Journal: REVIEW ARTICLE for Fetal Diagnosis and Therapy

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

Satoshi Ishikawa, Hokkaido Univ. e-mail; sat4@odn.ne.jp, corresponding author

Takashi Yamada, Hokkaido Univ. e-mail; yamataka@med.hokudai.ac.jp

Tomoyuki Kuwata, Jichi Medical School e-mail; kuwata@jichi.ac.jp

Mamoru Morikawa, Hokkaido Univ. e-mail; mmamoru@med.hokudai.ac.jp

Takahiro Yamada, Hokkaido Univ. e-mail; taka0197@med.hokudai.ac.jp

Shigeki Matsubara, Jichi Medical School e-mail; matsushi@jichi.ac.jp

Hisanori Minakami, Hokkaido Univ. e-mail; minasho@pop.med.hokudai.ac.jp

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 (*KNNQ1*, *KCNH2*, and *SCNSA*) associated with the most frequently encountered LQTS variants (LQT1, LQT2, and LQT3), seven other genes (*ANK2, KCNE1, 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

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

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]). 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, 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”.

REFERENCES

1. Crotti L, Celano G, Dagradi F, Schwartz PJ. Congenital long QT syndrome. Orphanet Journal of Rare Diseases 2008; 3: 18 doi:10.1186/1750-1172-3-18

2. Southall DP, Arrowsmith WA, Oakley JR, Mcenery G, Anderson RH, Shinebourne EA. Prolonged QT interval and cardiac arrhythmias in two neonates: sudden infant death syndrome in one case. Arch Dis Child 1979; 54: 776-9.

3. Bharati S, Dreifus L, Bucheleres G, Molthan M, Covitz W, Isenberg HS, Lev M. The conduction system in patients with a prolonged QT interval. J Am Coll Cardiol 1985; 6: 1110-9.

4. Presbitero P, Mangiardi L, Antolini R. Congenital long QT syndrome inducing 2:1 atrioventricular block: early detection in fetal life. Int J Cardiol 1989; 24: 109-12.

5. Trippel DL, Parsons MK, Gillette PC. Infants with long-QT syndrome and 2:1 atrioventricular block. Am Heart J 1995; 130: 1130-4.

6. Vigliani M. Romano–Ward syndrome diagnosed as moderate fetal bradycardia: a case report. J Reprod Med 1995 ; 40: 725–728.

7. Yamada M, Nakazawa M, Momma K. Fetal ventricular tachycardia in long QT syndrome. Cardiol Young 1998; 8: 119-122

8. Ohkuchi A, Shiraishi H, Minakami H, Eguchi Y, Izumi A, Sato I. Fetus with long QT syndrome manifested by tacharrhythmia: a case report. Prenat Diagn 1999; 19: 990-2.

9. Hamada H, Horigome H, Asaka M, Shigemitsu S, Mitsui T, Kubo T, Kandori A, Tsukada K. Prenatal diagnosis of long QT syndrome using fetal magnetocardiography. Prenat Diagn 1999; 19: 677-80.

10. Donofrio MT, Gullquist SD, O'Connell NG, Redwine FO. Fetal presentation of congenital long QT syndrome. Pediatr Cardiol 1999; 20: 441-4.

11. Schneider U, Haueisen J, Loeff M, Bondarenko N, Schleussner E. Prenatal diagnosis of a long QT syndrome by fetal magnetocardiography in an unshielded bedside environment. Prenat Diagn 2005; 25: 704-8.

12. Collazos JC, Acherman RJ, Law IH, Wilkes P, Restrepo H, Evans W. Sustained fetal bradycardia with 1:1 conduction and long QT syndrome. Prenat Diagn 2007; 27: 879-81.

13. Acherman RJ, Evans WN, Schwartz JK, Dombrowski M, Rollins RC, Castillo W, Haltore S, Berthody DP. Right ventricular noncompaction associated with long QT in a fetus with right ventricular hypertrophy and cardiac arrhythmias. Prenat Diagn 2008; 28: 551-3.

14. Horigome H, Iwashita H, Yoshinaga M, Shimizu W. Magnetocardiographic demonstration of torsade de pointes in a fetus with congenital long QT syndrome. J Cardiovasc Electrophysiol 2008; 19: 334-5.

