Short QTc interval as an important factor in sudden infant death syndrome

In 1997, 403 babies in England and Wales died suddenly, unexpectedly, and for no reason (despite a thorough post-mortem examination)—a rate of 0.63 per 1000 live births (press release from the Foundation for the Study of Sudden Infant Death, August 1998). It is salutary to recall that 10 years ago the rate of sudden infant death syndrome (SIDS) was 2.3 per 1000 live births. Much of this remarkable improvement, a trend shared by many other Western countries, is attributed to the simple four point advice included in the “reduce the risk” campaign first launched in Britain in November 1991, in particular, the importance of avoiding the prone sleeping posture (although it is worthy of note that the incidence of SIDS had begun to fall a few years before this). This success story should however, not be allowed to conceal the continuing tragedy of about nine babies each day who are victims of SIDS. This residuum (still constituting the largest single group of deaths in infants 1 week to 1 year old) is stubbornly resisting attempts to shift it—the incidence of SIDS has not changed significantly since 1995.

Most of these deaths are in families where mothers smoke during pregnancy and where there is household exposure to tobacco smoke after birth. Some view this association a direct one: exposure to products of cigarette smoke before and after birth perhaps interfering with lung growth or neural mechanisms involved in the control of breathing. Stopping parents smoking, it has been estimated, could reduce the risk of SIDS by almost two thirds. Much of this remarkable improvement, a trend shared by many other Western countries, is attributed to the simple four point advice included in the “reduce the risk” campaign first launched in Britain in November 1991, in particular, the importance of avoiding the prone sleeping posture (although it is worthy of note that the incidence of SIDS had begun to fall a few years before this). This success story should however, not be allowed to conceal the continuing tragedy of about nine babies each day who are victims of SIDS. This residuum (still constituting the largest single group of deaths in infants 1 week to 1 year old) is stubbornly resisting attempts to shift it—the incidence of SIDS has not changed significantly since 1995.

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Multifactorial pathophysiology: the “jigsaw” hypothesis

We also have to recognise that it is still not known, in spite of much research and speculation, how sleeping posture influences risk; indeed, one study from Victoria, Australia, examining ethnic variation and risk of SIDS, did not show sleeping position or cigarette smoking as having any influence on the risk of death. We remain ignorant of the pathophysiology of SIDS, although a defect in the neural control of breathing is viewed as an important possible mechanism. There is no reason that the cause of SIDS should not be multifactorial. I believe all infants are potentially vulnerable to sudden unexpected death, risk factors for this being as pieces of a jigsaw; only when the puzzle is complete will the baby die. According to this hypothesis, each baby has a different and unique jigsaw of risk factors and what we are doing by reducing the risk is to manipulate the pieces we know for the whole infant population, an approach that has met with remarkable success. Or, as Bergman has so eloquently put it: “SIDS is like a nuclear explosion where the critical mass must be obtained before the event is to occur.” Avoidance of risk factors prevents this critical mass being attained. To reduce the risk further, study is needed to identify other risk factors and, if possible, mechanisms of their action.

Prolongation of QT interval

It is against this background that the recently reported prospective study, by Schwartz et al from the University of Pavia, Italy, of the clinical association between prolongation of the QT interval in electrocardiographs (ECGs) of neonates and risk of later SIDS, is of particular interest. In this remarkable study, 33 034 ECGs taken on the 3rd or 4th day after birth from healthy babies born in 1976–94 were analysed to measure QT interval corrected for heart rate (QTc) and the babies followed for one year. During this period there were 34 deaths, 24 attributed to SIDS, an incidence of 0.7 per 1000 live births. Twelve of the 24 SIDS victims had a longer QTc interval (mean (SD) 435 (45) ms) than infants who were alive at 1 year (400 (20) ms) or who died from other causes (393 (24) ms). Half of the infants who died of SIDS had a prolonged QTc compared with none of the survivors or infants who died from other causes. The odds ratio for SIDS in infants with a prolonged QTc (>440 ms) was about 41, significantly higher than the odds ratio for traditional factors such as prone posture and maternal smoking.

The QTc interval is a marker for ventricular repolarisation; prolongation of this interval, a developmental abnormality in cardiac sympathetic innervation, points to reduced cardiac stability favouring susceptibility to potentially lethal ventricular fibrillation. It is associated with death in some clinical conditions and in apparently healthy people. This is not the first time a cardiac arrhythmia has been postulated to explain SIDS but, until now, substantial evidence has not been forthcoming. The QTc increases during the 2nd month of life, peaks between the 2nd and 3rd, and declines to birth values by about 6 months. Thus a tendency towards reduced cardiac stabil-
ity closely parallels the known epidemiology of SIDS. Available evidence suggests that 30% to 35% of infants later to become victims of SIDS can be expected to have a prolonged QTc interval in the first week. 

