Genetic testing in sudden infant death – a wolf in sheep’s clothing?

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Accepted: 19 October 2018 / Published online: 7 December 2018
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A little learning is a dangerous thing
Alexander Pope (1688–1744)

The pathological investigation of unexpected and/or sudden infant deaths is not a straightforward process. Seemingly well infants may die rapidly from a variety of congenital and/or acquired natural conditions which may have either no, or only very subtle, manifestations [1]. In fact, sudden infant death syndrome, or SIDS, which is responsible for a significant number of these deaths has by definition no diagnostic markers, i.e. it is the sudden unexpected death of an infant <1 year of age, with onset of the fatal episode apparently occurring during sleep, that remains unexplained after a thorough investigation, including performance of a complete autopsy and review of the circumstances of death and the clinical history [2]. For this reason it has been called a “diagnosis in search of a disease” [3].

Inflicted or accidental injuries in infancy may also be difficult to detect. Death from suffocation is a classic example where a lethal event has occurred that may have left no pathological evidence. One case from the literature details an infant found unresponsive beneath her mother, who had collapsed from a heroin overdose in a public toilet. Very careful examination of the infant in hospital and later at autopsy after her death from hypoxic ischemic encephalopathy demonstrated no other features to support the presenting history of crush and positional asphyxia with likely suffocation [4]. Thus, suffocation in infancy and SIDS usually appear identical at autopsy. This has resulted in vigorous debate for many years

concerning the correct way to classify infant deaths that have occurred in shared sleeping situations [5]. This lack of diagnostic clarity also impacts on the courts in cases where there is a possibility of deliberate suffocation. Very often, a range of obscure entities are raised to suggest that there may be a number of other possible causes of death.

The issue with asphyxia is not, of course, limited to childhood. Adults who commit suicide by placing a plastic bag over the head, sometimes augmented by inert gas inhalation, usually have no pathologic findings at autopsy [6]. Thus, a finding of suicide would be much less likely to occur if family members have altered the death scene, removed the apparatus and not provided an accurate description of how the decedent was discovered. While it was once considered that certain features at autopsy such as fluidity of the blood, petechiae, congestion, cyanosis and engorgement of the right side of the heart were strong indicators of an asphyxial event, this has been eloquently dismissed as “an obsolescent diagnostic quintet” [7].

One of the very positive developments in pediatric forensic pathology in recent years has been the formulation of autopsy protocols clearly specifying the need to perform as many ancillary investigations as possible (or as is practicable) in order to identify occult conditions which may have been responsible for infant death [8]. Various professional organizations have published guidelines recommending genetic testing for autopsy-negative sudden death [9, 10]. Improved laboratory technology has also made many more of these techniques accessible at a much lower cost. Unfortunately, this has expanded the complexity of cases. While we may be getting better at identifying rare genetic variants associated with sudden death, we are often far from understanding their fatal mechanisms or showing exactly how, or if, this gene variant was responsible for death in a specific case. Genotype does not necessarily result in a specific phenotype. In other words, are we simply documenting a gene abnormality that an infant has died *with*, rather than *from*? This issue has been very concisely reviewed by Gando et al in the current issue of FSMP [11] with an excellent

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accompanying commentary detailing the approach of the New York Chief Medical Examiner's Office to these problematic cases [12].

As a counterpoint, from the clinical perspective, a pathogenic cardiac gene variant discovered in a child who has died can be monumentally important to risk stratify surviving family members. All first degree relatives will need to be evaluated for the variant to see if they also have a risk of sudden death. Thus, in many cases, the pathologist can have a critical role in saving the lives of other members of the family.

The problems arise, however, when gene variants are not clearly pathogenic. In a recent cohort of SIDS children, 46% were found to have at least one ultra-rare variant in the 90 cardiac-related genes analyzed [13]. Sorting through these variants takes time and expertise. In the end, for their cohort, only 4.3% were clinically actionable findings.

