Letters to the Editor

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Cost effectiveness of neonatal ECG screening for the long QT syndrome

We read with interest the recent article by Quaglini et al.1 in the European Heart Journal, concerning cost efficacy of proposed neonatal ECG screening for long QT syndrome. We all agree that undiagnosed cases of LQTS likely play a role of as yet undetermined magnitude in sudden death in very young children, including sudden infant death syndrome. A similar study has been previously published.2 We have some concerns, however, which we would like to voice.

We are sceptical concerning the issue of costs related to the process of establishing a correct diagnosis. The cost of a cardiologist visit is likely underestimated, and the contention that there are no costs associated with training adult cardiologists to read neonatal ECGs is unrealistic. We are most concerned, however, about the very real implications of making an incorrect diagnosis leading to inappropriate treatment.

Neonatal screening has been an area of active discussion and health policy deliberation in the paediatric community for decades. Unfortunately, as a screening test for LQTS, the ECG is disappointing when compared with other accepted neonatal screening tests. For example, congenital hypothyroidism (CH) has a similar incidence to LQTS (∼1/1800) and neonatal screening has a sensitivity of ∼95%, a specificity of 99.9%, and a positive predictive value of 29%. In a recent review of 430 764 infants screened from the Netherlands,3 this amounted to 772 positives of which 224 were true CH patients. In this case, however, evaluating infants with positive screening tests to rule out the disease is fairly simple—a repeat blood test.

For LQTS, on the other hand, there is no comparable, simple, and definitive follow-up test to rule out the disease in an asymptomatic individual with an initially prolonged QT. Genetic testing is far too expensive for wide application and is certainly not comprehensive enough to allow one to rule out the diagnosis of LQTS. Paediatric cardiologists and electrophysiologists face the problem of asymptomatic QT prolongation regularly, and the process is typically time consuming and anxiety provoking for the physicians and families concerned, as it involves a careful study of family history, ECGs obtained from parents and other relatives, and often other testing. Accepting the authors’ figures of an incidence of 1/2500, a positive rate of 1% for a QTc cutoff of 470 ms, and a sensitivity of 80% yields a positive predictive value of only 3%. In the USA, with a birth rate of 4 million/year, one would predict a cohort of 1280 LQTS patients hiding among 40 000 infants with prolonged QT intervals, each and every year. It is not clear that the resources exist to manage such an onslaught of patients in whom the possibility of a life-threatening illness has been raised. Inevitably, a significant number of normal infants would be treated for long QT syndrome, and such treatment involves more than just beta-blocker therapy with its potential side effects. One can expect a lifelong restriction from competitive physical activity, difficulties obtaining life insurance, avoidance of a host of medications, and the potential for more invasive therapies such as ICD implantation. These costs may be difficult to quantify but are significant and not addressed in the article by Quaglini et al. Most distressingly, the psychological and emotional impact on the family of a child incorrectly labelled as having LQTS is ignored in the authors’ analysis. We support the focused use of ECGs in subjects for whom the prior probability of arrhythmic risk is elevated (such as those with a positive or suggestive family history), but we cannot support a recommendation for mass screening in the general population. Currently, at least half of LQTS patients are diagnosed by familial screening, and another large fraction of patients are diagnosed by ECG after an initial seizure or faint. We would be very interested in a recalculation of the cost efficacy of ECG screening in which the realistic costs of initial screening are included, as well as the downstream costs associated with investigating LQTS in all false positives and those costs associated with unnecessary lifelong treatment. A comparison of the two approaches, mass screening vs. focused screening, could then be assessed.

References

forgotten (or never properly learnt) how to read a neonatal or paediatric ECG, this is their problem. They should go back to their books and study. The State will not pay for their additional instruction (taxes to attend medical schools in Italy are negligible and formal training to become a certified specialist in cardiology is paid by the State, for those admitted). Furthermore, the European Society of Cardiology has published specific Guidelines exactly for this purpose. If adult cardiologists will follow them, they will identify most problems. Additional voluntary training will be useful and possible, at no cost.

It is true that no single test exists to rule out LQTS in general and specifically in an asymptomatic individual with an initially prolonged QT interval, but diagnostic defeatism is unwarranted. We, as cardiologists, have been able to diagnose and exclude (with a reasonable degree of medical certainty) LQTS well before the advent of molecular cardiology. If an asymptomatic child (say, 3 years old) without a family history of LQTS and with a normal QT interval, confirmed in repeated ECGs during the last couple of years, comes to us and the mother says that in the first month of life the infant had a QT prolongation (subsequently vanished and never observed again), who among us would diagnose LQTS and recommend beta-blockers? No one, if competent. Thus, the risk of an occasional and transient QT prolongation in the first month of life leading to a ‘perpetual’ diagnosis of LQTS with life-long medical treatment (and with the attendant catastrophic scenarios imagined by Van Hare et al.) is almost non-existent if the cardiologists use knowledge and common sense.