What are the implications of these findings for paediatric practice, especially for the prevention of SIDS? There can surely be no justification to consider all newborn babies for routine ECGs on the 3rd or 4th day of life. The main drug treatment for prolonged QTc interval is β blockers and Schwartz et al postulate that 100 infants would need to be treated to save the lives of two babies. Even if this were to be remotely successful, considering iatrogenic harm to the remaining 98 significantly weakens the case, let alone the enormous worry to families in revealing this diagnosis. But in babies with a family history of SIDS, prolonged QTc or other unexplained life threatening events, selective ECGs on days 3–4 of life could be taken with a view to treating those babies discovered to have a prolonged QTc for as long as it takes the QTc to return to normal. We will have to be guided by our cardiology colleagues for some of the answers to these difficult issues if effective preventive intervention is ever to be targeted for those particularly at risk.

**QTc interval and stress**

Let us make a lateral move and return to the increased risk of SIDS in families who live in a parlous state of serious social disadvantage containing the various elements of social adversity and personal stress I have previously alluded to. If we recognise that there will be babies born to these families who have a prolonged QTc, could it be that this vulnerability, under certain circumstances, might lead to a life threatening arrhythmia? Lethal arrhythmias associated with prolonged QTc interval are usually triggered by sudden increase in sympathetic activity. Does stress in a baby cause increased catecholamine release? We know infants undergoing heel stab blood tests cry, show facial grimacing, have an increase in baseline heart rate, and increased variability of heart and respiratory rate, features strongly suggesting increased catecholamine release associated with pain. Preterm infants receiving intensive care have been shown to have lower adrenaline concentrations when sedated with morphine. Studies in infant and adult rodents have apparently shown that the “innate fear paralysis reflex” produced by a range of frightening stimuli of the type that commonly occur in daily life transiently prolongs the QT interval and is associated with bradycardia and changes in the T wave. Visiting the homes of many SIDS victims often shows a picture of chaos, a smokey atmosphere, very poor housing, obvious social stresses, and a pre-existence of child abuse or drug abuse in the family (Davis P, personal communication, 1998). Expressions of this social dysfunction include irregualar feeding, being left alone for long periods of time, infrequent changes of nappies, exposure to cold, poor hygiene, and haphazard sleeping routines. It is likely, therefore, that this type of home environment is a source of potential serious stress for the baby. Could it be that this stress is, on occasion, another piece of the jigsaw causing increased catecholamine release that increases the risks of cardiac arrhythmias where there is a prolonged QTc interval? We need to research how severe social adversity and its parenting consequences might stress the baby, along with its pathophysiological consequences. How encouraging, therefore, to discover that one of the new directions of research into SIDS, currently supported by the Foundation for the Study of Sudden Infant Death, is to look into wider issues of general infant care—especially in low income families at relatively high risk of SIDS. Ignorance of the influences of parenting on babies’ physiology should not prevent us from continuing to emphasise to parents the common sense of good, responsible, infant care. Babies must be fed regularly, changed frequently, sleep routines encouraged, not left alone for long periods, physical and emotional contact nurtured, as well as obvious issues of laying babies on their backs and avoiding smoking. They must be cherished, looked after with great care, and considered extremely vulnerable—a concept highlighted by Gentley et al in their anthropological study of Bangladesh parents and infant caregiving practices in Cardiff, a population at particularly low risk for SIDS. A mismatch in a baby of a prolonged QTc with stress factors could increase Bergman’s critical mass, with its tragic outcome.

Is this stretching speculation too far? I believe no more so than many other hypotheses that have been proposed to explain sudden and unexplained infant death. No more than the empirical observations many years ago that simply putting babies to lie on their backs from the prone posture would significantly reduce risk. In 1984, in a study highlighting the rarity of SIDS in Hong Kong, I reflected that “influences of lifestyle and caretaking practices on risks of cot death were being underestimated in preference for more exotic and esoteric explanations”. I am still of this opinion and hope Schwartz et al’s studies will indirectly continue the momentum of researching the home environment in which young babies are nurtured at such a critical stage of their development. One consequence of this might be a continuing reduction in the risk of SIDS.

