Postmortem Investigations

44

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Key Facts

- All cases of sudden and unexpected death in childhood should be evaluated for a possible underlying metabolic disorder.
- A history of "normal" newborn screening for metabolic disorders is not a sufficient reason to decline postmortem evaluation.
- The most important specimens to collect at autopsy are blood and bile, spotted on filter paper.

The high mortality rate that is associated with acute episodes of metabolic decompensation has led to a perceived association between sudden unexpected death in early life (www.sudc.org) and several inborn errors of amino acid, organic acid, ammonia detoxification, and energy metabolism (Dott et al. 2006). However, in most cases, these conditions do cause acute illness with obvious clinical symptoms that precede death by hours or days. The situation is significantly different when considering the large number of cases affected with a fatty acid oxidation (FAO) disorder who were diagnosed either postmortem or, retrospectively, after the identification of an affected sibling. The latter situation has become a relatively common event since the achievement of greater awareness (Bennett and Rinaldo 2001) and, particularly, because of the broad implementation of expanded newborn screening for these disorders (Watson et al. 2006). Based on numerous observations, it has been postulated that without preventive intervention (i.e., newborn screening) FAO disorders could be responsible for up to 5 % of children who die suddenly and unexpectedly from birth to 5 years of age, particularly among those with evidence of acute infection that routinely would not represent a life-threatening event (Boles et al. 1998). While newborn screening eventually will bring the number of unexpected fatalities in infants and children close to none (Rosenthal et al. 2015), it will take several decades to have the same impact on adults who were not screened at birth. Therefore, it would be prudent for medical examiners to keep FAO disorders in the differential diagnosis of sudden adolescent and adult death with diverse clinical history (Raymond et al. 1999; Randall et al. 2015).

Figure 44.1 shows a flow chart for the evaluation of sudden and unexpected death that is

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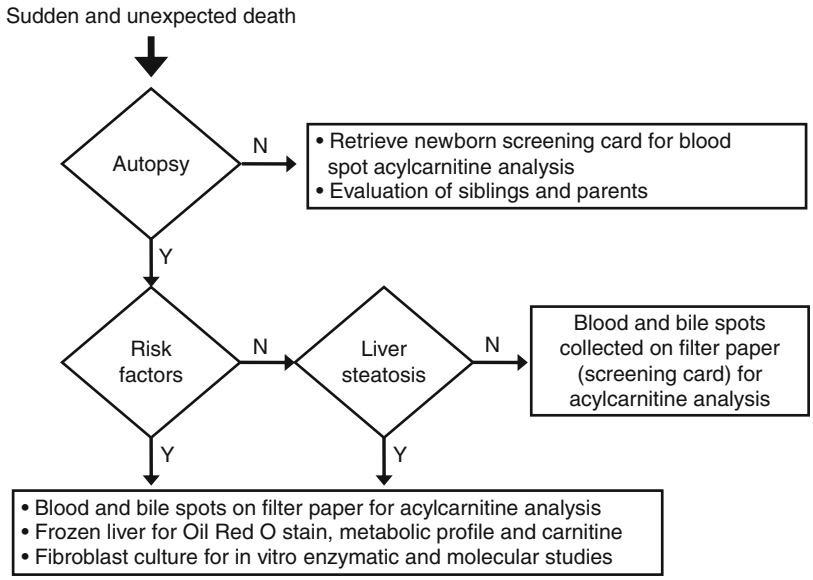

Fig. 44.1 Protocol for the postmortem screening of FAO disorders (From Rosenthal et al. (2015))

