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<tr>
<th>Category</th>
<th>Text</th>
</tr>
</thead>
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<td>Instructions</td>
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<td>Author(s)</td>
<td>Ishikawa, Satoshi; Yamada, Takashi; Kuwata, Tomoyuki; Morikawa, Mamoru; Yamada, Takahiro; Matsubara, Shigeki; Minakami, Hisanori</td>
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<tr>
<td>Citation</td>
<td>Fetal Diagnosis and Therapy, 33(1): 1-7</td>
</tr>
<tr>
<td>Issue Date</td>
<td>2013-01</td>
</tr>
<tr>
<td>Doc URL</td>
<td><a href="http://hdl.handle.net/2115/53261">http://hdl.handle.net/2115/53261</a></td>
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<td>article (author version)</td>
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<td>Fetal Diagn Ther_33(1)_1-7.pdf</td>
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Hokkaido University Collection of Scholarly and Academic Papers: HUSCAP
Fetal long QT syndrome

Journal: REVIEW ARTICLE for Fetal Diagnosis and Therapy

Title: Fetal presentation of long QT syndrome: evaluation of prenatal risk factors. A systematic review

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Abstract

OBJECTIVE: This systematic review was conducted to determine prenatal sings suggestive of fetal manifestation of long QT syndrome (LQTS).

METHODS: Prenatal cardiac findings suggestive of fetal LQTS were studied in the 30 English literature reports that were abstracted from the database of PubMed (1979 – December 2011) using the search terms including “long QT syndrome”, “fetal arrhythmia”, and “congenital heart disease.

RESULTS: LQTS accounted for 15% to 17% of fetal bradycardias < 110 bpm among fetuses with a normally structured heart. Seventeen to 35% of the patients with significant prenatal findings of LQTS exhibited a slightly reduced baseline fetal heart rate (FHR) of 110 – 120 bpm on electronic cardiotocography. Other prenatal sings were sinus or intermittent bradycardia < 110 bpm arising from atrioventricular block, tachyarrhythmias, pleural effusion and hydrops. More than 30% of Japanese infants with LQTS born at or after the mid-1980s exhibited the above-mentioned in-utero signs.

CONCLUSIONS: Fetal factors including a slightly reduced baseline FHR of 110 – 120 bpm, bradycardia < 110 bpm, tachyarrhythmias, or clinical signs of heart failure, such as pleural effusion and hydrops were associated with a higher frequency of LQTS. The use of these signs might help to increase a fraction of patients with perinatally diagnosed LQTS.

Key Words: antenatal diagnosis, atrioventricular block, cardiotocography, fetal bradycardia, long QT syndrome
INTRODUCTION

Long QT syndrome (LQTS) is a hereditary cardiac disease characterized by a prolongation of the QT interval on a basal electrocardiography and is associated with a high risk of life-threatening arrhythmias [1]. Since the identification, in 1995 and 1996, of the first three LQTS genes (KCNQ1, KCNH2, and SCN5A) associated with the most frequently encountered LQTS variants (LQT1, LQT2, and LQT3), seven other genes (ANK2, KCNNE1, KCNE2, KCNJ2, CACNA1c, CAV3, and SCN4B) have been confirmed or suspected of being associated with other LQTS variants (LQT4 through LQT10) [1]. The disease prevalence is estimated to be close to 1 in 2,500 live births [1]. LQTS accounts for more than 10% of the causes of sudden infant death syndrome [1]. Although several reports have described the prenatal cardiac findings of single or multiple cases of LQTS [2-21], some patients with LQTS show only a slightly reduced baseline fetal heart rate (FHR) of 110 to 120 beats per minute (bpm) in utero, as shown in Fig. 1. Since some fetuses with LQTS die in utero or during the neonatal period and because effective measures exist that are capable of preventing life-threatening episodes, such as syncope and ventricular tachycardia [1], antenatal diagnosis or a suspicion of LQTS may be helpful for improving the outcomes of fetuses with LQTS. Accordingly, we conducted this literature review to determine which fetuses should be suspected of having LQTS.

METHODS AND RESULTS

Cases included in this review

We identified a total of 30 English literature reports concerning the fetal presentation of LQTS using PubMed (1979 – December 2011). The search terms “long QT syndrome”, “fetal arrhythmia”, and “congenital heart disease” were used. The 30 reports were classified into three categories according to content: 20 reports [2-21] describing 21 patients with LQTS documented abnormal cardiac findings found in utero (Table 1); five reports [23-27] described series of LQTS patients and included prenatal cardiac findings for some of the fetuses (Table 2); and five reports [28-32] described series of fetuses, some of who were subsequently diagnosed as having LQTS, for whom echocardiography examinations had been performed because of abnormal cardiac
findings found incidentally during antenatal care (Table 3).

