Original Article

Symptoms and Signs Associated with Syncope in Young People with Primary Cardiac Arrhythmias

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Background: **It is often reported that clinical symptoms are useful in differentiating cardiac from non-cardiac syncope. Studies in the young are rare. This study was designed to capture the symptoms and signs reported by patients with cardiac syncope before the patients or their attending clinicians knew the final diagnosis.**

Methods: **Retrospective case-note review of 35 consecutive unrelated gene-positive probands with a proven cardiac channelopathy.**

Results: **The presentation leading to diagnosis of cardiac channelopathy was resuscitated sudden cardiac death in 7 patients; syncope in 20; collapse with retained consciousness in 2; palpitations in 1 and an incidental finding in 5. For the 20 patients with syncope (LQTS 18, Brugada syndrome 2), median age at presentation was 13.9 years (1.8 day to 40.8 years). Of the 17 patients able to describe the onset of syncope, 11 (65%) had at least one symptom prior to collapse, though none reported nausea. Dizziness or lightheadedness was the most frequent symptom, being experienced by 8 (47%). Nine (of 20) patients (45%) had witnessed seizure-like activity and 8 (40%) had urinary incontinence. Nineteen patients were capable of describing the post-syncopal period, of whom 15 (79%) reported symptoms, the most common (12; 65%) being drowsiness or exhaustion.**

Conclusions: **Cardiac syncope in the young frequently presents with symptoms and signs that are typically associated with other causes of transient loss of consciousness, including vasovagal syncope and seizure disorders. The presence of symptoms may not be as helpful in differentiating arrhythmic from non-arrhythmic events as is often supposed. A thorough history, appropriate investigations and a high index of suspicion remain essential in the assessment of syncope.**

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Keywords. Long QT syndrome; Brugada syndrome; Syncope; Symptoms; Arrhythmia; Seizure

Introduction

Whilst reflex syncope, orthostatic hypotension and primary seizure disorders are relatively common in the general population, cardiac syncope is rare. Studies examining symptomatic presentation of syncope have mostly included older patients and/or have been dominated by orthostatic or neurocardiogenic syncope [1,2]. Although syncope is common in the young [3], events due to cardiac arrhythmias have important prognostic implications, and are often the first evidence of a life threatening arrhythmic condition [4–10]. Prompt recognition of cardiac events is important, as appropriate intervention can significantly reduce mortality and

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Abbreviations: LQTS, long QT syndrome; RSCD, resuscitated sudden cardiac death; *KCNQ1*, official symbol of the potassium voltage-gated channel, KQTlike subfamily member 1 gene; *HERG*, human ether a go-go related gene (also know as *KCNH2*); *SCN5A*, official symbol of the "sodium channel, voltage gated, typeV, alpha sub-unit" gene.

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morbidity [11–15]. We have previously reported that misdiagnosis as seizure disorder is common in LQTS, resulting in inappropriate treatments and potentially preventable deaths of family members in some cases [16]. It is often reported that symptoms are useful in differentiating cardiac from non-cardiac syncope. Our observations from clinical practice suggested that this may not be correct. We aimed to describe the symptoms and signs associated with syncopal episodes in a series of patients with subsequently diagnosed cardiac channelopathies. In particular, we wanted to capture these aspects of the history as they were originally reported before the final diagnosis was known to the patients or their attending clinicians.

Methods

Patients were identified from the New Zealand Cardiac Inherited Disease Registry. This registry enables confidential storage of clinical and genetic information for the purposes of clinical management and research into inherited cardiac disease. Ethical approval for the registry has been obtained from the regional ethics committee.

Between 2000 and 2005, 84 families underwent molecular diagnostic screening through the Cardiac Inherited Disease Registry. A member of each family underwent genetic screening of five long QT (LQT) syndrome genes: *KCNQ1*, *HERG*, *SCN5A*, *KCNE1*, and *KCNE2*, and the spectrum of mutations have been previously described [17,18]. The current review is limited to living probands with a genetically confirmed cardiac channelopathy, who consented for the storage of detailed clinical information. There were 35 consecutive unrelated New Zealand patients who fulfilled these criteria.

A retrospective review of patient medical records was undertaken. Use of national unique patient identification codes allowed inclusion of cases from nine different centres. The notes from the initial presentation, either to the emergency department or specialist outpatient clinic, were reviewed by the first author. Routine demographic data was collected. Detailed information regarding the presenting event was extracted from the patient records. This included the patient's description of symptoms before and after the event, as well as any witness observations.