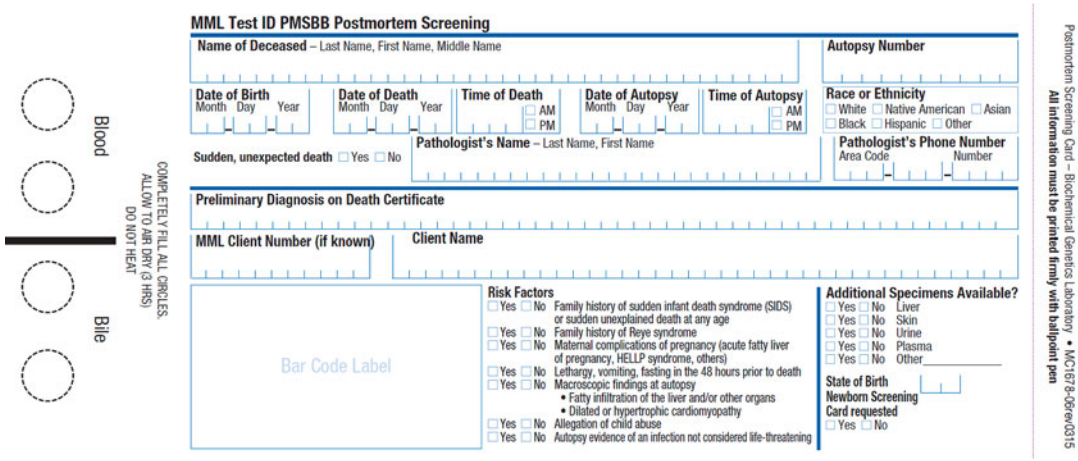

Fig. 44.2 Example of filter paper card for collection of postmortem blood and bile specimen

centered on the analysis of acylcarnitines in blood and bile spots (Rinaldo et al. 2002). Postmortem blood (Chace et al. 2001) and bile (Rashed et al. 1995) could be conveniently collected on a single filter paper card (Fig. 44.2), very similar to those used for newborn screening, which can be shipped at room temperature once properly dried. It is important to underscore the fact that both specimens should be collected in order to detect patients who may show mild or no apparent abnormalities in blood alone (Rinaldo et al. 2005). In cases with a higher level of suspicion, an effort should be made to collect a skin biopsy (Gray et al. 1995). It has been possible to grow a viable line of cultured fibroblasts from a biopsy of the Achille's tendon collected as long as 72 h after death.

Although fatty infiltration of the liver and/or other organs (heart, kidneys) is a common observation in FAO disorders, the finding of macroscopic steatosis cannot be used as the only criterion in deciding whether to investigate a possible underlying FAO disorder during the postmortem evaluation of a case of sudden death (Dott et al. 2006; Boles et al. 1998). Special attention should be paid to the risk factors listed in Table 44.1, and allegations of child abuse should also be fully investigated, with the exception of obvious cases of trauma/physical harm. The frozen skin biopsy could be discarded at a later time without further testing when a credible cause of death has been established, but could otherwise be crucial to reach a proper diagnosis and conclusive confirmation in vitro. If parental permission to perform an autopsy is not granted, it might be possible to retrieve leftover specimens collected during resuscitation efforts which may still be available in the clinical laboratory. In cases when no autopsy was performed, retrieval of any unused portion of the blood spots collected for newborn screening could be arranged via a request submitted in writing to the local laboratory (for a template, see The metabolic autopsy: postmortem screening in cases of sudden, unexpected death), as long as the period of storage, ranging from only a few weeks to indefinitely, had not expired already in the state where the patient was born (Lewis et al. 2011).

Table 44.1 Factors which increase the risk of an undiagnosed FAO disorder

Birth at a location not yet providing expanded newborn screening by MS/MS
Family history of sudden infant death syndrome (SIDS) or other sudden, unexplained deaths at any age
Family history of Reye syndrome
Maternal complications of pregnancy (acute fatty liver of pregnancy, HELLP syndrome, others)
Lethargy, vomiting, fasting in the 48 h prior to death
Macroscopic findings at autopsy
Fatty infiltration of the liver and/or other organs
Dilated or hypertrophic cardiomyopathy
Allegation of child abuse (excluding obvious cases of trauma, physical harm)
Autopsy evidence of infection that routinely would not represent a life-threatening event

44.1 Specimen Requirements

44.1.1 Blood and Bile

Blood specimen collection is usually drawn into heparin-containing tubes from the proximal aorta or by intracardiac puncture. Bile collection is obtained by direct puncture of the gallbladder. These specimens are well preserved when spotted on a filter paper card. Two circles of the card are used for blood, two circles for the bile (each 25 µl of volume). Blood and bile have to be dried before sending the filter paper card to the laboratory which performs the analysis. Relevant demographic patient information should be provided, together with a summary of relevant autopsy findings.

44.1.2 Skin/Tendon for Fibroblast Culturing

In cases with any risk factors, a 5 × 5-mm skin specimen should be collected and placed in culture media. If culture media is unavailable, the specimen can be placed in sterile saline. Although saline is not an optimal media for skin, it will be sufficient in most cases if the specimen is forwarded immediately for cell culturing. The skin specimen should be shipped at room temperature via overnight delivery.

44.1.3 Urine

If urine is present, it should be collected and stored for all cases of sudden, unexpected death. Urine may be collected on a second filter paper card by swabbing the bladder. The

specimen should be allowed to dry for 2–3 h. The urine specimen should be stored at room temperature until the results of the postmortem screen on blood and bile and the results from the original newborn screening card are available.

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