.454	0.464
Maximum Q-Tc in Holter in sec	Not done	0.528	0.514	0.511	0.593	0.510	0.513	0.548
Twave abnormality	Y	Y	Y	Y	Y	Y	Y	Y
Asymptomatic family members detected on screening	3sisters 1brother	4sibs	Fr, Mr-borderline 4 sibs	Fr-border line	-	-	3 siblings	NK (adopted child)
FH/O deafness	N	N	N	N	N	N	N	NK
FH/O syndactyly	N	N	N	N	Y	N	N	NK
SIDS in family	N	N	N	N	N	N	N	NK
Other history			G6PD deficiency					Adopted Expreterm, FTT, right orchidopexy
Treatment	prop	prop	prop	prop	NA	prop	prop	prop

Abbreviations: ASD sec- atrial septal defect secundum;, Bid- Bidayuh; C- Chinese; cbz- carbamezapine; F- female; Fr- father; FTT- failure to thrive; G6PD- glucose-6-phosphate dehydrogenase; GTCS- generalized tonic, clonic seizures; FHO- Family history of; Lamo- lamotrigine; M- male; Mr- mother; mo- months; N- no; NA- not available for follow up; NK- not known; prop- propranolol; Rec- recurrent; sec- second; spont- spontaneously; VSD- ventricular septal defect; valp- valproate; wk- weeks; y- years; Y- yes.

Presentation may be from the neonatal period to adulthood.[2] Symptomatic LQTS is rare in neonates.[2] The usual presenting symptoms such as syncope, palpitation and seizures may be triggered by exercise, swimming, diving, abrupt auditory stimuli or emotional stress; they may also occur during sleep.[2] Episodes of dizziness, light-headedness, blackouts or loss of consciousness followed by seizures suggest TdP. Physical examination is usually unremarkable except in Andersen Tawil and Timothy syndromes.[2] Some patients may have bradycardia.[2] Acquired LQTS may be drug induced,[3,5] or due to electrolyte abnormalities such as acute hypokalemia or chronic hypokalemia, hypocalcemia, hypomagnesemia or medical conditions such as complete atrioventricular block, myocarditis, cardiac failure, encephalitis, stroke, head trauma, subarachnoid hemorrhage, anorexia nervosa, hyperparathyroidism, hypothyroidism and phaeochromocytoma.[1]

Diagnostic investigations include a resting and exercise electrocardiogram (ECG), 24-hour continuous ECG monitoring and genetic testing. The normal QT-c in childhood ranges from 0.37-0.44 sec.[9] A QT-c greater than 0.46 sec. has a positive predictive value of more than 90%,[1] while a QT-c between 0.42-0.46 sec is considered borderline below 15 years of age.[1] The 1993 Diagnostic criteria based on QT-c, TdP, T-wave changes, bradycardia, syncope, congenital deafness and family history may be helpful in predicting the probability of LQTS.[10] It has excellent specificity (99%) but low sensitivity.[11] According to Hofman et al.[11] analysis of Q-Tc alone with a cut off value of 430 msec has superior sensitivity (72%) and acceptable specificity (86%) to screen for carrier state and it should preferably be combined with genetic testing.

T-wave abnormalities characteristic of LQTS may be: wide-based, slowly generated T; wide-based, double-hump, notched T; low amplitude deflection on the descending limb indistinct termination of T-wave (T-U complex); sinusoidal, slowly generated T-wave; or T-wave inscribed after prolonged ST segment.[1] These are gene specific.[2] A normal resting ECG does not rule out LQTS and DNA markers should be used whenever possible.[7] Normal QT-c may present in 10-25% of gene positive patients. Approximately 25-30% may not have any known genetic abnormality. Other tests to detect the underlying medical conditions include; echocardiogram for structural abnormalities, profiles of potassium, calcium and magnesium in the serum.

Management includes a trial of ß-blockers such as propranolol, nadolol, atenolol, and metoprolol (which may prevent cardiac events in approximately 70% of cases), as well as implantation of cardioverter-defibrillators in high risk patients with or without left cervicothoracic sympathectomy.[4] Electrolyte abnormalities should be corrected promptly and offending drugs should be avoided. Treatment reduces the 10-year mortality from 50% to 5%.[1] Gene-specific therapy using potassium, spironolactone, mexiletine, flecainide, nicorandil and other drugs is under evaluation.[4] These children should not participate in competitive sports activities, rather they should go with buddies to swim and play.[8]

Genetic counselling and screening of family members is important. Educating family members and school personnel in basic life support procedures may be helpful, but overall, lifelong follow up is essential.

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