15. Simpson JM, Maxwell D, Rosenthal E, Gill H. Fetal ventricular tachycardia secondary to long QT syndrome treated with maternal intravenous magnesium: case report and review of the literature. Ultrasound Obstet Gynecol 2009; 34: 475-80.

16. Takahashi K, Shiraishi H, Ohkuchi A, Matsubara S, Kuwata T, Yada Y, Izumi A, Suzuki M. Irregular peak-to-peak intervals between ascending aortic flows during fetal ventricular tachycardia in long QT syndrome. Ultrasound Obstet Gynecol 2009; 33: 118-20.

17. Fujimoto Y, Matsumoto T, Honda N, Tojo R, Furuya M, Kasai K, Saito S, Mochimaru F, Ishikawa Y. Prenatal diagnosis of long QT syndrome by non-invasive

fetal electrocardiography. J Obstet Gynaecol Res 2009; 35: 555-61.
18. Tomek V, Skovranek J, Gebauer RA. Prenatal diagnosis and management of fetal long QT syndrome. Pediatr Cardiol 2009; 30: 194-6.
19. Furushima H, Chinushi M, Sato A, Aizawa Y, Kikuchi A, Takakuwa K, Tanaka K. Fetal atrioventricular block and postpartum augmentative QT prolongation in a patient with long-QT syndrome with KCNQ1 mutation. J Cardiovasc Electrophysiol 2010; 21: 1170-3.
20. Fukushima A, Nakai K, Matsumoto A, Strasburger J, Sugiyama T. Prenatal diagnosis of polymorphic ventricular tachycardia using 64-channel magnetocardiography. Heart Vessels 2010; 25: 270-3.
21. Komarlu R, Beerman L, Freeman D, Arora G. Fetal and neonatal presentation of long QT syndrome. Pacing Clin Electrophysiol 2011 Mar 14. Doi: 10.1111/j.1540-8159.2011.03040.x.
22. Green DW, Ackerman NB, Lund G, Wright D. Prolonged QT syndrome presenting as fetal bradycardia. J Maternal–Fetal Med 1992 ; 1: 202–205
23.V illain E, Levy M, Kachaner J, Garson A. Prolonged QT interval in neonates: benign, transient, or prolonged risk of sudden death. Am Heart J 1992; 124: 194-7.
24. Garson A, Dick M, Fournier A, Gillette PC, Hamilton R, Kugler JD, Van Hare GF, Vetter V, Vick GW. The long QT syndrome in children: an international study of 287 patients. Circulation 1993; 87: 1866-72.
25. Hofbeck M, Ulmer H, Beinder E, Sieber E, Singer H. Prenatal findings in patients with prolonged QT interval in the neonatal period. Heart 1997; 77: 198-204.
26. Beinder E, Grancay T, Menedez T, Singer H, Hofbeck M. Fetal sinus bradycardia and the long QT syndrome. Am J Obstet Gynecol 2001; 185: 743-7.
27. Horigome H, Nagashima M, Sumitomo N, Yoshinaga M, Ushinohama H, Iwamoto M, Shiono J, Ichihashi K, Hasegawa S, Yoshikawa T, Matsunaga T, Goto H, Waki K, Arima M, Takasugi H, Tanaka Y, Tauchi N, Ikoma M, Inamura N, Takahashi H, shimizu W, Horie M. Clinical characteristics and genetic background of congenital long-QT syndrome diagnosed in fetal, neonatal, and infantile life: a nationwide questionnaire study in Japan. Circ Arrhythmia Electrophysiol 2010; 3: 10-7.
28. Lin MT, Hsieh FJ, Shyu MK, Lee CN, Wang JK, Wu MH. Postnatal outcome of fetal bradycardia without significant cardiac abnormalities. Am Heart J 2004; 147: 540-4.
29. Cuneo BF, Strasburger JF, Wakai RT, Ovadia M. Conduction system disease in fetuses evaluated for irregular cardiac rhythm. Fetal Diagn Ther 2006; 21: 307-13.
30. Hsiao SM, Wu MH, Jou HJ, Lee CN, Shyu MK, Shih JC, Hsieh FJ. Outcome for fetuses with prenatally detected congenital heart disease and cardiac arrhythmias in Taiwan. J Formos Med Assoc 2007; 106: 423-31.
31. Hahurij ND, Blom NA, Lopriore E, Aziz MI, Nagel HT, Rozendaal L, Frank PHA, Vandenbussche FPHA. Perinatal management and long-term cardiac outcome in fetal arrhythmia. Early Hum Dev 2011; 87: 83-7.
32. Eliasson H, Wahren-Herlenius M, Sonesson SE. Mechanisms in fetal bradyarrhythmia: 65 cases in a single center anlyazed by Doppler flow echocardiographic techniques. Ultrasound Obstet Gynecol 2011; 37: 172-8.

