Arrhythmias in the congenital long QT syndrome: how often is torsade de pointes pause dependent?

S Viskin, R Fish, D Zeltser, B Belhassen, K Heller, D Brosh, S Laniado, H V Barron

Abstract

Objective—to determine the frequency and predictors of pause dependent torsade de pointes among patients with the congenital long QT syndrome and spontaneous ventricular tachyarrhythmias.

Design—The literature on the “congenital long QT” was reviewed. Articles with illustrations demonstrating the onset of spontaneous polymorphic ventricular arrhythmias in the absence of arrhythmogenic drugs were included.

Results—Illustrations of 62 spontaneous episodes of torsade de pointes among patients with congenital long QT syndrome were found in the literature. The majority (74%) of documented arrhythmias were “pause dependent”;

Conclusion—Available data suggest that the majority of spontaneous arrhythmias in the congenital long QT syndrome are pause dependent. Torsade de pointes that is not preceded by pauses appears to be limited to patient subgroups with severe forms of the disease, like symptomatic infants. These findings have important implications regarding the use of cardiac pacing for arrhythmia prevention.

Table 1 Patients with congenital long QT syndrome and documented torsade de pointes reported in the literature

<table>
<thead>
<tr>
<th>Patients reported in our original series</th>
<th>Patients reported by others†‡‡§</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients.</td>
<td>15</td>
<td>47</td>
</tr>
<tr>
<td>Age (SD) [in years]</td>
<td>28 (19)*</td>
<td>16 (16)§</td>
</tr>
<tr>
<td>Infants (&lt; 3 years old)</td>
<td>1 (7%)</td>
<td>9 (21%)§</td>
</tr>
<tr>
<td>Females</td>
<td>12 (80%)</td>
<td>28 (72%)§</td>
</tr>
<tr>
<td>Deafness</td>
<td>0</td>
<td>6 (15%)</td>
</tr>
<tr>
<td>Mean (SD) QTc (ms)</td>
<td>580 (85)</td>
<td>575 (82)</td>
</tr>
<tr>
<td>QT score [range]</td>
<td>5.2 (4.6-5.5)</td>
<td>5.5 (4.6-5.5)</td>
</tr>
<tr>
<td>No β blocker treatment‡</td>
<td>13 (87%)</td>
<td>33 (76%)§</td>
</tr>
<tr>
<td>Pause dependent TdP</td>
<td>14 (93%)</td>
<td>32 (68%)§</td>
</tr>
</tbody>
</table>

*P < 0.05 when comparing the results in our series with those published by others.
†Including one patient reported by us after publication of our original series.
‡At the time of arrhythmia documentation.
§Data on age, sex, history of deafness and number of patients receiving treatment at the time of arrhythmia documentation was not available for 5, 6, 7 and 4 patients published by others, respectively.
cycle length by at least 40 ms. Also, if torsade followed a period of ventricular bigeminy, it was considered to be pause dependent (even if the undisturbed basic cycle length was unknown) as long as the postextrasystolic interval was longer than the coupling interval of the preceding extrasystole by at least 40 ms. The 40 ms value was chosen because this was the smallest interval increment that could be reproducibly recognised. As in a previous study, the identified pauses were, in fact, considerably longer than the basic cycle length (see below).

**Results**

In addition to the 15 patients with congenital long QT syndrome reported in our original series, we found 62 illustrations of torsade de pointes in 54 articles published by others. Fifteen of these patients were excluded for the following reasons. Five patients with a congenital long QT syndrome and pause dependent torsade were excluded because the illustrated arrhythmias occurred during hypokalaemia, hypomagnesaemia or during treatment with imipramine, astemizole or after amiodarone discontinuation. One patient with non-pause dependent tachycardia was excluded because the arrhythmia appeared to be related to an old myocardial infarction. Five patients were excluded because the poor quality of the ECG or the absence of ≥3 complexes before arrhythmia initiation precluded classification of the arrhythmia. In addition, four arrhythmia illustrations that were repeatedly published—first in original articles and later in reviews—were included only once. Thus, the present report includes 62 patients with documented torsade de pointes, including 15 patients reported in our original series and 47 patients reported by others.

The majority of arrhythmia illustrations, in patients with congenital long QT syndrome reported by others, also demonstrated pause related arrhythmias (table 1, fig 1). However, the percentage of arrhythmias preceded by pauses among patients reported by others (68%) was less than the preponderance of pause dependent arrhythmias (93%) observed in our original series. Based on all available data (62 patients), it appears that torsade de pointes is pause dependent in roughly three out of four symptomatic patients with congenital long QT syndrome (table 1). Only two patients demonstrated both type of arrhythmias (fig 2).