Results are expressed as median values with ranges for nonparametric data and frequency (percent) for categorical variables.

Results

Thirty-five consecutive unrelated probands were identified as gene-positive cases (Fig. 1). Diagnoses were LQT1 in 18 (with mutations in *KCNQ1*) and LQT2 in 10 (with mutations in *HERG*). Seven had mutations in the cardiac sodium channel gene (*SCN5A*); presenting as LQT3 in 3, Brugada Syndrome in 3 and Progressive Cardiac Conduction Disorder in 1. There were 24 females (69%) and 11 males (31%). Median age at presentation was 13.4 years (1 day to 54.2 years). Probands self-identified their ethnicity as European in 25 (71%), Maori in 4 (11.5%), Pacific in 4 (11.5%) and Chinese in 2 (6%).

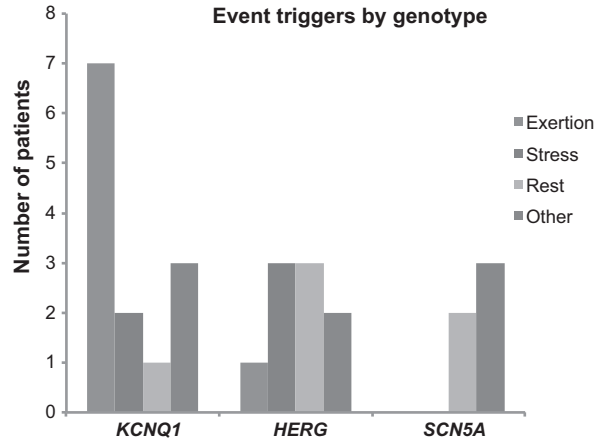

Fig. 1. *Triggers for cardiac events (syncope or cardiac arrest) by genotype amongst 27 patients with cardiac channelopathies in whom the trigger could be obtained from the history (see text). KCNQ1, linked to long QT type 1; HERG linked to long QT type 2, SCN5A linked to long QT type 3 and Brugada syndrome.*

Mode of Presentation

Resuscitated sudden cardiac death requiring DC cardioversion (RCSD) was the presenting event leading to diagnosis of a cardiac channelopathy in seven patients, four of whom had mutations in the *SCN5A* gene. Twenty patients presented with syncope or transient loss of consciousness. Other symptomatic presentations included collapse with retained consciousness in two patients and palpitations in one. In the remaining probands, the diagnosis of channelopathy was entertained following incidental findings: electrocardiographic QTc prolongation in three, prenatal bradycardia in one, and ventricular tachycardia on Holter monitoring in one.

Of the 20 patients with transient loss of consciousness, 15 presented acutely to a hospital emergency department, whilst five were initially seen in an outpatient clinic.

Triggers for Cardiac Events

Triggers for the 27 events involving either RSCD or syncope were identified (Fig. 1). Two of the exercise-associated syncopal events occurred following, rather than during, exertion. An additional two patients had post-exertion symptoms without syncope. One collapsed with retained consciousness following jogging. The other experienced a headache after playing soccer, with corresponding ventricular tachycardia on Holter monitoring (and subsequent detection of an *SCN5A* mutation).

Symptoms Prior to Syncope

Excluding the patients with RSCD, there were 20 patients with transient loss of consciousness or syncope (Table 1), with median age 13.9 years (1.8 days to 40.8 years). Of these 20 patients, 17 were capable of reporting symptoms experienced immediately prior to their event. Eleven

Table 1. *Clinical details for patients presenting with syncope.*

Disease	Demographics		Trigger	Event details		Associated symptoms		Associated signs		
	Gender	Age (yrs)		Time of day	Duration of unresponsiveness (min)	Prodromal	Post-syncopal	Colour change	Seizure activity suspected	Urinary incontinence
LQT1	F	3.5	Exertion	X	1–3	Y	Y			Y
LQT1	M	9.1	Exertion (water)	D	1–3	N	Y	Y		
LQT1	M	9.2	Exertion (water)	D	1–3	Y	Y	Y		
LQT1	M	9.5	Exertion	D	1–3	Y	Y		Y	Y
LQT1	M	10	Exertion	X	X	X	X			
LQT1	F	12.6	Emotion (stress)	X	X	X	N			
LQT1	F	15.1	Post-exert (water)	D	<1	Y	Y		Y	
LQT1	F	26.3	Emotion (fright)	X	1–3	Y	Y	Y	Y	Y
LQT1	F	35.9	Post-partum	D	<1	Y	Y			Y
LQT1	F	40.8	Sleep	O	1–3	N/A (asleep)	Y	Y		
LQT2	M	11.2	Sleep	O	1–3	N/A (asleep)	Y		Y	Y
LQT2	F	12.7	Post-exert	E	1–3	Y	Y			
LQT2	F	21.3	Emotion (fright)	D	1–3	Y	X	Y		
LQT2	F	24.6	Emotion (fright)	O	1–3	Y	Y	Y		
LQT2	F	28.8	Regular activity	O	>3	N	Y	Y	Y	Y
LQT2	F	34.8	Rest	O	1–3	X	X		Y	
LQT2	F	37.3	Emotion (stress)	X	<1	Y	Y		Y	Y
LQT3	F	16.9	Regular activity	E	1–3	Y	Y		Y	Y
Brugada	F	1.8	Febrile	E	1–3	N/A (non-verbal)	N/A		Y	N/A
Brugada	F	9.7	Rest	E	1–3	N	Y	Y		

