

QT Interval in Newborns of Different Ethnic Origin: Usefulness of Neonatal ECG Screening

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The cost-effectiveness of neonatal electrocardiographic (ECG) screening has been questioned. The objective of this study was to establish normal values for the QT interval in newborns of different ethnic origin. Between 2005 and 2006, ECGs were obtained during the first 48 h of life from 1305 full-term newborns at the Hospital del Mar in Barcelona, Spain. The mean corrected QT interval (QTc) was 417.79 (28.47) ms. A QTc longer than 440 ms was observed in 240 newborns (18.33%). The frequency of a pathologic QTc in Spanish newborns was 17.9%, compared with 27.7% in those of Maghreb or Near Eastern origin ($P=0.016$), and 28.2% in those of Indian or Pakistani origin ($P=0.033$). The QTc may vary for genetic reasons. A routine neonatal ECG is advisable only in ethnic groups in which the QTc is lengthened, to help counter the greater risk of sudden death in these infants.

Key words: *Ion channel defects. Neonatal electrocardiogram. Ethnicity.*

Intervalo QT en recién nacidos de diferente origen étnico: utilidad del cribado con ECG neonatal

La rentabilidad del cribado electrocardiográfico neonatal está en discusión. El objetivo es conocer los valores normales del intervalo QT en recién nacidos de diferentes orígenes étnicos. Durante 12 meses entre 2005 y 2006 se realizó un ECG a 1.305 neonatos a término en el Hospital del Mar (Barcelona), en las primeras 48 h de vida. El intervalo QTc medio fue 417,79 \pm 28,47 ms. Se halló un QTc > 440 ms en 240 (18,33%) neonatos. Se encontró un 17,9% de QTc patológicos en neonatos autóctonos, frente a un 27,7% en el grupo de Magreb y Próximo Oriente ($p = 0,016$) y un 28,2% en el grupo de India-Pakistán ($p = 0,033$). El intervalo QTc puede ser diferente por causas genéticas. Sería recomendable hacer un ECG neonatal sólo en los grupos étnicos con QTc más largos, para evitar un posible mayor riesgo de muerte súbita del lactante.

Palabras clave: *Canalopatías. Electrocardiograma neonatal. Etnia.*

INTRODUCTION

Long QT syndrome (LQTS) is produced by alterations in the genes that encode different ion channels (mainly the potassium and sodium channels) that lead to potentially malignant cardiac arrhythmias.¹ They are included among the so-called channelopathies, and genetic studies have enabled us to identify them as entities in their own right.² Some of them may be suspected on the basis of the surface electrocardiogram (ECG), although, given the differences

in penetrance, there are patients with these disorders and high risk of sudden death in whom they may be masked. The channelopathies most easily recognized by means of ECG, in addition to LQTS, are the Brugada syndrome (BS), which affects the sodium channel, and the short QT syndrome (SQTS), which affects the potassium channel. Some authors attribute a percentage of sudden infant death syndrome (SIDS) to these channelopathies.³

The prevalence of these entities in Spain is unknown. In the case of LQTS, there is a large-scale Italian registry⁴ including more than 34 000 newborn infants that established a cutoff point for a normal QT interval corrected for heart rate (QTc) at 440 ms, with a prevalence of 0.9 per 1000 newborns. With respect to BS, there are no data on Japanese infants, but the prevalence among adults is 146.2/100 000 population.² Finally, the SQTS was identified recently,⁵ and its prevalence among newborn infants is also unknown.