The R-R cycles that preceded the onset of pause dependent arrhythmias are shown in fig 3.
The QT interval is giant and there is sinus tachycardia with marked T wave alternans. Although there appears to be some R-R alternans (the R-R intervals are shown in millisecond), the interval immediately preceding the sinus complex from which torsade originates, which would be expected to be the longest interval if this was a pause dependent arrhythmia (*), is actually short (420 ms). In such cases, the post-extrasystolic interval if this was a pause dependent arrhythmia (*), is actually short (420 ms).

The pauses eventually leading to torsade de pointes were mainly “compensatory pauses” following extrasystoles. These postextrasystolic pauses were observed in 28 patients reported by others and in all but two of the patients reported by us. In all, postextrasystolic pauses, sudden sinus pauses, or both, preceded the onset of torsade de pointes in 73%, 14%, and 15% of all patients with pause dependent arrhythmias, respectively.

**Table 2: Mode of onset of torsade de pointes in patients with congenital long QT syndrome and documented arrhythmias**

<table>
<thead>
<tr>
<th></th>
<th>Pause dependent arrhythmias</th>
<th>Non-pause dependent arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>46 (74%)</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>Age (SD in years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infants (&lt; 3 years old)</td>
<td>1 (2%)*</td>
<td>8 (53%)</td>
</tr>
<tr>
<td>Females</td>
<td>33 (80%)</td>
<td>7 (54%)</td>
</tr>
<tr>
<td>Deafness</td>
<td>3 (7%)</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>Mean (SD) QTc (ms)</td>
<td>569 (77)</td>
<td>620 (49)</td>
</tr>
<tr>
<td>Mean (SD) QT score</td>
<td>5.4 (0.6)</td>
<td>5.6 (0.8)</td>
</tr>
<tr>
<td>Stress related arrhythmias</td>
<td>26 (79%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>No β blocker treatment</td>
<td>35 (79%)</td>
<td>12 (86%)</td>
</tr>
</tbody>
</table>

*p < 0.05.

† Data from all patients shown in table 1.

‡ All in-hospital arrhythmias in newborns were presumed to be stress related. For older patients, a history of out-of-hospital syncope or cardiac arrest following physical or emotional stress (including sudden arousal) was used as evidence for stress related arrhythmias (data were not available for 15 patients reported by others).

§ Data on age, sex, history of deafness, and number of patients receiving treatment at the time of arrhythmia documentation was not available for 5, 6, 7 and 4 patients published by others, respectively.

was used as a definition of “pause” (see Methods), in fact 85% and 82% of the “pauses” preceding torsade were longer than the basic cycle length by > 60 ms or by > 100 ms, respectively. Moreover, a “short-long-short” sequence (an extrasystole, followed by a postextrasystolic pause) immediately preceded the onset of torsade de pointes in most arrhythmic events (see below). In such cases, the postextrasystolic “long cycle” leading to torsade was longer than the previous “short cycle” (created by the extrasystole) by more than 200 ms in 84% of events. Finally, electrocardiographic features supporting the causative role of pauses—like observation of “post-pause U wave augmentation”, reproducible arrhythmia initiation after pauses, or an escalating sequence of events (in which longer pauses are followed by faster bursts of ventricular tachycardia)—were common among our patients and were seen in the majority of illustrations reported by others.

The fact that arrhythmias were preceded by pauses does not prove cause and effect. It could be argued that torsade de pointes should be labelled “pause related” rather than “pause dependent”. However, the marked QTU changes, that become apparent immediately after pauses, appear to represent enhanced early after depolarisations (or increased dispersion of...
repolarisation) following sudden increments in cycle length.\(^5\)\(^6\)\(^7\)\(^8\) Furthermore, the escalating sequence of events, in which longer pauses are followed by faster runs of torsade de pointes,\(^5\)\(^6\) supports the notion that pauses indeed favour the onset of torsade de pointes. In contrast, idiopathic polymorphic ventricular tachycardia in patients without a long QT syndrome are generally not preceded by pauses.\(^1\)\(^2\)

The univariate association between female sex and pause dependent torsade de pointes is of interest because acquired forms of the long QT syndrome, which are essentially always pause dependent, are also more common in women.\(^6\)\(^9\)\(^10\) However, this association was not confirmed by multivariate analysis in our series.