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Post-traumatic stress disorder

A 1996 report from the Child Accident Prevention Trust reminds us that “Every year in the UK about 700 children die, 120 000 are admitted to hospital, and over 200 000 attend accident & emergency departments as a result of accidents.” (The most common accidents were falls, followed by road traffic accidents.) Overall, 9% of the children attending three A&E departments scored so highly on a screening scale for post-traumatic stress disorder (PTSD) that a diagnosis of PTSD was extremely likely. Half the children involved in road traffic accidents were judged likely to have PTSD. Other, larger studies of child survivors of road traffic accidents found that 35% met criteria for a diagnosis of PTSD, with even more showing subthreshold clusters of distressing symptoms. After six months, one in six still presented with the full blown syndrome.

Until 15 years ago, it was widely accepted that most children responded to frightening events with transient distress and that not all children who experienced a potentially traumatic event reacted with disabling stress reactions. One reason for underestimating the effects of traumatic events on children was that the evidence was incomplete. Put simply, the bulk of the existing evidence came from data provided by parents and teachers. Few investigators had done what is now so obvious—they had not asked the children themselves! PTSD was first officially recognised as a syndrome by the American Psychiatric Association in 1980. It was classified as an anxiety disorder and three main groups of symptoms were seen as characteristic: distressing and recurring recollections of the traumatic event; avoidance of stimuli associated with the trauma; and a range of signs of increased physiological arousal.

Today, PTSD has become so widely discussed that trauma counsellors and specialists are expected to arrive in droves whenever major, and often minor, disasters occur. To some, it may seem that the disorder is potentially so commonplace as to have lost all credibility. I believe that PTSD is susceptible to clear diagnosis, that it is real, that it is distressing and disabling, that it can be long lasting, and that it can be treated. Moreover, paediatricians are very likely to encounter it among children who present following accidents, particularly road traffic accidents, and so they should consider ways to ameliorate the predictable emotional consequences of acts that bring children to A&E departments.

Characteristics of PTSD

When a child is faced with a very frightening, perhaps life threatening, situation he or she may become very distressed: crying, clinging, shaking with fear. If the upset is very great, they may go into shock and be largely unresponsive to outside stimulation for some time. These are normal reactions that have evolved as protective mechanisms. At times of danger, we need to be able to concentrate on what is threatening us to the exclusion of other, less relevant stimuli; we also need to be prepared to fight or flee. When the danger passes, a slow return to normal can usually be expected. But in some cases, such return to a normal state is elusive. Symptoms persist both day and night. This is when an adjustment reaction may develop into PTSD.

Following a traumatic event, children often need to be close to their parents for comfort and reassurance. This clinginess is understandable but may be extremely irritating to parents. Even teenagers may need to be reassured at night and often regress to sharing the parental bed. But the most troublesome symptom from the child’s point of view can be the intrusive images of the event. These can occur at any time and are notable for their vividness. Usually the child “sees” the event replaying over and over again, but this can be accompanied by repetitive memories in any of the senses: sound, smell, touch, and motion. Occasionally, children will report that the experience is so vivid that they truly believe it is happening again. Such dissociative experiences are called flashbacks. Bad dreams and nightmares are also very common.

The intrusive images often come to the children as they are settling down for the night. They can be so distressing that children will fight against sleep and try to stay awake. It is ironic that children who are extremely tired try to stay awake with the obvious consequence that they become more tired, irritable, and unable to concentrate. The irritability can lead to anger that can be difficult to deal with. Children develop fears, especially of stimuli that were present when the traumatic event happened. For example, after the sinking of the cruise ship Jupiter, teenagers reported a profound increase in fear of drowning, fear of water in general, and fear of death and travel. Following road traffic accidents, children are likely to find it difficult to get back into cars for some time. Obviously, these fears have a survival value, but when extreme they can disrupt the child’s and family’s life.

In the immediate aftermath of an accident, children sometimes experience a great pressure to talk about what happened. Then, they often find it difficult to talk, especially with parents and friends. Anecdotally, many children report that they do not want to upset their parents when they talk about what happened and so they keep their feelings to themselves. In such circumstances, being able to talk to someone outside the family has obvious potential benefit.

Survivors have learned that life is very fragile. This can lead to a loss of faith in the future or a sense of foreshortened future. Their priorities change. Some feel they should live each day to the fullest and not plan far ahead. Others realise they have been over concerned with materialistic or petty matters and resolve to rethink their values. Their “assuming world” has been challenged.

Adolescent survivors report significantly high rates of depression, some becoming clinically depressed, having suicidal thoughts, and taking overdoses in the year after a disaster. A significant number become very anxious after accidents, although the appearance of panic attacks is sometimes considerably delayed. When children have been bereaved, they may need bereavement counselling.

Preschool children also develop distress that lasts beyond being an adjustment disorder and probably qualifies for the diagnosis of PTSD. In general, the DSM system is inadequate to reflect the stress reactions of very young children which include playing out the traumatic event repetitively, drawing it repetitively, and more unfocused aggression.