Fetuses suspected or diagnosed as having LQTS in utero (Table 1)

Table 1 shows the in utero clinical signs of fetuses with LQTS. Details of the prenatal findings for 21 fetuses were reported in 20 literature reports (Table 1). The time of presentation varied from 16 to 38 weeks of gestation. Although the family history suggested the possibility of LQTS in some patients, all 21 patients exhibited disturbances of cardiac rhythm or abnormalities related to cardiac function in utero: 16 (76%) exhibited bradycardia ≤ 110 bpm; 4 (Cases 7, 15, 16, and 21) (19%) exhibited ventricular tachycardia or tachyarrhythmia; and 1 (Case 17) exhibited pleural effusion. Eleven fetuses (52%) were confirmed to have atrioventricular block (AVB) either pre- or postnatally. Of note, 4 fetuses (Cases 6, and 9-11) (19%) exhibited mild bradycardia ranging from 100 to 110 bpm and a decreased baseline fetal heart rate (FHR) variability on cardiotocography. Thus, fetuses with LQTS can exhibit bradycardia as a result of AVB, sinus bradycardia, and tachyarrhythmias leading to a prenatal suspicion or diagnosis of LQTS. The antenatal diagnosis of a long QT interval was possible using fetal magnetocardiography [9, 11, 14, 20] or fetal electrocardiography [17].

In-utero incidence of signs of cardiac disease in patients with LQTS (Table 2)

As expected, not all the fetuses with LQTS were suspected of having LQTS in utero. In a report by Villain et al. [23], at least five out of 15 neonates (33%) with a prolonged QT interval were documented as having bradycardia in utero, and one of the 5 fetuses was affected by hydrops [23] (Table 2). Since the relevant information was not described in the report, the prenatal findings of the remaining 10 patients are unknown. In a report by Garson et al. [24] dealing with 287 patients with LQTS who were under the age of 21 years, they stated that “the age at presentation ranged from in utero (presenting with bradycardia) to 21 years of age”. However, the number of patients with documented prenatal bradycardia was not specified in their report. A retrospective analysis of fetal echocardiography was conducted in 9 of the 46 patients with LQTS diagnosed at a single center by Hofbeck et al. [25]. Six of the 9 (67%) patients exhibited abnormalities in utero: bradycardia < 110 bpm in four and ventricular tachycardia (VT) and AVB in two. Of note, the remaining three patients (33%) exhibited a reduced FHR of 110 – 120 bpm [25]. Hofbeck et al. [25] did not mention the prenatal cardiac findings
Fetal long QT syndrome

for the remaining 37 patients. Beinder et al. [26] expanded the number of patients whose cardiotocography data during gestation were available by the addition of 8 new patients to the 9 patients reported by Hofbeck et al. [25]. Six of the 17 fetuses (35%) exhibited bradycardia < 110 bpm, and six additional fetuses (35%) exhibited a reduced FHR of 110 – 120 bpm [26]. Horigome et al. [27] reported 58 patients in whom LQTS was diagnosed at an age of < 1 year. Forty-one were born between 1999 and 2008, 14 between 1989 and 1998, 1 in 1986, and 2 in 1984. Among the 18 patients with fetal presentation, clues to the diagnosis or a suspicion of LQTS included bradycardia in 15, AVB in 8, VT/torsade de pointes in 7, and a family history of LQTS in 6 (the items overlapped in some cases). Although the definition of bradycardia was not mentioned, at least 9 fetuses (50%) exhibited bradycardia < 110 bpm and three additional fetuses (17%) exhibited a slightly reduced FHR of 110 – 119 bpm [27], consistent with the results of Beinder et al. [26]. The prenatal findings of the 40 patients with clinical presentation after birth were not described [27].

Thus, based on the reports by Hofbeck et al. [25] and Horigome et al. [27], at least 20% to 30% of patients with LQTS exhibit initial signs suggestive of cardiac diseases in utero. Of those with prenatal findings, 17% to 35% exhibit a slightly reduced FHR of 110 – 120 bpm. However, whether the remaining 70% to 80% of patients with LQTS exhibited significant findings in utero remained unknown. Beinder et al. [26] suggested that approximately one-third of fetuses with LQTS exhibit a normal FHR > 120 bpm, although the study population consisted of 17 patients with LQTS whose cardiotocograms during the early stage of maternal labor and/or during pregnancy were available.