Van Hare et al. rightly call attention to the issue of false positives, but correct quantifications are essential. They quote our figures but make a gross error as they refer to ‘a positive rate of 1% for a QTc cut-off of 470 ms’. The findings we reported, based on 33 000 ECGs analysed prospectively, were 0.9/1000 (almost 1/1000). Actually, the now complete analysis on the 45 000 infants enrolled shows that the prevalence of infants with a QTc >470 ms has further decreased to 0.7/1000. Thus, the magnitude of the problem of infants with markedly ‘prolonged QT interval’ is quite different from the one portrayed by Van Hare et al.

In our analysis the rate of 1% has been assumed for the false positives at the first ECG (QTc >440 ms). Probably, the label ‘Markov model for inappropriate therapy’ in Figure 1, where the decision tree is represented, was not fully appropriate and may have generated misinterpretations for which we apologize. In fact, the entire model considers the continuation of the diagnostic procedures. The 1% false-positive rate at first ECG decreases to 0.03% (3/10 000) when considering the entire diagnostic process (two or more ECGs, Holter, family history, and so on), as recommended. Owing to space limitation, we could not include a clarifying figure depicting the final phase of the Markov process related to the false-positive cases. Our model obviously takes into account the cost of every additional test done for false-positive individuals and for the treatment of the 0.03% among them who will start beta-blockers. Moreover, the Markov process considers that 80% of the false-positive children under treatment will stop the therapy within few years.

Using our correct figures for prevalence (1/2500), sensitivity (80%), and false-positive rate (0.03%) for the entire diagnostic process, the positive predictive value calculated applying Bayes’ rule is 51.7%. This is quite at variance with the positive predictive value ‘of only 3%’ incorrectly calculated by Van Hare et al. (in their calculation, there must have been an additional error besides the 1% vs. 1/1000). If one considers the overall financial national burden, in Italy the entire screening on 550 000 newborns would cost ~23 million Euros/year.

Van Hare et al. are expert paediatric cardiologists. They would not take a QTc of 450 ms in a 3-week-old infant as a sign of LQTS and initiate beta-blocker therapy for life. Neither would we. The European Guidelines, to which two leading American paediatric cardiologists (Dr A. Garson, Jr and Dr V.L. Vetter) have significantly contributed, have been careful in outlining the sequence of steps to be followed once the first ECG has revealed a QTc exceeding 440 ms. We truly recommend that Van Hare et al., as anyone interested in this issue, read them carefully. Some points are critical. If the second ECG is normal, the case is dismissed; if it shows a QTc between 440 and 470 ms, then several specified checks, including family history, are suggested and if negative, ‘no treatment is currently recommended’. We did specifically mention that ‘even in infants with a very prolonged QTc in the first month of life, the ECG may normalize’ and that ‘if subsequent ECGs and diagnostic procedures do not confirm the presence of LQTS, it is logical to progressively withdraw therapy’. The bottom line is that a careful adherence to the Guidelines will lead to a very small number of infants treated with beta-blockers and most of them will truly need therapy.

Their final point addresses ‘the psychological and emotional impact on the families incorrectly labelled as having LQTS’. First, this applies to only three infants per 10 000 and for the 2-3 years necessary to rule out LQTS (as mentioned earlier). For those with a QTc between 440 and 470 ms at the first ECG, using the procedure mentioned earlier and a cautious approach, anxiety can be reduced to a minimum. In any case, however, one has to look at the counterpart. We have seen, over the last 30-35 years, the eyes of too many parents who lost their infants because of undiagnosed LQTS to be swayed by ‘some transient anxiety’. Any choice carries its errors, but there is no remedy for sudden death.

‘Mass screening’ looks like mandatory screening. We never thought of that. We just recommend that our countries make available a service of neonatal ECG screening for the interested families. What we consider, however, a precise responsibility of neonatologists and physicians is to inform the families of a newborn about the existence of LQTS, its prevalence, its dangers even in the first year of life, its effective treatments, and the fact that it can be diagnosed or suspected by a simple ECG. At that point, it will be the free choice of individual families to have an ECG made or not. In some countries, a free screening may be offered, in others not. What matters to us is that the parents are provided with the essential information to make a reasoned choice. We believe that this approach will contribute to reduce the number of avoidable deaths due to LQTS in infancy or later on in life.