Precipitants of PTSD

PTSD can follow any frightening event that is perceived by the child as being life threatening. Large scale disasters, such as shipping disasters, hurricanes, earthquakes, school shootings, and terrorist bombings seem so remote from everyday life that education, health, and social services took a long time to realise that children are more likely to
be affected by a myriad of smaller, more personal disasters, which are nonetheless equally terrifying. Schools should prepare for children being maimed or killed while on the way to or from school. Children may get injured on school outings. Deranged individuals may enter school premises and hold children hostage or harm them. That is why schools have been urged to be “wise before the event” and prepare contingency plans to meet the emotional needs of children following such crises.

An important cause of PTSD in children is witnessing severe domestic violence, especially intrafamilial homicide. Civil conflict, urban violence, and war all affect large numbers of children, and one has to be aware that refugees from such conflicts may carry a heavy burden of traumatic stress.

Persistence and high risk groups

Nader et al reported a 14 month follow up of 100 children involved in a sniper attack on children at their school. The level of exposure to danger was strongly related to the severity of PTSD symptoms. In the most exposed group—the children who had been directly in the line of fire—the scores on the measure of PTSD were very stable over the 14 month period.

In the seven year follow up of adolescent survivors of the Jupiter sinking, now in their early 20s, preliminary findings indicate that overall 50% of the survivors had presented with PTSD at some point, mainly in the first few months. At follow up, around 15% still met the criteria for PTSD with many more showing several signs of stress reaction that were not sufficient to meet diagnostic criteria. A high proportion were depressed and, although the numbers are small, the rate of suicide attempts was threefold that of a group of matched controls. Thus, PTSD must be considered as a seriously disabling disorder that can lead to interference in development and adjustment over many years.

In general, girls are more susceptible to PTSD than boys, and less able children are more badly affected than more able children. The objective severity of the trauma is directly proportional to the stress reactions, but subjective factors also mediate the effects. Both must be taken into account in formulating effective intervention. This means that when assessing a child, not only should one try to get a clear account of their perception of what occurred, one should also ask directly whether at any point they thought they were going to die. If people did die in the accident, or if people were badly injured, then the child is at greater risk of developing a stress reaction. Risk and protective factors are more fully discussed elsewhere.

TREATMENT

Critical incident stress debriefing was originally developed to assist emergency personnel adjust to their emotional reactions to events encountered in the course of their rescue work. It makes use of group support techniques and has now been adapted for use with children following a wide variety of traumas. Following transport accidents, debriefing has been found to reduce levels of stress, particularly those manifested in intrusive thoughts. However, we still do not know when best to offer such debriefing to survivors of a disaster, nor indeed whether all survivors benefit.

GROUP TREATMENT

Where natural groupings exist in communities and schools, it makes sense to direct some support through such groups. The aims of such groups should include the sharing of feelings, boosting children’s sense of coping and mastery, and sharing ways of solving common problems. Different incidents may require different types of group intervention, for parents as well as children.

INDIVIDUAL TREATMENT

There is little evidence that drug treatment has a central role in PTSD, so the focus has been mainly on cognitive behavioural treatments that aim both to help the survivor make sense of what happened and to master their feelings of anxiety and helplessness.

Asking children to draw their experience often assists recall of both the event and the emotions, and are used as ways of assisting talking about the experience.

Most survivors recognise that sooner or later “they must face up to the traumatic event”. The problem for the therapist is how to help the survivor re-experience the event and the emotions that it engenders in such a way that the distress can be mastered rather than magnified. Therapeutic exposure sessions that are too brief may sensitize rather than desensitize, so therapists may need to use much longer exposure sessions than normal. Recently, a procedure known as EMDR (eye movement desensitization and reprocessing) has shown promise as a rapid treatment for children. More comprehensive suggestions of useful techniques to promote emotional processing are given elsewhere.

To date, there are insufficient controlled treatment interventions with individual cases, let alone randomised control trials; moreover, it is far from clear how best to involve families in treatment. There are clear pointers that parental reactions can help or hinder recovery, and treatment plans should take a family perspective even when the main thrust may be individual exposure work with the child.

Implications for child health services

Recent studies have clearly identified road traffic accidents and other childhood accidents as significant causes of serious and long lasting psychopathology in children and adolescents. While every effort must continue to reduce the number of road traffic accidents involving children, secondary prevention of the emotional consequences should be a priority in the already hard pressed A&E departments. Whatever the accident that leads a child to attend, part of the procedure should involve screening for emotional reactions and providing the child and parents with simple explanatory leaflets about possible emotional consequences and where to obtain further help locally should such reactions persist.

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