Proportion of fetuses with LQTS among fetuses who underwent echocardiography for various reasons (Table 3)

Fetal bradycardia was defined as a consistent fetal heart rate of < 100 bpm, accounting for approximately 5% of all fetal arrhythmias [33]. Approximately half of these fetuses have associated structural cardiac abnormalities, such as the corrected transposition of the great arteries, an atrioventricular septal defect, or left isomerism [34,35]. Table 3 allows us to estimate the percentage of patients with LQTS among all fetuses with abnormal cardiac findings found incidentally during routine antenatal care. Lin et al. [28] determined the underlying mechanisms of fetal bradycardia < 100 bpm in
18 fetuses without cardiac malformations using echocardiography (Table 3). Three fetuses with LQTS exhibited intermittent bradycardia and tachycardia and accounted for 17% of the 18 fetuses with a normally structured heart and bradycardia < 100 bpm and 50% of the 6 fetuses with AVB and a normally structured heart. The bradycardia of patients with LQTS was caused by sinus bradycardia or AVB [28].

An irregular cardiac rhythm, including “skipped beats”, is a common indication for fetal echocardiography, with a frequency of at least 2% of all pregnancies [36]. Cuneo et al. [29] determined the prevalence of AVB using echocardiography in 306 fetuses with an irregular cardiac rhythm detected during routine fetal heart auscultation in the obstetrician’s office or during an obstetrical ultrasound. The majority of fetuses (97.4% [298/306]) had isolated extrasystoles that were transient and benign. The remaining eight fetuses (2.6%) exhibited AVB in the absence of cardiac malformations. Two fetuses with LQTS exhibited sinus bradycardia and AVB, accounting for 25% of the eight fetuses with both AVB and a normally structured heart [29].

Hsiao et al. [30] analyzed the outcomes of 123 fetuses with prenatally detected cardiac malformations and/or cardiac arrhythmias. Cardiac malformation was present in 103 fetuses, and five of them also had cardiac arrhythmias, accounting for 20% of the 25 fetuses with arrhythmias. Three patients with LQTS accounted for 2.4% of this population and 15% of the 20 fetuses with arrhythmias and a normally structured heart [30].

As shown by Cuneo et al. [29], most fetal arrhythmias reflect transient, isolated ectopic beats. Isolated ectopy is generally benign and self-limited [37]. However, sustained episodes of tachy- or bradyarrhythmia can lead to congestive heart failure, hydrops, or fetal or neonatal demise. Hahurij et al. [31] analyzed the causes and outcomes of 44 fetuses with prenatally detected tachy- and bradyarrhythmias after excluding sinus tachycardia, transient sinus bradycardias, premature atrial or ventricular contractions, and ventricular tachycardias. The AVB accounted for 20% (9/44) of these arrhythmias. Two patients with LQTS accounted for 22% of the 9 fetuses with AVB and 50% of the 4 fetuses with both AVB and a normally structured heart, after excluding five fetuses with both AVB and cardiac malformations [31].

Eliasson et al. [32] determined the underlying mechanisms in 65 fetuses with bradyarrhythmias < 110 bpm. Twenty-five fetuses with AVB and 11 fetuses with sinus bradycardia accounted for 38% and 17% of these fetal arrhythmias. Eight and three
fetuses with cardiac malformations accounted for 32% of the 25 fetuses with AVB and 27% of the 11 fetuses with sinus bradycardia. Four patients with LQTS, including one with AVB and three with sinus bradycardia, accounted for 4.0% of the 25 fetuses with AVB, 27% of the 11 fetuses with sinus bradycardia, 5.9% of the 17 fetuses with both AVB and a normally structured heart, and 38% of the 8 fetuses with both sinus bradycardia and a normally structured heart. Thus, four patients with LQTS accounted for 16% of the 25 fetuses with both bradycardia < 110 bpm and a normally structured heart [32].