LQT, long QT syndrome; D, daytime 06:00–18:00 h; E, evening 18:00–24:00 h; O, overnight 24:00–06:00 h; X, not recorded; Y, yes; N, no; N/A, not applicable.

Table 2. *Details of prodromal and post-syncopal symptoms.*

	Symptom	Number of patients	Percentage[a]
Prodromal	Dizziness/lightheadedness	8	47
	Palpitations	3	18
	Temperature change	3	18
	Visual disturbance	2	12
	Weakness	1	6
	Breathing difficulty	1	6
	Abdominal pain	1	6
	Tingling extremities	1	6
Post-syncopal	Drowsiness/exhaustion	12	63
	Confusion/disorientation	5	26
	Nausea/vomiting	4	21
	Weakness	2	11
	Dizziness	2	11
	Headache	2	11
	Breathing difficulty	1	5
	Visual disturbance	1	5

[a] Percentage of total patients capable of reporting symptoms prior to syncope (17) and post-syncope (19).

(65%) of these 17 patients had described such symptoms. The most frequently reported symptom was dizziness or lightheadedness, which was present in eight patients (47%). Other symptoms included palpitations, temperature change, visual disturbance, weakness, difficulty breathing, abdominal pain and tingling of the extremities (Table 2). In addition, symptoms were reported by four patients who did not experience syncope, including weakness in the two who collapsed but retained consciousness, palpitations in one and headache in one (corresponding with documented ventricular tachycardia).

Symptoms Following Syncope

For the same 20 syncopal patients, 19 were able to report whether or not they experienced post-syncopal symptoms (Table 1). A total of 15 (79%) reported symptoms occurring following the event. Drowsiness or exhaustion was the most commonly recorded symptom, occurring in 12 probands (64%). Other reported symptoms included confusion, nausea, vomiting, weakness, dizziness, headache, breathing difficulty and visual disturbance (Table 2).

Duration of Syncope

The approximate duration of unresponsiveness was available from the patient records in 18 of the 20 patients with syncope. Fifteen (75%) were estimated to have been unconscious for longer than a minute. In only three cases (15%) the duration of syncope was reported as being less than 1 min.

Associated Signs

Nine (45%) of the 20 patients with syncope had seizure-like activity reported by witnesses (Table 1). Descriptions ranged from brief limb-jerking and eye-rolling to generalized tonic-clonic movements. Eight patients (40%) had urinary incontinence. A change in colour to either blue or grey was described in eight (40%) cases. No patients suffered injuries with syncope. In four cases (20%) there was a family history of unexpected sudden death in a first degree relative at less than 40 years of age. Electrocardiograms were obtained in 19 of the 20 patients at the presentation leading to diagnosis, with definite abnormalities in 15 and borderline abnormalities (QTc 440–480 ms) in three. The median QTc was 500 ms (range 410–630 ms).

Discussion

Syncope is a common diagnosis with a lifetime cumulative incidence in the general population of 35% and a bimodal age distribution. The peak prevalence in the young is around the age of 15 years [19], with a second spike in the elderly. Syncope is more frequent in women than men [19–21].

There are several causes for non-traumatic transient loss of consciousness, including syncope and seizures. Whilst syncope is relatively common in the young population [3], cardiac syncope is rare. Studies of symptomatology with syncope in the young are also scarce. Cardiac causes of syncope without structural heart disease are particularly difficult to identify, given the absence of findings on clinical examination. Such events can be mistakenly attributed to other diagnoses. The present study gives some clues as to why delayed diagnosis may be occurring. The proportion of cases with witnessed seizure activity (45%) or urinary incontinence (40%) is strikingly high. One might presume that in cardiac syncope, as opposed to primary seizure disorders, the onset of seizure activity would occur following the initial loss of consciousness. This would be difficult to assess in episodes occurring at night or whilst asleep, which is common in LQT2.