Van Hare et al. ‘cannot support a recommendation for mass screening’, a legitimate position. If this position, however, was based on the grossly incorrect figures and views reported in their letter (1% of infants with QTc >470 ms, a large number of false positives diagnosed with LQTS and treated for life with beta-blockers), perhaps our reply may help them to reconsider. When confronted with the correct facts, we trust that they will recognize that proper information on LQTS should be given to the parents of a new baby and that the consideration of a service, available to all families, to provide an ECG during the first month of life—at least for those countries endowed with an NHS—is not without foundation.

References

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Myopathic background of non-compaction in children

With interest, we read the article by Lilje et al.1 on the clinical findings and outcome of 66 paediatric patients with left-ventricular hypertrabeculation (LVHT), also known as left-ventricular non-compaction. The study raises concerns.

Though repeatedly mentioned, the non-compaction hypothesis is insufficient to explain the pathogenesis of LVHT, since it does not explain acquired LVHT developing during life-time.2 To explain acquired LVHT, pathogenetic concepts other than the non-compaction hypothesis have been proposed.2

Acquired LVHT is also the reason why ‘non-compaction’ should be replaced by a more descriptive term.

Concerning the mortality of LVHT, only few data are available. Among 86 adult LVHT patients, we calculated a mortality of 5.3% per year. Predictors for mortality in this study were advanced age, the presence of a neuromuscular disorder, exertional dyspnoea, oedema, heart failure, left anterior hemiblock, and reduced systolic function.3

The genetic background of LVHT is far more heterogeneous than reported. LVHT was not only associated with mutations in G4.5, cypher/ZASP, DTNA (dystrobrevin), and lamin A/C genes, but also with mutations in GAA, DMPK, AMPD1, mitochondrial, frataxin, CSX, and PMP22 genes.3,4 LVHT has been also found in Turner syndrome, Ohtahara syndrome, Roifman syndrome, Noonan syndrome, nail-patella syndrome, Melnick-needles syndrome, MIDAS syndrome, DiGeorge syndrome, congenital adrenal hyperplasia, distal 4q-trisomy/distal 1q-monosomy, distal 5q-deletion, trisomy-11, and trisomy-13.4 Because of the heterogeneous genetic background and the familial occurrence of LVHT, it should be mentioned how many patients were related to each other and whether a family screening had been carried out.

There is no consensus on the definition of LVHT.3 The authors contribute to this confusion by introducing a further echocardiographic definition, which additionally measures the X/Y ratio at the level of papillary muscles and the mitral valve, locations where LVHT is usually difficult to distinguish from normal cardiac structures. Was the ratio measured at end systole or end diastole? How often was LVHT located at the septum? How were false tendons and aberrant bands discriminated from LVHT?

Also, the distinction between isolated and non-isolated LVHT does not contribute to the understanding of LVHT. Is LVHT with ECG abnormalities or relative tricuspid or mitral insufficiency isolated or non-isolated? Which cardiac abnormalities were found among the non-isolated cases?

Basic information is not provided. Were any abnormalities found on blood tests? Which ECG abnormalities were found? Which were the indications for echocardiography? How many patients had a reduced systolic function? How many had dilated or wall-thickened left ventricles? Were coronary abnormalities found? Which cardiac therapy was given? How many patients were lost to follow-up? Did LVHT localization or morphology change during follow-up?

It is mentioned that the echocardiograms were evaluated by two independent investigators. How often did they disagree on the diagnosis? What happened if they disagreed? In up to 80% of patients, LVHT is associated with neuromuscular disorders such as dystrophinopathies, dystrobrevinopathies, myotonic dystrophy, zaspathies, myoadenylate-deaminase deficiency, Charcot–Marie–Tooth disease, mitochondrial disorder, Barth syndrome, Friedrich ataxia, or Pompe’s disease.4 Were patients seen by a neurologist and how many had neuromuscular disorders?

Overall, a common definition of LVHT for paediatric and adult LVHT is warranted. Furthermore, more clinical information about paediatric LVHT patients is required to compare them with adult cases.

References


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Myopathic background of non-compaction in children: reply

We appreciate the interest of Finsterer et al.1 in our article.1 Unfortunately, not all of their numerous concerns can be addressed here, some of which have been raised and replied to previously.

(i) Chin et al.2 were among the first to describe NCVM. It was considered to result from an arrest in the process of embryonic myocardial compaction. There is much evidence, including excellent work on animal models, to support this pathogenic concept and the term NCVM.3 Both have been widely accepted. The evidence for ‘acquired’ NCVM is scarce. A few reports, mostly by Finsterer et al., have been published on single patients with ‘acquired’ NCVM. Although there is a variety of reasons for secondary left ventricular hypertropanecardulation.