To address this concern, the U.S. National Institutes of Health and the American College of Medical Genetics in 2015 began a collaborative framework to analyze and “curate” the strength of evidence for suspected disease causing gene variants [14]. Prior to this time, each individual laboratory offering genetic testing had its own proprietary interpretation of which genes were causative of disease. Patients with the same variants tested with one laboratory might be told the results were “positive” for a mutation, whereas another service might return a finding of “uncertain.” The current framework now includes strict definitions in five categories: benign, likely benign, variant of uncertain significance, likely pathogenic, and pathogenic. This methodology has recently been applied to Brugada syndrome, a disorder caused by gene mutations in the *SCN5A* gene that encodes for the α -subunit of the cardiac sodium channel and can result in sudden cardiac death. Of the previous 21 disease-associated variants, only one was found to meet the strict definitions of likely pathogenic or pathogenic and considered to have “definitive evidence as a cause for Brugada syndrome” [15].

In the future, the complexity of genetic medicine will have a striking potential to impact on sudden death cases undergoing police investigation. As we perform more testing, we increase the finding of rare variants in cardiac sudden death-related genes. It is quite likely that it may then prove difficult to completely exclude that a particular genetic abnormality has contributed to, or caused, death. In cases where inflicted suffocation is suspected, this provides a very fertile field for lawyers to argue that a genetically “abnormal” infant could well have died from a natural condition; or at least that this cannot be excluded, particularly as there are no autopsy findings to support an asphyxial mode of death. It could be argued that the prosecution in their zeal to achieve a conviction are promoting a cause of death with absolutely no pathological evidence behind it whatsoever, while deliberately and possibly perniciously ignoring a plausible alternative.

Adding an apparently credible scientist or pathologist who will agree with this may be a difficult strategy to

counter. The emergence of new diseases such as Timothy syndrome that can cause sudden death in the very young from cardiac arrhythmias [16] but were completely unrecognized two decades ago also demonstrates that our state of knowledge in this area is incomplete. More importantly, as knowledge increases, known genetic variants can often change categories. In a retrospective review from 2006 to 2016, 24.9% of genetic test results provided to patients were later reclassified [17]. Fortunately, of reclassified variants of uncertain significance, 91% were redesignated as benign; however, it is important to note that 8.7% were upgraded to pathogenic/likely pathogenic. Does this open up the future for court appeals if a decedent's gene variants become reclassified? Current testing of genes is more commonly done using smaller panels; however, in the near future the cost of whole genome sequencing is predicted to fall to less than \$1000US [18]. This would, in essence, create a searchable electronic library in each case. Whenever a new paper is published with a disease-gene association, it might only be a few key-strokes to see if a client could appeal a former conviction, even years later.

Jurors have the potential to be confused by the introduction into evidence that the decedent had “abnormalities in sudden death genes”. While one rare variant can be explained away perhaps, would several variants in these genes have an additive effect and be sufficient to raise a doubt? Is it possible that the ease with which we can now perform gene sequencing is going to lead to the emergence of a new category of defense witness, that of the “pediatric forensic geneticist”; an expert who will wade through the “tsunami” of laboratory information that will be presented and quite correctly state that the significance of many of these previously unidentified variants is uncertain.

Perhaps it is time to learn from our clinical colleagues? Hosseini et al. in their study of the genetic basis of Brugada syndrome concluded very succinctly that “These findings warrant a systematic evidence-based evaluation for reported gene-disease association before use in patient care” [15]. To paraphrase this for a forensic context: merely because a gene variant is present does not make it significant. Any abnormal findings must have the backing of a systematic evidence-based evaluation for reported gene-disease association before being presented to, considered by and accepted in the court. Gene variants should meet the strict definition of either pathogenic or likely pathogenic before being introduced as evidence. While observational data will remain very important in medicolegal situations, selectively presenting and misinterpreting non-evidence based information must be avoided at all costs as the consequences may be long lasting and devastating [19, 20].

Compliance with ethical standards

Ethical approval Not required.

Conflict of interest The authors declare that they have no conflicts of interest.

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