Focused Perspective

Stillbirths, Sudden Infant Deaths, and Long-QT Syndrome
Puzzle or Mosaic, the Pieces of the Jigsaw Are Being Fitted Together

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Stillbirths contribute substantially to perinatal mortality in developed countries. Their prevalence ranges between 4 and 6 per 1000 births. Despite careful investigation, at least 25%, and possibly 50%, remain unexplained. Another mysterious cause of early sudden death is represented by sudden infant death syndrome (SIDS), which is still the leading cause of mortality during the first year of life. Finally, a relatively large number of sudden deaths in the young (infants, children, and teenagers) is due to long-QT syndrome (LQTS).

Are these entities completely unrelated or is there a link between them, such that the latter might be a contributor to the former? As a matter of fact, this specific hypothesis has already been proposed. Its interest lies in the fact that, beyond the scientific and conceptual implications, if proven correct it could offer an opportunity to prevent those fetal or infant deaths sharing the same genetic and arrhythmogenic mechanism.

The value of scientific hypotheses lies in the possibility of testing them to be either dismissed or confirmed, advancing knowledge. The relatively small number, in absolute terms, of stillbirths and SIDS makes prospective studies difficult, albeit not impossible. Thus, to a large extent, the scientific community still has to rest on the evidence provided by well-documented case reports which sometimes can offer unexpected insights and can represent proof of concept. One such example is represented by the article by Miller et al in this issue of Circulation.

Their study was prompted by what initially appeared just one more case of LQTS presenting in utero with tachyarrhythmias and 2:1 atrioventricular block requiring an emergency cesarean section. A number of these cases have been reported, as previously reviewed. This is a very malignant form of LQTS that is difficult to manage, and at 5 months of life an orthotopic heart transplant became necessary and was successful. The mother appeared unaffected and, in the absence of paternal data, this raised the possibility of a de novo mutation, a not infrequent occurrence in LQTS.

Thus far, despite its clinical importance, there was not much of scientific interest. What followed, however, was significant. Someone among the authors realized, by the time honored careful assessment of clinical history, that the mother had already had a pregnancy that ended in stillbirth at 28 weeks. The likelihood of the same disease, LQTS, being involved in the 2 troubled pregnancies was clearly contradictory to the idea of a de novo mutation. At this point molecular screening was performed.

The molecular abnormality of the living infant was found to be a point mutation (R1623Q) in SCN5A, the gene encoding the cardiac sodium channel. The mutations on SCN5A that are associated with LQTS are expected to lengthen the QT interval, further prolong QTc at low heart rates and to respond to sodium channel blockers with QTc shortening, and to favor occurrence of lethal arrhythmias either at rest or during sleep. DNA sequencing of maternal DNA did not identify the mutation; however, prompted by an ambiguous result with the initial single-strand conformational polymorphism analysis, the curiosity and determination of the investigators led them to a sophisticated analysis which eventually resulted—after testing several different maternal tissues—in the diagnosis of maternal somatic mosaicism for the R1623Q mutation. During the course of the investigation, the mother had a third pregnancy that similarly ended in stillbirth at 28 weeks. Molecular screening of DNA extracted from fetal cord blood revealed the presence of the same mutation.

A mosaic is an organism that consists of cells of more than 1 genotype. The strict definition requires that the genotypically different cells all derive from a single zygote. If the term is used more broadly to describe any organism of mixed genotype, then chimeras—organisms that consist of cells derived from more than one individual, usually of different genotype—would be a subset of mosaics. Germline mosaicism can explain unusual patterns of inheritance, as when healthy parents have 2 or more children with a dominantly inherited disease. There are 2 possibilities for such a mosaicism to occur. The first is that the mutation occurs in a germ cell that continues to divide. The second, and probably more relevant from a clinical standpoint, is that the mutation occurs very early in a somatic cell before the separation to germinatal cells and is therefore present in both somatic and germinatal cells. De novo mutations may be present as mosaics and their frequency is probably higher than hitherto anticipated. When the carriers of a mosaicism are asymptomatic, the phenomenon can be suspected and identified only when they are the parents of more than one affected patient. Another major reason for the likely underestimation of the frequency of mosaicism in somatic cells is the fact that...
the degree of mosaicism is different in different tissues. Not infrequently, mosaicism is not detectable in white blood cells, but in fibroblasts. The examination of several different tissues may increase the probability of detecting mosaicism; for example, the mutation may be absent in white blood cells and present in other tissues, such as muscle, buccal smear, or hairs.23,24 This careful search is exactly what Miller et al14 did, as they found mutant DNA not only in some circulating lymphocytes but also in buccal epithelium and in skin fibroblasts. Until very recently, germline mosaicism was still unknown in cardiac diseases.23 Apparently, the first case of female germline mosaicism without somatic mosaicism was described by Forissier et al25 in familial hypertrophic cardiomyopathy. The present case by Miller et al14 suggests strongly that also in cardiology greater attention has to be paid to this intriguing possibility and that cardiologists facing puzzling inheritance patterns, such as more than one offspring of apparently healthy parents suffering from a dominant genetic disorder, should suspect the presence of mosaicism. It should go without saying that this process becomes logical only after the failure to find the mutation in one parent, as the existence of low penetrance—which explains the presence of mutation-carriers without the clinical phenotype—has already been demonstrated in LQTS.26