DISCUSSION

The present literature review underscored the finding that fetuses with LQTS can exhibit bradycardia as a result of AVB, sinus bradycardia, or tachyarrhythmias. At least 20% to 30% of patients with LQTS born at or after the mid-1980s initially exhibited signs suggestive of cardiac diseases in utero. Among the patients with LQTS for whom documented prenatal findings were available, 17% to 35% of the fetuses exhibited a slightly reduced FHR of 110 – 120 bpm in utero, and some of these fetuses also exhibited a decreased baseline FHR variability on cardiotocograms. Among the fetuses with a normally structured heart, LQTS accounted for 15% to 17% of fetal bradycardias < 110 bpm and 5.9% to 50% of fetal AVB.

More than two-thirds of the patients with LQTS were first suspected of having LQTS after birth [25, 27]. Whether these patients with LQTS who were initially suspected of having LQTS after birth actually exhibited significant findings in utero remains unknown, since no systematic studies focusing on the prenatal findings of patients with LQTS have been conducted to date. However, some fetuses with LQTS did indeed present with an FHR of more than 120 bpm [26].

As suggested by Beinder et al. [26] and Horigome et al. [27], a significant number of patients with LQTS exhibited a slightly reduced FHR of 110 – 120 bpm in utero, although most obstetricians presently consider a baseline FHR of 110 – 120 bpm to be normal [38, 39]. Therefore, these fetuses with a baseline FHR of 110 – 120 bpm may be overlooked, even though the fetuses are affected by LQTS. Because the case presented in Fig. 1 was born to a mother with LQTS, a postnatal investigation proved that the neonate was also affected by LQTS. Cardiotocography is routinely used to monitor fetal wellbeing in many countries. Persistent fetal bradycardia < 120 bpm reportedly occurs
Fetal long QT syndrome

in < 3% of all term infants [26]. Two (0.5%) and 9 (2.1%) of 430 consecutive fetuses at
or after 34 weeks of gestation exhibited persistent bradycardia of 110 – 115 bpm and
115 – 120 bpm, respectively (own unpublished data). Although not verified, a much
higher prevalence of LQTS can be reasonably expected among fetuses with a slightly
reduced FHR of 110 – 120 bpm than among the general population (estimated to be one
in 2,500 [1]). Suspicion of LQTS in such fetuses with a baseline FHR of 110 – 120
bpm irrespective of the presence or absence of a family history may increase the
proportion of patients with perinatally diagnosed LQTS.

As the corrected QT interval is an independent predictor of cardiac events among
patients with LQTS [40] and as LQTS accounts for more than 10% of the causes of
sudden infant death syndrome [1], the early diagnosis and treatment of LQTS may help
to prevent life-threatening events such as ventricular tachycardia, cardiac arrest, and
syncope in some patients with LQTS. In particular, attention should be paid to fetuses
with a slightly reduced FHR of 110 – 120 bpm as well as fetuses with bradycardia < 110
bpm, tachyarrhythmias, or clinical signs of heart failure, such as pleural effusion and
hydrops. As shown in Cases 6, 9, 10, and 11 in Table 1, some fetuses with LQTS exhibit
a reduced heart rate variability [6, 9-11]. Fetal magnetocardiography is able to detect the
prolongation of the QT interval [9, 11, 14, 20] as well as subtle changes in the
short-term heart rate variability [41], thereby facilitating the prenatal diagnosis of LQTS
[9, 11, 14, 20]. Prenatal suspicions and early postnatal electrocardiograms and/or
genetic analysis may help to diagnose LQTS correctly. Such efforts may reduce the
number of patients with so-called “sudden infant death syndrome”.

Fetal long QT syndrome

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Fetal long QT syndrome
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FIGURE LEGEND

Fig. 1: Cardiotocogram obtained during labor showing a fetus with long QT syndrome.

This unpublished case was born to a mother with long QT syndrome and showed a baseline fetal heart rate of 115 bpm during labor at 39 weeks of gestation. The infant was diagnosed as having long QT syndrome soon after birth.
### Table 1. Significant in utero cardiac findings in 21 fetuses reported in 20 previous reports

<table>
<thead>
<tr>
<th>Case, author, year [Ref. no.]</th>
<th>FH</th>
<th>GW</th>
<th>Abnormal cardiac rhythms in utero</th>
<th>Abnormal cardiac rhythms after birth</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>*9, Hamada et al, 1999 [9]</td>
<td></td>
<td>37</td>
<td>110bpm, decr V, No accel</td>
<td>6 months, alive</td>
<td></td>
</tr>
<tr>
<td>*17, Fujimoto et al, 2009 [17]</td>
<td></td>
<td>34</td>
<td>PE, 110-130bpm</td>
<td>alive</td>
<td></td>
</tr>
<tr>
<td>18. Tomek et al, 2009 [18]</td>
<td></td>
<td>26</td>
<td>100bpm, AVB</td>
<td>6 months, alive</td>
<td></td>
</tr>
</tbody>
</table>