33. Wladimiroff JW, Stewart PA, Tonge HM. Fetal bradyarrhythmia: diagnosis and outcome. Prenat Diagn 1988;8:53–7.

34. Huhta JC. Uses and abuses of fetal echocardiography: a pediatric cardiologist's view. J Am Coll Cardiol 1998;31:451– 8.

35. Machado MVL, Grawford DC, Anderson RH, et al. Atrioventricular septal defect in prenatal life. Br Heart J 1988;59:352–5.

36. Southall DP, Richards J, Hardwick RA, Shinebourne EA, Gibbens GL, Thelwall-Jones H, de Swiet M, Johnston PG. Prospective study of fetal heart rate and rhythm patterns. Arch Dis Child 1980; 55: 506 – 511.

37. Reed Kl: Fetal arrhythmias, etiology, diagnosis, pathophysiology and treatment. Semin Perinatol 1989; 13: 294–304.

38. National Institute of Child Heath and Human Development Research Planning Workshop. Electronic Fetal heart rate monitoring: Research guidelines for interpretation. Am J Obstet Gynecol 1997; 177: 1385-90.

39. Minakami H, Hiramatsu Y, Koresawa M et al. Guidelines for obstetrical practice in Japan: Japan Society of Obstetrics and Gynecology (JSOG) and Japan Association of Obstetricians and Gynecologists (JAOG) 2011 edition. J Obstet Gynaecol Res 2011; 37: 1174-97.

40. Priori SG, Schwartz PJ, Napolitano C, Bloise R, Ronchetti E, Grillo M, Vicentini A, Spazzolini C, Nastoli J, Bottelli G, Folli R, Cappelletti D. Risk stratification in the long-QT syndrome. N Engl J Med. 2003; 348:1866-74.

41. Schiermeier S, van Leeuwen P, Lange S, Geue D, Daumer M, Reinhard J, Grönemeyer D, Hatzmann W. Fetal heart rate variation in magnetocardiography and cardiotocography--a direct comparison of the two methods. Z Geburtshilfe Neonatol. 2007; 211:179-84. (in Germany)

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.

