Fetal Presentation of Long QT Syndrome – Evaluation of Prenatal Risk Factors: A Systematic Review

Satoshi Ishikawa^a Takashi Yamada^a Tomoyuki Kuwata^b Mamoru Morikawa^a
Takahiro Yamada^a Shigeki Matsubara^b Hisanori Minakami^a

^aHokkaido University, Sapporo, and ^bJichi Medical School, Shimotsuke, Japan

Key Words

Long QT syndrome • Prenatal risk factors • Fetal arrhythmia

Abstract

Objective: This systematic review evaluated the existence of risk factors for the fetal manifestation of long QT syndrome (LQTS). **Methods:** Prenatal cardiac findings suggestive of fetal LQTS were studied using 30 English literature reports extracted from the Pubmed database (1979 to December 2011) using the search terms 'long QT syndrome', 'fetal arrhythmia' and 'congenital heart disease'. **Results:** LQTS accounted for 15–17% of fetal bradycardias <110 bpm among fetuses with a normally structured heart. Of the patients with significant prenatal findings of LQTS, 17–35% exhibited a reduced baseline fetal heart rate (FHR) of 110–120 bpm on electronic cardiotocography. Other prenatal signs 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 may help to increase the perinatal diagnosis of LQTS.

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Introduction

Long QT syndrome (LQTS) is a hereditary cardiac disease characterized by a prolongation of the QT interval on basal electrocardiography and is associated with a high risk of life-threatening arrhythmias [1]. Since the identification, in 1995 and 1996, of the first 3 LQTS genes (*KNNQ1*, *KCNH2* and *SCNSA*) associated with the most frequently encountered LQTS variants (LQT1, LQT2 and LQT3), 7 other genes (*ANK2*, *KCNE1*, *KCNE2*, *KCNJ2*, *CACNA1c*, *CAV3* and *SCN4B*) have been confirmed or suspected of being associated with other LQTS variants (LQT4–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 110–120 bpm in utero, as shown in figure 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.

Fig. 1. Cardiotocogram obtained during labor showing a fetus with LGTS. This unpublished case was born to a mother with LQTS and showed a baseline FHR of 115 bpm during labor at 39 weeks of gestation. The infant was diagnosed as having LQTS soon after birth.

Methods

We identified a total of 30 English literature reports concerning the fetal presentation of LQTS using Pubmed (1979 to 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); 5 reports [23–27] described series of LQTS patients and included prenatal cardiac findings for some of the fetuses (table 2), and 5 reports [28–32] described series of fetuses, some of whom were subsequently diagnosed as having LQTS, for whom echocardiography examinations had been performed because of abnormal cardiac findings detected incidentally during antenatal care (table 3).

Results

Fetuses Suspected or Diagnosed as Having LQTS in utero

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 car-

diac 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 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

As expected, not all the fetuses with LQTS were suspected of having LQTS in utero (table 2). In a report by Villain et al. [23], at least 5 out of 15 neonates (33%) with a prolonged QT interval were documented as having bradycardia in utero, and 1 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

Table 1. Significant in utero cardiac findings in 21 fetuses reported in 20 previous reports: abnormal cardiac rhythms

Case No.	Authors, year	FH	GW	In utero	After birth	Outcome
1	Southall et al. [2], 1979	–	37	<100 bpm	2:1 AVB	neonatal death
2	Southall et al. [2], 1979	–	32	90 bpm	deafness	2 years, alive
3	Bharati et al. [3], 1985	–	ND	bradycardia	2:1 AVB	4 months, died
4	Presbitero et al. [4], 1989	ND	16	50 bpm	2:1 AVB	7 days, died
5	Trippel et al. [5], 1995	–	28	bradycardia, 2:1 AVB	2:1 AVB	neonatal death
6	Vigliani [6], 1995	+	38	100–110 bpm	decr. V	alive
7	Yamada et al. [7], 1998	+	27	110 bpm	VT	
8	Ohkuchi et al. [8], 1999	–	26	tachyarrhythmia (240 bpm)	TdP	alive
9 ^a	Hamada et al. [9], 1999	+	37	110 bpm, decr. V	no accel.	6 months, alive
10	Donofrio et al. [10], 1999	+	32	100 bpm, decr. V	no accel.	2:1 AVB, alive
11 ^a	Schneider et al. [11], 2005	+	30	100 bpm, decr. V	no accel.	alive
12	Collazos et al. [12], 2007	–	34	96 bpm	50 bpm	1 year, alive
13	Acherman et al. [13], 2008	–	28	arrhythmia, AVB	AVB, tachycardia	5 months, alive
14 ^a	Horigome et al. [14], 2008	–	28	105 bpm, AVB, VT	AVB, 50–70 bpm	alive
15	Simpson et al. [15], 2009	–	30	VT (220 bpm), hydrops	AVB	neonatal death
16	Takahashi et al. [16], 2009	–	38	VT (210–240 bpm)	TdP	ND
17 ^a	Fujimoto et al. [17], 2009	+	34	PE, 110–130 bpm		alive
18	Tomek et al. [18], 2009	–	26	100 bpm	AVB	6 months, alive
19	Furushima et al. [19], 2010	+	22	bradycardia	2:1 AVB	alive
20 ^a	Fukushima et al. [20], 2010	+	24	60 bpm, 2:1 AVB, ascites	VT, 2:1 AVB	alive
21	Komarlu et al. [21], 2011	+	34	>200 bpm, hydrops	TdP	alive

