Investigation of Unexplained Infant Deaths in Israel: Time for a Different Approach
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Sudden infant death syndrome is the most common cause of mortality among infants in the developed world after the neonatal period. The incidence of SIDS in Israel has been estimated at 2.8–4.2 cases per 10,000 live births, and the incidence of unexplained deaths in Israel in this age group including SIDS is approximately 7 cases per 10,000 live births annually [1,2].

Although SIDS is perhaps the best known cause of sudden and unexpected infant death, it is important to recognize that not all unexpected deaths of ostensibly healthy infants are due to SIDS. Since its cause is unknown, SIDS remains a diagnosis of exclusion that can be formally assigned only after an extensive series of investigations are performed to exclude possible identifiable medical or environmental causes of death. Accordingly, the most widely accepted case definition for SIDS requires that specific criteria be met. Sudden infant deaths not meeting all of these criteria are defined variously by different forensic classifications as either sudden unexplained deaths in infancy or unclassified sudden infant deaths [3].

To the physician not involved in pediatrics, forensic medicine or public health, the distinction between SIDS and SUDI may appear to be inconsequential. However, the importance of postmortem investigations after the unexplained death of an infant is well illustrated by reports analyzing the results of these studies. For example, a recent report from King's College in Britain described the results of 546 infant death investigations [4]. A specific cause of death could be identified in 37% of the cases. Infection was the most commonly assigned diagnosis. However, a number of other causes were also found, including congenital malformations, accidents, non-accidental injury (i.e., infanticide), and a variety of medical conditions. In this study, histopathologic examination of tissues was found to be the single most important investigation for determining the cause of death. Other researchers have reported similar findings [5-7]. Thus, the likelihood that postmortem studies in cases of SUDI will yield an unexpected and significant diagnosis is substantial.

Numerous biological causes of SUDI involving many organ systems have been described. Prominent among them are disturbances of cardiac electrical conduction (prolonged QT syndrome) [8,9], disorders of fatty acid metabolism [10], and congenital adrenal hyperplasia [11]. Postmortem diagnosis of these conditions may be of more than academic importance. Some of the “medical mimics” of SIDS are genetically transmitted and may recur in infants born subsequently into the same family. Furthermore, between 1% and 5% of SUDI may be due to undisclosed infanticide [4-7,12-14], and in these instances the risk for recidivism by the perpetrator may be high. Finally, postmortem studies in infants who died unexpectedly may identify environmental factors that may pose a danger to healthy infants on a wider scale. To take one recent example, it was postmortem studies that identified an association between the use of over-the-counter cold remedies and sudden death among infants, leading to recommendation that these medications be banned in infants under 2 years of age [15]. Taken together, these considerations have led one public health official to observe that besides being a tragedy, an infant death is also a “sentinel event that can be used to identify other children who are at risk for illness of injury” [16].

In addition to possible health benefits, establishing a specific medical diagnosis following SUDI may also have psychological value for the bereaved family [17]. In one report, parents were interviewed several months after an autopsy was performed to investigate a pediatric death. Most reported that they felt autopsy was psychologically beneficial. One reason offered was that the procedure answered a perceived need to know why the child had died. Another was that by advancing medical knowledge, autopsy had provided a way to give meaning to their child’s death [18]. However, not all studies report universal parental satisfaction with their decision to permit autopsy. A recent study from Australia found that while 41% of bereaved parents felt that autopsy had helped them to live with their loss, another 42% felt that autopsy...
had added to their grief, and 8% regretted having permitted the procedure [19]. The authors note that it is not known which factors can predict different parental reactions, and that future studies addressing this question would be useful.