Prodromal symptoms may be falsely reassuring that an event is not cardiac. Recently published guidelines in both the USA and Europe suggest that absence of prodromal symptoms is common with cardiac syncope [22,23]. Whilst our findings do not refute this suggestion, we propose that peri-syncopal symptoms may not be as clinically helpful in differentiating between arrhythmic and non-arrhythmic syncope as is often supposed. A recent study by Colman et al. used a retrospective questionnaire to assess patients under 40 years of age and compare symptoms in those with LQTS to those experiencing vasovagal syncope [24]. They reported nausea prior to syncope in 29% of the LQTS patients compared with 60% of vasovagal patients. In other respects, the prodromal symptoms described by our patients were similar to the findings of Colman et al., who had reported symptoms of sweating, light-headedness and blurred vision occurring with equal frequency in both groups. Lightheadedness and dizziness were particularly common in our series. A previous study examining an older cohort of patients (median age 53.4 years), found that the absence of nausea or vomiting before syncope predicted a cardiac cause [25]. Our findings were consistent with this, in that no patients reported nausea before syncope, despite other symptoms prior to their events being common.

The presence of post-syncopal drowsiness may also be misleading. The recent American Heart Association scientific statement comments that "episodes of neurocardiogenic syncope are typically associated with post-episode fatigue or weakness" [23]. Our case series would suggest that drowsiness and weakness following an event are also common in syncope secondary to cardiac arrhythmia (64%). This is a higher frequency than has been previously reported [26].

A thorough history from both the patient and witnesses remains important in cases of syncope. Known identifiable risk factors that raise suspicion for a cardiac event include onset during exercise or whilst supine, triggers of an emotional or auditory nature, a personal history of heart disease and family history of premature sudden cardiac death [22–24,27]. It has been proposed that syncope following chest pain or palpitations is more likely to be cardiac [22,24]. Events during swimming are particularly common in those with LQT1 and this was reflected in our patient population [28]. We propose that post-exertional events, as well as those occurring mid-stride should raise suspicion for an underlying

arrhythmic substrate when accompanied by other concerning features.

Our findings differed from those of Colman et al. in the area of family history. They reported a positive family history of young sudden death in 63% (20/32) of the patients with LQTS, compared to 0% (0/113) of typical syncopal subjects in an emergency department. The presence of a positive family history for young sudden death was much lower in our series, at only 20%. This difference might be explained by the fact that the present series of syncopal patients only includes young sudden death in first degree relatives and that the probands were unrelated individuals.

There has been little previously published specifically focusing on the clinical characterization of syncope in patients with LQTS. The patients in our review generally presented at a younger age (median 13.9 years), compared with those in prior studies evaluating peri-syncopal symptoms. The current series is a retrospective review and is subject to all the usual limitations of such work. However, by reviewing the original history recorded at the time of presentation, we have been able to capture symptoms that were described before the final diagnosis was known to either the patient or the clinician. If no symptoms were recorded, they were assumed to be negative for the purposes of our study. This may have led to an underestimation of the proportion of patients experiencing symptoms. Although the total number of cases is small, this is a series of unrelated patients with confirmed diagnoses of a rare clinical disorder. The inclusion of only unrelated patients avoids the confounding effect of evaluating individuals with the same familial gene defect. It should also be acknowledged that the events reviewed in this series are presumed to be arrhythmic in light of the final diagnosis, but the possibility of neurocardiogenic events occurring in patients with LQTS cannot be excluded.

Conclusions

In our series of unrelated patients with genetically confirmed cardiac channelopathies, symptoms both preceding and following syncope were common. Peri-syncopal symptoms are unlikely to be as helpful in distinguishing cardiac from non-cardiac events as is often thought. The presence of dizziness prior to, and drowsiness following, syncope may be falsely reassuring. Seizure-like activity and urinary incontinence are common in those with cardiac syncope and these features alone should not be used to diagnose primary seizure disorder. Careful history should always include identification of activity at onset, triggers and a family history of young sudden death. Evaluation is not complete without interpretation of a 12 lead ECG including careful assessment of the corrected QT interval. A high index of suspicion should be maintained by the clinician. Large prospective trials of young people presenting with syncope are required to further clarify clinical features of cardiac syncope in the young.

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