*Cases that were diagnosed as having LQTS in utero: FH, family history; +, family history was present but does not necessarily mean that the family history was a clue to the diagnosis; AVB, atrioventricular block; decr V, decreased baseline fetal heart rate variability on cardiotocography; GW, gestational week at presentation; ND, not described; No accel, no acceleration on cardiotocography; PE, pleural effusion; PVC, premature ventricular contractions; TdP, torsade de pointes; VT, ventricular tachycardia. A case reported by Green et al [22] was not included in this table because bradycardia was noticed during parturition only.
Table 2. Five reports describing LQTS patients with prenatal cardiac findings in some patients

<table>
<thead>
<tr>
<th>Author, year [Ref. no.]</th>
<th>No. of patients with LQTS</th>
<th>No. of patients with fetal presentation</th>
<th>Rhythm disturbance in fetus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villain et al, 1992 [23]</td>
<td>15</td>
<td>5</td>
<td>bradycardia in five, one with hydrops</td>
</tr>
<tr>
<td>Hofbeck et al, 1997 [25]</td>
<td>46</td>
<td>9</td>
<td>bradycardia (70-100bpm), AVB in one, bradycardia (90-100bpm) in one, bradycardia (100-110bpm) in two, 110-120bpm in three, VT, AVB in two</td>
</tr>
<tr>
<td>Beinder et al, 2001 [26]†</td>
<td>ND</td>
<td>17</td>
<td>bradycardia &lt;100bpm in one, bradycardia (100-109bpm) in five*, 110-119bpm in six*, ≥120bpm in five</td>
</tr>
<tr>
<td>Horigome et al, 2010 [27]‡</td>
<td>58</td>
<td>18</td>
<td>bradycardia in 15, AVB in 8, VT/TdP in 7 (overlapped in some cases)</td>
</tr>
</tbody>
</table>

†, The report included 9 cases described by Hofbeck et al [25]; ‡, The report included two cases reported by Hamada et al [9] and Horigome et al [14] in Table 1; *one case exhibited intermittent ventricular tachycardia; ND, not described; AVB, atrioventricular block; VT, ventricular tachycardia; TdP, torsade de pointes
Table 3. Five reports describing fetuses who underwent echocardiography because of cardiac abnormalities found incidentally during antenatal care and prenatal findings of patients with long QT syndrome.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study population</th>
<th>No. of patients (%)</th>
<th>Specified abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lin et al, 2004 [28]</td>
<td>18 with fetal BC (&lt; 100bpm)¶ (6 with AVB)</td>
<td>3 (17%)</td>
<td>BC, AVB, and VT in three</td>
</tr>
<tr>
<td>Cunco et al, 2006 [29]</td>
<td>306 with fetal arrhythmias (8 with AVB, 298 with isolated extrasystole*)</td>
<td>2 (0.7%)</td>
<td>BC and AVB in two</td>
</tr>
<tr>
<td>Hsiao et al, 2007 [30]</td>
<td>123 with fetal heart diseases† (25 with arrhythmia, 5 of the 25 had cardiac malformations)</td>
<td>3 (2.4%)</td>
<td>Arrhythmia in three</td>
</tr>
<tr>
<td>Hahurij et al, 2011 [31]</td>
<td>44 with fetal tachy- or bradyarrhythmia# (9 with AVB, 5 of the 9 had cardiac malformations)</td>
<td>2 (4.5%)</td>
<td>AVB in two</td>
</tr>
<tr>
<td>Eliasson et al, 2011 [32]</td>
<td>65 with fetal bradycardia &lt;110bpm (25 with AVB, 11 with sinus BC§)</td>
<td>4 (6.2%)</td>
<td>AVB in one and sinus BC in three</td>
</tr>
</tbody>
</table>

BC, bradycardia; AVB, atrioventricular block; VT, ventricular tachycardia; ¶, fetuses with transient bradycardia or with cardiac malformation were not included; *, including three with cardiac malformation; †, including 103 patients with cardiac malformation; #, cases with sinus tachycardia, transient sinus bradycardia, premature atrial or ventricular contractions and ventricular tachycardias were excluded; ‡, including 8 with cardiac malformations; §, including 3 with cardiac malformations.