

The Metabolic Autopsy Comes of Age

The concept of sudden infant death syndrome (SIDS) was introduced in the early 1970s in an attempt to categorize death in a group of infants who died suddenly and unexpectedly and in whom a thorough postmortem investigation failed to provide a credible diagnosis (1). The diagnosis of SIDS or sudden unexpected death in early life, which encompasses a greater number of cases, remains the largest single cause of death in children in the industrialized nations. The reported frequency is ~1:1000 live births, a figure that represents 25% of all deaths in the first year of life.

In the beginning, the first clue that a subset of these infants may have a metabolic derangement came from the pioneering autopsy studies of Professor John Emery (2). By investigating 200 infants who were initially given the diagnosis of SIDS, Emery recognized that 5% of them had diffuse fatty change of the liver. It was suggested that these children had been in some state of metabolic "poisoning" or had suffered an acute metabolic decompensation such as that seen in Reye syndrome. The first factual diagnosis of an inborn error of metabolism in an infant initially classified as SIDS was made in 1984 (3). A 14-month-old infant who died suddenly after a 48-h history of nonspecific malaise, was found at autopsy to have diffuse fatty changes to viscera, and was eventually shown to have had medium-chain acyl-CoA dehydrogenase deficiency. Additional cases of medium-chain acyl-CoA dehydrogenase deficiency were quickly recognized in SIDS cases, along with a very high incidence of previous sibling deaths (4-5).

After these observations, a series of studies on cohorts of infants dying suddenly and unexpectedly produced somewhat controversial results. The studies that focused too closely on a single genetic defect, medium-chain acyl-CoA dehydrogenase deficiency, did not identify a significant number of cases to justify continuing the investigation (6-7). Studies that aimed to recognize multiple genetic defects produced a considerably greater yield of positive cases (8-10). We now recognize that most of the disorders of mitochondrial fatty acid β -oxidation can present with sudden unexpected childhood death. Other causes include mitochondrial respiratory chain disorders and some of the organic acidemias. Although the frequency of metabolic disease among unexpected death cases is ~5%, postmortem screening of pediatric cases of sudden and unexpected death has received only limited attention, and then only because of the isolated but persistent effort of a few laboratories.

One of the major stumbling blocks to the acceptance of a metabolic protocol for all pediatric autopsies has been the complexity of the testing procedures. Many of the earliest studies had complex sample collection and analytical requirements, including skin biopsy for fibroblast culture and immediate storage of frozen body fluids and tissues. The types of testing that were performed included metabolite analysis by gas chromatography-mass spec-

trometry and metabolic flux, enzymatic and molecular studies in vitro. Facilities to enable this type of testing were limited to a few major centers where there was an active interest by the medical examiner or pathologist and an appropriately equipped diagnostic laboratory. By contrast, toxicology studies are routinely performed at autopsy despite little or no evidence that they provide a more effective service in the evaluation of pediatric cases of sudden death.

Seventeen years after the first postmortem diagnosis was made, this situation is about to change. In this issue of *Clinical Chemistry*, Chace et al. (11) report the outcome of a prospective study of postmortem blood and bile specimens collected as dried spots on filter paper for the biochemical screening of numerous metabolic disorders. They identified 65 probable metabolic cases among 7058 cases investigated over a 5-year period, patients who would have otherwise been reported as sudden death cases or attributed to other, nondescriptive causes of death. Families were provided a plausible reason for the unexpected demise of their children and an opportunity to prevent morbidity and mortality in asymptomatic but affected siblings, to receive genetic counseling, and to seek prenatal diagnosis. As has happened before, including in a highly visible criminal case (12), allegations of child abuse and/or neglect were dispelled in two instances (Donald H. Chace, personal communication). The impact of this effort in improving the standards of quality of patient care could not be more obvious.

The work of Chace et al. (11) offers a detailed presentation of informative findings and also of common, potentially misleading artifacts. These are tools of great utility to laboratories that might not have extensive experience in the interpretation of metabolic profiles for the diagnosis of inborn errors of metabolism. This study has convincingly shown the feasibility of a simple and reliable method to potentially screen all cases of pediatric sudden death. Blood and bile (13) could be conveniently collected on the same filter paper card, one identical to those used for newborn screening, stored at room temperature, and submitted for analysis once dried. Both specimens should be collected to provide a better chance of detecting and independently confirming the largest possible number of disorders. In addition to the recommendations made by Chace et al. (11), we believe that in cases with greater suspicion, for example, in the presence of diffuse fatty infiltration of the liver, an effort should be made to collect a frozen specimen of liver and a skin biopsy (5). When a credible cause of death has been established, these additional specimens could be discarded without further testing; however, these specimens could otherwise be crucial to reach a proper diagnosis and conclusive confirmation in vitro. Finally, a preliminary copy of the autopsy findings should be sent along with the specimens to allow a better interpretation of results and to gather epidemiology

logic information. This item was not consistently provided in the present study (11).

Pediatricians and geneticists should request an autopsy report of any case of sudden death in one of their patients. They should aggressively pursue the investigation of all cases with fatty infiltration of viscera, a family history of sudden death, Reye-like syndrome, or myopathy, especially if vomiting and/or fasting before death occur after a history of lethargy (9, 10). However, caution should be exercised not to use steatosis as the sole criterion to indicate a possible underlying fatty acid oxidation disorder during the postmortem evaluation of a case of sudden death. All cases should be investigated.

The current limited interest of many medical examiners in investigations of metabolic disorders postmortem is similar to the reluctance of public health officials to introduce tandem mass spectrometry in the newborn screening arena (14). The understanding of inborn errors of metabolism and the ability to diagnose them have improved dramatically in the last decade. The basic metabolic autopsy championed by Chace and colleagues has not only come of age, but is long overdue in clinical practice.

References

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