**INVESTIGATION OF SUDI IN ISRAEL**

In Israel, there are numerous legal and social impediments to performing forensic autopsies, which greatly influences how unexpected deaths at all ages are investigated. To better define how the sociopolitical and legal milieu might influence investigation of SUDI, we retrospectively reviewed cases occurring in Jerusalem during the years 1996–2003. In the 96 cases we identified, only a single forensic autopsy was performed. Additionally, we found that in only 42% of cases were any tests to determine the cause of death performed in a hospital. In some cases there was no record of the corpse being brought to a hospital at all. A diagnosis of SIDS was assigned in 37% of cases, while 29% were considered deaths of unknown cause or manner [20]. A second essential component of SUDI evaluation is examination of the death scene by a team of investigators with special training in infant death investigation. Although cases of SUDI in Israel are routinely reviewed by Ministry of Health district health officers, the death scene is not routinely investigated by a team of forensic experts immediately after death. It is therefore possible and indeed likely that a number of genetically transmissible diseases and/or cases of non-accidental injury went undetected. A further implication of these findings is that reported data concerning the incidence of SIDS in Israel cannot be obtained according to the standard case definition.

It is worth noting that incomplete investigation of SUDI was not always the norm in Israel. In 1973, a report from the Ashkelon district by Dr. A. Bloch described 24 infant deaths investigated as possible SIDS during the period 1961–1970. Forensic autopsies were performed in nearly all cases, the author personally visited the home in 23 instances, and a non-SIDS cause of death was identified in 14 cases [21]. However, while religious perspectives concerning autopsy have not changed during the ensuing 38 years, for better or worse the social and legal landscape in which forensic pathologists perform their work appears to have changed substantially during this time.

Israel Ministry of Health policy clearly states that examination of the corpse including autopsy at the Institute of Forensic Medicine is required in all cases of “sudden and unexpected death of a person known to be healthy prior to death” [22]. This guideline would appear to apply to SUDI. However, current Israel jurisprudence makes it impossible to enforce. Two laws apply to the question of the circumstances under which forensic autopsy can be authorized by the state against parental objection: The Pathology law (1953) and The Law Concerning Investigation of the Circumstances of Death (1958). Taken together they effectively stipulate that autopsy cannot be compelled unless there is a clear *a priori* suspicion of an unnatural cause of death, and a reasonable likelihood that autopsy would reveal a cause that could not be discovered by other means. In view of the fact that 1–5% of SUDI may be due to infanticide, suspicion of an “unnatural cause of death” might be considered inherent following SUDI. Furthermore, the evidence cited above pointing to histologic studies as the most important means for establishing the cause of an otherwise unexplained infant death [4] might reasonably appear to further support routine autopsy under these circumstances. Although Israel’s Supreme Court has not directly addressed the question of autopsy following SUDI in particular, several decisions have addressed the question of forensic autopsy in general. Overall, the court has permitted autopsy despite objection by the family only in cases when it deems that the probability of discovering that a death was due to criminal violence or negligence is substantial. In support of their view, the justices cite the need to weigh the rights of the deceased against the public interest to ascertain the cause of death [23]. Left unanswered is the question of whether family members are always the best advocates for the rights of the deceased following SUDI, since in cases of infanticide the parent is the most likely perpetrator.

The reason most commonly given by parents for refusing autopsy following SUDI in Israel is religious belief. Religious leaders in Israel are widely perceived to oppose the practice of autopsy except under extenuating circumstances. The country’s two faiths with the largest numbers of adherents, Judaism and Islam, recognize the principle of preserving the dignity of the deceased. However, each faith also recognizes the paramount importance of obtaining medical information necessary to protect the health and lives of the living. Debate among Jewish scholars often centers around the likelihood that autopsy will identify a potentially preventable or treatable illness among the immediate living relatives of the deceased. Similarly, there is no blanket prohibition against autopsy in Islam. Legal interpretations (*fatwa*) exist concerning the specific circumstances under which autopsy can and cannot be performed [24]. Nevertheless, there will continue to be instances in which physicians and clergy disagree about the necessity of autopsy, and there are also families that object to autopsy because of personal conviction rather than on the basis of precepts of an organized religion.