The purpose of this study is to assess the prevalence of these channelopathies on the basis of changes in the

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Ethnic Origin of the Newborn Infants and the QTc Interval

| Ethnic Origin | Newborns, No. (%) | QTc, Mean (SD), ms | QTc >440 ms, Mean (95% CI), % | QTc >470 ms, Mean (95% CI), % |
|----------------------------|-------------------|--------------------|-------------------------------|-------------------------------|
| Spanish | 496 (38) | 416.27 (28.34) | 17.9 (11.3-24.1) | 3.8 (0.5-7.1) |
| African-Caribbean | 51 (3.9) | 417.75 (27.07) | 15.7 (0-35.2) | 5.9 (0-18.5) |
| Indian-Pakistani | 78 (5.9) | 423.24 (34.61) | 28.2 (8.6-47.8) | 9 (0-21.4) |
| Chinese | 40 (3.1) | 418.08 (21.17) | 10 (0-28.2) | 2.5 (0-12) |
| Eastern European | 42 (3.2) | 416.46 (28.72) | 9.5 (0-26.9) | 4.8 (0-17.4) |
| Southeast Asian-Philippine | 63 (4.8) | 416.23 (27.78) | 11.1 (0-26.3) | 4.8 (0-15.1) |
| Central and South American | 201 (15.4) | 418.89 (24.77) | 18.4 (7.9-28.9) | 4 (0-9.3) |
| Maghrebi and Near Eastern | 119 (9.1) | 424.81 (31.95) | 27.7 (12-43.5) | 10.9 (0-21.9) |
| Gypsy | 58 (4.4) | 419.18 (27.41) | 20.7 (0.3-41.1) | 1.7 (0-8.3) |
| Others | 14 (1.1) | 411.38 (34.45) | 16.1 (0-47.1) | 1.4 (0-31.4) |
| Mixed | 143 (10.9) | 414.46 (29.29) | 13.2 (4.3-27.9) | 6.7 (0-5.2) |

CI: confidence interval; SD: standard deviation.

neonatal ECG in a cohort of consecutive newborns from a hospital in a multiethnic city like Barcelona, Spain.

METHODS

Between November 2005 and November 2006, a consecutive series of full-term newborn infants underwent ECG at Hospital del Mar in Barcelona within the first 48 hours of life and with the infant in a tranquil state. The ECG was interpreted independently by 2 different cardiologists in order to avoid inter-observer variation. An approved Trim II electrocardiograph (Philips, Inc., Eindhoven, The Netherlands) was utilized. It was connected to a computer, in which the data were then analyzed, that allowed up to an 8-fold amplification of the recording and the use of markers for the correct measurement. The PR, RR, and QT intervals were measured in lead II and the QTc interval corrected for heart rate was calculated according to the Bazett formula, following the European guidelines for the interpretation of the neonatal ECG.⁶ In cases of discrepancies of over 10 ms, the value was agreed upon by consensus. The following variables were also recorded: birth weight, sex, water-electrolyte imbalances, or drugs taken by the mother that could have lengthened the QTc interval, and the ethnic group of the parents, according to the classification of Black.⁷ When the parents did not belong to the same ethnic group, the infants were included in a mixed group.

Pearson's χ^2 test (or Fisher's exact test) was employed for the differences in frequencies between the groups. The results were considered to be significant when the *P* value was less than .05 ($\alpha=.05$). One-factor ANOVA was utilized, with correction using Tukey's test for multiple comparisons, to determine whether

there were differences among ethnic groups. The statistical analysis was carried out with the SPSS v14 statistical software package (SPSS, Inc., Chicago, Illinois, United States).

RESULTS

Of the 1308 ECGs recorded during the study period, 3 were excluded from the analysis due to the suboptimal quality of the recording. The mean birth weight of the 1305 newborns studied was 3260.97 (938.59) g; 674 (51.5%) were boys. Eleven different ethnic groups were identified. The mean heart rate was 133.15 (18.34) beats/minute. There were no ECG recordings suggestive of BS or showing a QTc interval less than or equal to 300 ms, a sign of SQTs. The measurement of the QTc interval followed a normal distribution, with a mean of 417.79 (28.47) ms. There were no sex-related differences. Nor were there differences among the ethnic groups (Table). The PR interval was 109.27 (9.76) ms. None of the ECG detected congenital atrioventricular block or preexcitation syndrome.