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 FHR variability on cardiotocography; GW = gestational week at presentation; ND = not described; no accel. = no acceleration

on cardiotocography; PE = pleural effusion; TdP = torsade de pointes; VT = ventricular tachycardia. A case reported by Green et al. [22] was not included in this table because bradycardia was noted during parturition only.

^a Cases that were diagnosed as having LQTS in utero.

Table 2. Five reports describing LQTS patients with prenatal cardiac findings in some

Authors, year	Patients with LQTS	Patients with fetal presentation	Rhythm disturbance in fetus
Villain et al. [23], 1992	15	5	bradycardia in 5; 1 with hydrops
Garson et al. [24], 1993	287	ND	bradycardia
Hofbeck et al. [25], 1997	46	9	bradycardia (70–100 bpm), AVB in 1; bradycardia (90–100 bpm) in 1; bradycardia (100–110 bpm) in 2; 110–120 bpm in 3; VT, AVB in 2
Beinder et al. [26] ^a , 2001	ND	17	bradycardia <100 bpm in 1; bradycardia (100–109 bpm) in 5 ^b ; 110–119 bpm in 6 ^b ; ≥120 bpm in 5
Horigome et al. [27] ^c , 2010	58	18	bradycardia in 15; AVB in 8; VT/TdP in 7 (overlapped in some cases)

ND = Not described; AVB = atrioventricular block; VT = ventricular tachycardia; TdP = torsade de pointes.

^a The report included 9 cases described by Hofbeck et al. [25].

^b One case exhibited intermittent ventricular tachycardia.

^c The report included 2 cases reported by Hamada et al. [9] and Horigome et al. [14] mentioned in table 1.

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 4 and ventricular tachycardia and AVB in 2. Of note, the remaining 3 patients (33%) exhibited a reduced FHR of 110–120 bpm [25]. Hofbeck et al. [25] did not mention the prenatal cardiac findings 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 6 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, ventricular tachycardia/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 3 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 20–30% of patients with LQTS exhibit initial signs suggestive of cardiac diseases in utero. Of those with prenatal findings, 17–35% exhibit a slightly reduced FHR of 110–120 bpm. However, whether the remaining 70–80% 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

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%, i.e. 298/306) had isolated extrasystoles that were transient and benign. The remaining 8 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 8 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 5 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

Table 3. Five reports describing fetuses who underwent echocardiography because of cardiac abnormalities found incidentally during antenatal care and prenatal findings of patients with LQTS

Authors, year	Study population	Patients with LQTS	Specified abnormality
Lin et al. [28], 2004	18 with fetal BC (<100 bpm) ^a (6 with AVB)	3 (17%)	BC, AVB and VT in 3
Cuneo et al. [29], 2006	306 with fetal arrhythmias (8 with AVB, 298 with isolated extrasystole ^b)	2 (0.7%)	BC and AVB in 2
Hsiao et al. [30], 2007	123 with fetal heart diseases ^c (25 with arrhythmia, 5 of the 25 had cardiac malformations)	3 (2.4%)	arrhythmia in 3
Hahurij et al. [31], 2011	44 with fetal tachy- or bradyarrhythmia ^d (9 with AVB, 5 of the 9 had cardiac malformations)	2 (4.5%)	AVB in 2
Eliasson et al. [32], 2011	65 with fetal bradyarrhythmia <110 bpm (25 with AVB ^e , 11 with sinus BC ^f)	4 (6.2%)	AVB in 1 and sinus BC in 3

In the study population, numbers of specified abnormalities are indicated in parentheses. BC = Bradycardia; AVB = atrioventricular block; VT = ventricular tachycardia.

^aFetuses with transient bradycardia or with cardiac malformation were not included.

^bIncluding 3 with cardiac malformation.

^cIncluding 103 patients with cardiac malformation.

^dCases with sinus tachycardia, transient sinus bradycardia, premature atrial or ventricular contractions and ventricular tachycardias were excluded.

^eIncluding 8 with cardiac malformations.

^fIncluding 3 with cardiac malformations.

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 5 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 3 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 1 with AVB and 3 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, 4 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 20–30% 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, 17–35% 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 15–17% of fetal bradycardias <110 bpm and 5.9–50% 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, al-

though 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 figure 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 well-being in many countries. Persistent fetal bradycardia <120 bpm reportedly occurs 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 and 115–120 bpm, respectively [own unpubl. 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]). Suspicions 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 or 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’.

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