In practical terms, in the absence of an enforceable policy requiring that all cases of SUDI undergo autopsy, the decision concerning whether or not to petition the courts to refer
corpses for forensic examination despite parental objection is currently made on a case-by-case basis by law enforcement officers in consultation with Emergency Department physicians and social workers. This situation creates serious practical difficulties. For example, the hospital social worker may be asked to assume two inherently conflicting roles when a dead infant is brought to the Emergency Department. On the one hand, she or he is asked to provide emotional support and guidance to the grieving family, as well as anticipatory psychological education to prevent potential post-traumatic stress disorder. On the other hand, she or he may also be asked to take part in an ad hoc investigation to determine whether suspicion of the parents is sufficient to warrant recommending additional postmortem studies against their wishes. It was recently argued that it is unreasonable to expect one individual to fulfill both of these conflicting roles simultaneously [25]. Moreover, compulsory forensic autopsy has in the past sparked social unrest in ultra-Orthodox (Jewish) communities in Israel. Hospital administrators are cognizant of this fact and are obliged to consider the feelings of the communities that their institutions serve before proceeding in tendentious cases involving possible autopsy. Current solutions to these dilemmas are not satisfactory and alternative procedures should be sought.

THE STATUS OF “VIRTOPSY” AS A POTENTIAL ALTERNATIVE TO TRADITIONAL AUTOPSY

During the past 10 years, developments in the nascent field of forensic radiology have raised the possibility that imaging studies might be used as a non-invasive alternative for evaluation of SUDI when autopsy is not possible.

For many years, conventional radiographs have been an essential component of standard postmortem evaluations. Emphasis on skeletal development and dysplasias in fetuses, and postmortem radiology for suspected child abuse in infants and young children (“skeletal survey”) continues to be recommended by authors and academies as part of the evaluation of unexplained death in pediatrics. However, in the last 10 years there has been a revolution in the field of postmortem imaging. This began at the Institute of Forensic Medicine at the University of Bern, Switzerland, with the Virtopsy (or minimally invasive autopsy) Project with the initial goal of detecting forensic findings using computed tomography, magnetic resonance imaging and other modalities and comparing these to autopsy findings [26]. The United States military currently performs CT scans on military personnel killed in combat, and recently a new subspecialty of postmortem imaging was proposed [27]. In 2009, the Department of Justice in the UK stated its commitment to make minimally invasive autopsy available as an alternative to conventional autopsy, and experts have called for wider use of less invasive autopsy methods [28,29].

Virtopsy has also been evaluated in non-forensic cases. Extensive research in fetal and perinatal death has demonstrated superiority to autopsy in the evaluation of congenital malformations of the central nervous system, which are among the most frequent congenital anomalies [30]. In the evaluation of civilian trauma, postmortem CT has been shown to be comparable to autopsy in the detection of fractures, intracranial bleeding and cerebral edema [31]. At this time there is only one study evaluating the use of postmortem CT for detecting causes of sudden death in infants and children. In that study of 15 children, CT appeared useful for cases where pneumonia, cerebral edema and genitourinary diagnosis were the most likely cause of death. However, only 2 of the 15 cases had confirmatory autopsies. Nevertheless, it was felt that the cause of death could be presumed by combining the medical history, laboratory data, and clinical course before death and postmortem CT in nearly all cases [32]. Recent experience in Israel suggests that postmortem CT may sometimes be a useful, non-invasive way to identify the cause of death [33].

Because of its non-invasive or minimally invasive nature, virtopsy would appear to offer an inherently attractive alternative to conventional autopsy. However, there are important limitations to this technology as it stands today. Injuries that are frequently not detected by CT include contusions or superficial lesions of solid organs, small soft tissue contusions, brain contusions and hematomas smaller than 3 mm and vascular transections or lacerations. MRI may fail to detect complex cardiac malformations, anomalous connections between structures (tracheo-esophageal fistulas), and bowel perforations [34]. Neither modality allows for tissue sampling for cytogenetic, histologic or metabolic analysis.

In summary, at this stage, current research does not support the use of CT or MRI as equivalent to conventional autopsy for forensic purposes in SUDI. The combination of relatively small studies, substantial differences in design and study population, and the paucity of pediatric and adult data have led to substantial heterogeneity in the reported percentage agreement between minimally invasive autopsy and conventional autopsy (pooled sensitivities and specificities 69%–95% in fetal studies and 28%–64% in children and adults) [35]. Moreover, the critical role of histopathology for ascertaining the cause of death in SUDI studies that included conventional autopsy points to the serious inherent limitation of this technique. However, rigorous double-blinded large prospective studies are currently underway and will shed further light on the efficacy of virtopsy.
DEATH SCENE INVESTIGATION AND CHILD FATALITY REVIEW TEAMS

As noted above, an essential component of SUDI investigation in addition to forensic autopsy is investigation of the scene of death as soon as possible in order to identify possible environmental factors that may have contributed to the infant’s death [36]. It appears that a lack of the necessary resources rather than legal or social constraints is a major impediment to implementing a policy of mandatory death scene investigations following SUDI in Israel.