The article by Miller et al14 has both merit and significance. The merit lies in one feature essential in scientific research, namely the curiosity and drive that push clinical investigators beyond sheer diagnosis and treatment of their patients and lead them toward the search for explanation and understanding of puzzling medical cases. Much can be learned from this approach, and the very beginning of the knowledge on LQTS was branded just in such a way. The impressive evolution in the understanding of LQTS owes much indeed to the first and very thorough description of the disease made in 1957 by Professor Anton Jervell and his associate Dr Fred Lange-Nielsen.27 There are not many instances of a single case report so critical for the subsequent development of knowledge on a given disease. Indeed, when in 1958 Levine and Woodworth rushed to publish their own case,28 they admitted having observed their patient several years earlier but not having it reported because they had feared that “these extraordinary features” might have been regarded as just coincidental, an oddball.

The study by Miller et al14 is also significant because it has implications for a better understanding of the mechanisms involved in genetic transmission of cardiovascular disorders and for the strategies available for an early identification of infants affected by LQTS, be they still in utero or newborns. By suggesting a more critical approach to cases apparently due to de novo mutations, it may unmask cases actually due to mosaicism, with important implications for genetic counseling, given the obviously different probability of a recurrence.

There is scattered but growing evidence indicating that, as earlier proposed,11,12 a number yet to be defined of stillbirths is actually due to LQTS. Hoornjte et al29 reported in a consanguineous family the occurrence of a stillbirth followed by the premature birth of an infant in distress with 2:1 functional atrioventricular block and a QTc of 580 ms. Molecular analysis revealed that both the surviving child and the stillborn brother were affected by LQTS as they were carriers of a homozygous mutation leading to truncation of the HERG protein. Both parents, carriers of the heterozygous mutation, were asymptomatic and with a borderline QTc value. This observation was the consequence of close monitoring of the pregnancy that followed the occurrence of the stillbirth.

Similarly, Beinder and associates30 extended their observations on sinus bradycardia and ventricular arrhythmias in fetuses as intrauterine manifestations of LQTS31 and reported a case of an apparently healthy woman with an uneventful pregnancy terminated at the 40th week because of fetal arrhythmia. After the cesarean section, a boy was delivered with a QTc of 540 ms and episodes of torsades de pointes ventricular tachycardia. The child died few hours later. The authors made the meaningful observation that, as intrauterine death was imminent, if the fetus had indeed died in utero before the diagnosis of ventricular arrhythmia, this death, after routine postmortem examinations, would have been regarded as one more unexplained stillbirth and the diagnosis of LQTS would have never been suspected. The present study by Miller et al14 further points to the importance of fetal monitoring during the third trimester. It is important here to remember that LQTS is life threatening but is by no means always lethal, and with properly aggressive therapies it is possible to save most of the infants diagnosed as affected immediately after an emergency cesarean section.

It should surprise no one that a disease that kills young adults and children can do so also shortly before and after delivery. As a matter of fact, after our first reports of a near-miss35 and of an actual victim36 of SIDS that turned out to be due to apparently de novo mutations on 2 genes responsible for LQTS, SCN5A and KCNQ1, several other somewhat similar cases are now surfacing in the literature.34,35 What they have in common is that when an ECG was made, the QT intervals were grossly prolonged. The main difference between them concerns the fact that although some cases presented first with cardiac symptoms secondary to arrhythmias that led quickly to the diagnosis of LQTS,33,34 others31,32 had unexpected cardiac arrest as first manifestations and without molecular diagnosis would have been labeled as SIDS. As discussed here and prompted by study by Miller et al,14 this chain of events can well apply to a number of stillbirths.

The risk of sudden cardiac death for the infants carrying these life-threatening genetic mutations may become manifest at birth, or later on during childhood, or even afterward. The availability of very effective therapies10,20,21,36,37 makes it imperative that efforts should not be spared in trying to ensure early diagnosis of most infants born affected by LQTS. The simplest and most logical approach is that of performing an ECG during the first month of life in all newborns, if society is willing to absorb the costs. Besides the identification of the infants with the LQTS phenotype, this will allow early diagnosis of other cardiovascular disorders, including some dangerous congenital heart defects. The European Society of Cardiology has recognized that some European countries may in a near future introduce in their
National Health Service the performance of an ECG during the first month of life as a part of a cardiovascular screening program. Accordingly, it has created a task force with the goal of providing adult cardiologists with guidelines for the interpretation of the neonatal ECG. The first step in this direction has just occurred, as in early 2004, the Tuscany Region of Italy decided in the regional health plan for 2004 to 2006 to provide the 25 000 yearly newborns with a service including an ECG between the 20th and 30th day of life. A program of neonatal screening transcends the issue of SIDS because it aims at identifying newborns at risk for cardiovascular events either during infancy or later on in life. In the case of genetic and familial disorders, such as LQTS, the unexpected identification of affected individuals is also likely to unmask additional affected family members, thus extending the scope of this pragmatic approach to the prevention of sudden cardiac death in the young.

References

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