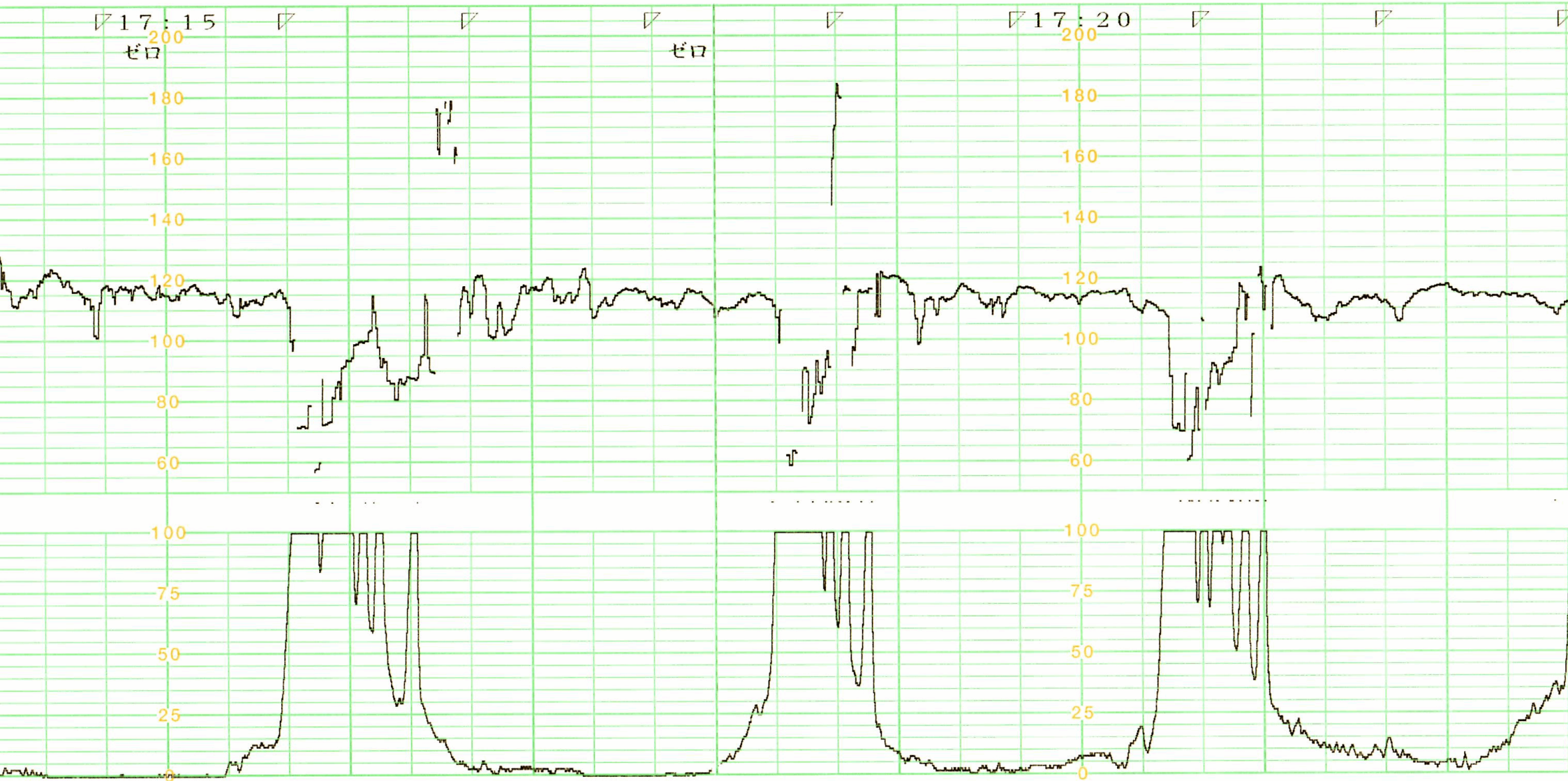
17:15
ゼロ
200
180
160
140
120
100
80
60
100
75
50
25
0
17:20
ゼロ
200
180
160
140
120
100
80
60
100
75
50
25
0

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

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

*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

Author, year [Ref. no.]	No. of patients with LQTS	No. of patients with fetal presentation	Rhythm disturbance in fetus
Villain et al, 1992 [23]	15	5	bradycardia in five, one with hydrops
Garson et al, 1993 [24]	287	ND	bradycardia
Hofbeck et al, 1997 [25]	46	9	bradycardia (70-100bpm), AVB in one bradycardia (90-100bpm) in one bradycardia (100-110bpm) in two 110-120bpm in three VT, AVB in two
Beinder et al, 2001 [26]†	ND	17	bradycardia <100bpm in one bradycardia (100-109bpm) in five* 110-119bpm in six* ≥120bpm in five
Horigome et al, 2010 [27]‡	58	18	bradycardia in 15 AVB in 8 VT/TdP in 7 (overlapped in some cases)

†, 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

Author, year [Ref. no.]	Study population (No. of specified abnormality)	Long QT syndrome	
		No. of patients (%)	Specified abnormality
Lin et al, 2004 [28]	18 with fetal BC (< 100bpm)¶ (6 with AVB)	3 (17%)	BC, AVB, and VT in three
Cuneo et al, 2006 [29]	306 with fetal arrhythmias (8 with AVB, 298 with isolated extrasystole*)	2 (0.7%)	BC and AVB in two
Hsiao et al, 2007 [30]	123 with fetal heart diseases† (25 with arrhythmia, 5 of the 25 had cardiac malformations)	3 (2.4%)	arrhythmia in three
Hahurij et al, 2011 [31]	44 with fetal tachy- or bradyarrhythmia# (9 with AVB, 5 of the 9 had cardiac malformations)	2 (4.5%)	AVB in two
Eliasson et al, 2011 [32]	65 with fetal bradyarrhythmia <110bpm (25 with AVB‡, 11 with sinus BC§)	4 (6.2%)	AVB in one and sinus BC in three

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.