RECOMMENDATIONS

In spite of the legal, social and technical limitations discussed above, we believe that much can and should be done to improve how SUDI and SIDS are addressed in Israel at a national level. Toward this overall goal, we offer the following suggestions for investigation following SUDI:

- We believe that some form of postmortem examination should be required in all cases of SUDI. The current state of affairs, in which little or no testing to determine the cause of death is the norm, is at variance with western standards and one that we consider unacceptable. Attaining this goal may require legal and/or policy changes to reconcile the law with Ministry of Health recommendations.

- Regardless of whether the postmortem examination includes a full autopsy or is limited to non-invasive tests, we believe that apart from a history and physical investigation, all studies should be performed at the Institute for Forensic Medicine at Abu Kabir. Such a policy would relieve emergency department physicians and social workers of the responsibility of interrogating bereaved families in the emergency department and free them to provide emotional support and guidance for them in their hour of need. In addition, all forensic investigations would be performed by physicians with specific training and expertise in this field.

- We are cognizant that virtual autopsy has not been adequately studied in SUDI. Furthermore, unless supplemented by imaging-guided tissue biopsy, this technique provides no histopathologic information on tissues. It is therefore likely that important diagnoses that would be reached by conventional autopsy would be missed if virtopsy were used routinely as a sole test. However, even if not appropriate in all cases, given the political, legal and social realities in Israel today, it would appear that even if imperfect, virtopsy may preferable to no examination at all when conventional autopsy is not possible.

- Commitment and goodwill on the part of physicians, social workers, jurists and religious leaders will be necessary to change the way unexplained infant deaths are investigated in Israel.

- Guidelines concerning the specific tests to be performed following SUDI, and under what circumstances, should be developed by a committee comprising experts in forensic medicine, pediatrics, public health, legal affairs, and the Jewish, Islamic and Christian faiths. We believe it would be far more productive to reach decisions in cooperation with rather than in conflict with religious leaders.

- Death scene investigations by forensic teams, performed according to established protocols, should become a standard part of SUDI investigation.

- Multidisciplinary child fatality review teams [37] should be established to review all cases of SUDI.

Although infant mortality is normally considered the province of public health officials and forensic physicians, we think this issue should be of concern to all physicians, social workers, and other providers of health services to children. Change in the way SUDI is investigated in Israel will not come easily. However, with the goodwill of all interested parties, the judicious use of newer technologies, and commitment to allocate the necessary resources, we believe comprehensive investigation of all cases of SUDI in Israel is a realistic possibility in the foreseeable future.

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**Capsule**

**Induction and molecular signature of pathogenic T<sub>H</sub>17 cells**

Interleukin 17 (IL-17)-producing helper T cells (T<sub>H</sub>17 cells) are often present at the sites of tissue inflammation in autoimmune diseases, which has led to the conclusion that T<sub>H</sub>17 cells are main drivers of autoimmune tissue injury. However, not all T<sub>H</sub>17 cells are pathogenic; in fact, T<sub>H</sub>17 cells generated with transforming growth factor-β1 (TGF-β1) and IL-6 produce IL-17 but do not readily induce autoimmune disease without further exposure to IL-23. Lee et al. found that the production of TGF-β3 by developing T<sub>H</sub>17 cells was dependent on IL-23, which together with IL-6 induced very pathogenic T<sub>H</sub>17 cells. Moreover, TGF-β3-induced T<sub>H</sub>17 cells were functionally and molecularly distinct from TGF-β1-induced T<sub>H</sub>17 cells and had a molecular signature that defined pathogenic effector T<sub>H</sub>17 cells in autoimmune disease.

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A child becomes an adult when he realizes that he has a right not only to be right but also to be wrong

Thomas Szasz (1920-2012), American psychiatrist and academic