**Non-Pause Dependent Torsade de Pointes**

Torsade de pointes that was not pause dependent was seen predominantly in infants (table 2). Typically, infants would develop torsade following periods of sinus tachycardia (mean (SD) heart rate 107 (21) bpm) with marked T wave alternans or ventricular bigeminy. In the last case, the coupling interval of the extrasystole and the post-extrasystolic interval were of similar duration. Thus, the “short-long” sequence of pause dependent arrhythmias was not identifiable. This could be related to our methodology in several ways. First, our definition of “pause” could have been too strict. However, most investigators will argue that our 40 ms cut off value was “too lenient” rather than “too strict”. Second, the huge and bizarre T U waves, commonly seen in symptomatic infants, probably made defining the onset of extrasystoles less accurate (fig 4). This could result in imprecise estimation of the intervals preceding the arrhythmias. Alternatively, the absence of pause dependent arrhythmias in infants could reflect a more severe disease. Onset of symptomatic arrhythmias at infancy denotes a rather malignant course.\(^5\)\(^7\)\(^8\) Sudden decrements in cycle length—“pauses”—merely facilitate the onset of torsade via two mechanisms: (1) cycle length dependent augmentation of ensuing early afterdepolarisations (which triggers more extrasystoles); and (2) differential prolongation of repolarisation (with greater prolongation in mid-endocardial zones), which worsens the dispersion of repolarisation and facilitates re-entrant arrhythmias.\(^5\)\(^6\)\(^7\)\(^8\) Indeed, it is possible that patients with more severe forms of the disease (like infants), can develop torsade even without the aid of pauses. In this regard, it is interesting that deafness (indicating homozygote inheritance of a long QT syndrome\(^2\) and a more severe disease),\(^5\) also seemed to be more common among patients with torsade de pointes not preceded by pauses (21% vs 7%). The last difference, however, did not reach significance, probably because of the small number of patients with deafness.

**Limitations**

A computerised literature search cannot be customised to find arrhythmia illustrations. This was an “old fashioned” non-automatic search and we probably overlooked more than one report. Also, genotype analysis of the patients with documented arrhythmias is lacking. Since the response of the QT interval to changes in heart rate varies considerably among genotypes,\(^4\) it is likely that sudden pauses are not equally arrhythmogenic for all genotypes. Finally, case reports tend to include illustrations of arrhythmias more often than large series. Thus, serial studies were under represented in our review. However, since the prevailing view in the literature has been that torsade de pointes in the congenital long QT syndrome is generally not pause dependent,\(^6\)\(^7\) there is no reason to believe that the authors of the articles reviewed opted for presenting only illustrations of arrhythmias preceded by pauses. Nevertheless, these limitations could have biased our results.

**Clinical Implications**

Some data suggest that cardiac pacing reduces the arrhythmic risk in the long QT syndrome.\(^1\)\(^2\)\(^5\)\(^7\)\(^8\) However, arrhythmias may recur despite treatment with β blockers and pacing. Unfortunately, these rare recurrences may be lethal.\(^7\)\(^8\) Our data suggest that sudden pauses, especially post-extrasystolic pauses, play a major role in the genesis of torsade de pointes. Post-extrasystolic pauses are not entirely prevented by cardiac pacing. Whenever an extrasystole occurs, the premature event is sensed by the pacemaker, resetting the escape interval. Although this represents normal pacemaker behaviour, it perpetuates the “short-long” sequence that we ought to interrupt. This is because the coupling interval of the extrasystole (a short cycle) is immediately followed by the escape interval, which is a relatively long cycle determined by the programmed lower rate limit. In contrast, post-extrasystolic pauses may be significantly shortened with specific pause-prevention pacing algorithms. Our clinical experience with the use of one such algorithm for preventing torsade de pointes has been rewarding, but is very limited.\(^1\)\(^2\) The results of the present study support the rationale for further careful evaluation of pause-prevention pacing algorithms to prevent torsade de pointes.

Pause dependent and adrenergic dependent torsade de points


IMAGES IN CARDIOLOGY

Ventricular pacing and right bundle branch block morphology: diagnosis and management

A 28 year old woman had atrioventricular (AV) conduction problems since her childhood and developed a complete AV block with junctional rhythm when she was 15 years old. She became progressively symptomatic from her AV conduction block.

A dual chamber pacemaker was implanted and no symptoms were noted during follow up of several years. This young patient was seen at the pacemaker outpatient clinic four years after the implant. The ECG shows a right bundle branch block pattern, a QRS transition in lead V5, and a frontal axis at +120°. The posterior–anterior (PA) x ray view shows the ventricular lead located at a higher level than usual and without synchronous movement with the tricuspid valve on PA fluoroscopy.

Transoesophageal echocardiography depicted the lead crossing the interatrial septum in the area of the foramen ovale and passing through the mitral valve, with a large thrombus attached to the lead’s extremity.

Considering the age of the patient and the presence of a thrombus with potentially disastrous consequences, atriotomy with removal of the left ventricular lead under extracorporeal circulation was decided. Surgery revealed the lead going through a permeable foramen ovale, with a large thrombus attached on the lead at the atrial level and the tip of the lead entrapped in the cordae of the mitral valve. The lead was removed and the foramen closed. A new ventricular lead was inserted in the right ventricle during the same procedure. No further problems occurred during follow up of 18 months.

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