In the analysis of the percentage of patients with prolonged QTc, 18.33% of the newborn infants had a QTc greater than or equal to 440 ms, and differences were observed among the ethnic groups: the incidence was 17.9% in Spanish newborns, 27.7% in those in the Maghrebi and Near Eastern group (*P*=.016), and 28.2% in the Indian-Pakistani group (*P*=.033). There were no differences when compared with the Central American and South American group: 18.4% (*P*=.91).

When the same criteria utilized in the large-scale Italian registry were applied, which defined prolonged QTc as an interval exceeding the 97.5 percentile in the largest group, in this case, that of the Spanish infants, the value

was 471.68 ms. With this new cutoff point, 4.52% of the sample still had a prolonged QTc, and differences between ethnic groups remained only between the Spanish infants (3.8%) and the Maghrebi and Near Eastern group (10.9%; $P=.04$), and just barely failed to reach statistical significance in the Indian-Pakistani group (9%; $P=.07$).

DISCUSSION

The results show that the mean QTc interval is slightly longer than that reported in the registry of Schwartz et al,⁴ probably because their study included infants of a single ethnic origin. In reality, the results of this study are in closer agreement with the values obtained in adults, with a cutoff point between a normal and an abnormally prolonged QTc of 470 ms.

The ethnic differences observed probably reflect genetic differences, although they may not necessarily be associated with a disease. Moreover, the differing degrees of penetrance make it difficult to rule out the possibility that QTc values within normal range in reality correspond to affected patients.⁸ On the other hand, Ackerman et al⁹ demonstrated the existence of differences among 4 ethnic groups in the United States (Asians, blacks, Hispanics, and whites) with regard to anomalies affecting the potassium channels implicated in LQTS.

The fact that 59 newborn infants had abnormally long QTc intervals does not necessarily indicate that they have the disease.^{4,10} In fact, a follow-up ECG was performed in this group 1 month after birth and only 2 of them maintained QTc intervals longer than 470 ms. Nevertheless, the possibility that some of them might have a low degree of penetrance of the disease can not be ruled out either, and this would make them sensitive to sodium or potassium channel blocking drugs, after which the disease would be expressed phenotypically.¹¹ On the other hand, the QTc interval may be abnormally prolonged during the first 48 hours after birth in infants with low penetrance due to alterations in the development of the autonomic nervous system, and come to be corrected during the first month of life.^{4,10} If even 1 of these newborns has the disease, the prevalence in this study approaches that reported in other series.⁴

The absence of infants with an electrocardiographic pattern of BS reflects the reality of a disease with a changing ECGs and, although some children were included in the initial description of BS, it is much more frequently detected in adults.¹² Thus, the performance of neonatal ECG would only be indicated in infants with a family history of BS or of sudden death.

With respect to SQTs, no QTc interval shorter than 300 ms was recorded, although the cutoff point initially reported may have been extremely short, and other authors⁵ have recommended a cutoff value of 340 ms.

While it is true that SIDS has only been attributed to the presence of LQTS in, at most, 10% of the cases,¹³

according to the postmortem study of Ackerman et al,¹⁴ around 30% of the mutations implicated in the case of LQTS alone remain unknown, and their identification could increase this percentage.

Finally, this study lends support to the performance of neonatal ECGs in the screening of newborn infants with possible electrocardiographic alterations.¹³ Although this issue has generated controversy among different groups,^{13,15} given that the performance of neonatal ECGs is inexpensive and noninvasive, its use should be recommended, not universally, but selectively,¹⁴ at least in certain ethnic groups (Maghrebi and Near Eastern, as well as Indian and Pakistani) or if there is a family history of sudden death or family members with a channelopathy demonstrated by genotyping. This ECG should be carried out at the age of 1 month, probably in primary care.

On the other hand, although the prevalence of SIDS is also known to be low, if the neonatal ECG is suggestive of LQTS, this finding should be confirmed by means of a genetic study and early treatment should be initiated.^{1,10,16}

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