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Review Article

Sudden death, especially in infancy – improvement of diagnoses by biochemistry, immunohistochemistry and molecular pathology

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ABSTRACT

One of the problems in the diagnosis of the cause of death in cases of sudden death, especially in infancy, is the rapidity of death and that the morphological correlates of the underlying diseases and cause of death may be scarce or even completely missing. This is especially true for functional disorders causing death (e.g. arrhythmias) or cases where death occurs in an initial stage of disease with still lacking morphological findings (e.g. myocarditis).

Molecular pathological techniques, which were initially of great importance for identification, today contribute also to the determination of the cause and manner of death, especially in cases, where classical methods do not reveal a clear anatomical cause of death. This will be addressed on the basis of several case groups, especially cases of sudden infant death syndrome (SIDS). Using immunohistochemical methods with qualification and quantification of interstitial leucocytes, PCR and Rt-PCR methods for identifying virus genome within the myocardium, it is possible to identify in about 25% of SIDS cases a myocarditis as cause of death. However, proposed limit values for the diagnosis of myocarditis have to be seen with caution since they lack any statistical power. The value of immunohistochemical and molecular pathological methods to identify the cause of death will also be addressed in cases of sudden death of young adults. At last pharmacogenomic investigations, e.g. on the metabolism of tramadol will be addressed which are of importance to declare adverse events, or even lethal outcome during medication.

1. Introduction

One of the problems in the diagnosis of the cause of death in cases of sudden and unexpected death is that due to the rapidity of death morphological correlates of the underlying diseases and the cause of death may be scarce or even completely missing. Especially if death is due to functional disorders causing death (for instance arrhythmias) or when death occurs in an initial stage of a disease morphological findings at autopsy may be scarce or even missing. In these cases molecular pathological techniques may help to determine the cause and even manner of death (for instance accident – suicide) [22,23].

About 10% of all deaths are sudden cardiac deaths. In the age group above 35 years coronary artery disease is a prevailing cause of death but in the age group below 35 years cardiomyopathies are the leading causes of death. Most of the cardiac sudden deaths have a genetic component and many genes have meanwhile been identified as cause for cardiomyopathies and channelopathies [21]. However, not only DNA technology but especially the combination of morphological methods together with toxicology, genetics and biochemistry offer a great tool in solving in the first instance unclear cases.

2. Postmortem biochemistry

Postmortem biochemistry may provide significant information in determining the cause of death. According to Coe [4] proper utilization of a wide variety of chemical determinations in blood, cerebrospinal fluid, vitreous humor, pericardial and other body fluids can help in solving forensic problems in nearly 10% of the routine natural deaths which comprise the majority of cases seen by a forensic pathologist. However, due to the rapid postmortem breakdown of metabolism and active membrane transport only analytes which are stable in blood can be determined on this fluid compartment, other parameters have to be analyzed on other fluid compartments like vitreous humor (VH). Using another fluid compartment as a mirror of blood at the moment of death involves several methodical problems. Vitreous humor analysis is of special importance for the post-mortem diagnosis of diabetic coma or disturbances of electrolyte metabolism. Yet unsolved problems in postmortem biochemistry are [12–15]:

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- What are the "normal values" in vitreous humor compared to blood and serum? Frequency distributions of antemortem serum and postmortem vitreous values in normal individuals must be calculated and compared. Correlations between antemortem serum and postmortem vitreous values must be calculated. From these correlations between antemortem serum and postmortem vitreous values with upper and lower 95% confidence bands inverse prediction intervals of serum values corresponding to observed vitreous values could be derived.
- Are chemical abnormalities of serum values reflected in vitreous humor and how fast are normal serum values (elevations and depressions) equilibrated in vitreous humor? Are these values stable postmortem in VH? (Fig. 1).

These questions are of course difficult to answer due to the following reasons:

- Normal values on VH during life are not and will not be available. We have to establish our normal VH values from postmortem studies on "normal individuals" and compare them to vital normal serum values. Antemortem vitreous values are known from animal experiments and quite large normal ranges were observed [15].
- The question if and how fast serum abnormalities are equlilibrated in vitreous humor can not be answered on living humans as well.

"Normal values" calculated as mean value ± 2nd standard deviation must fulfil threes suppositions (Fig. 2):

- Gaussean frequency distribution of values
- extensive investigations on healthy people or normal individuals
- extensive investigations on random samples with deviations and disturbances of the investigated parameter.

These suppositions are normally not given.

Especially investigations on random samples with deviations (elevations and depressions) of the investigated parameter are necessary to distinguish certainly normal from certainly abnormal values [14]. The upper and lower normal ranges are not sufficient to define a severe dysregulation. Discriminating values between normal and certainly abnormal can only be calculated after thorough and extensive investigations have been carried out on a well defined reference and control sample.

When chemical analytes, especially vitreous chemistry is used for postmortem diagnosis and as a mirror of serum chemistry at the moment of death the scientific gaps should be kept in mind. The correlation of serum and vitreous values was only investigated for a range of normal serum values and some values with moderate elevations or depressions but not with severe disturbances of homeostasis [15]. We have no reference material on cases with lethal serum values comparing these to vitreous values. Valid and reliable discrimination values are missing. These conclusions are valid for most analytes. However, for the postmortem diagnosis of fatal diabetes mellitus combined glucose and lactate values in vitreous humor have been proposed [25] (Table 1).

Especially the threshold values recommended by Sippel and Möttönen [25] are useful in practice and are based on a thorough statistical analysis. Combined values of glucose and lactate >410 mg/dl have the diagnostic significance of decompensated fatal diabetes mellitus.

2.1. Case history

2.1.1. Fatal juvenile diabetes type I

The value of postmortem vitreous findings together with histological and immunohistochemical investigations of the pancreas shall be outlined in the following case report.

An 11-year-old girl died 5 h after admission to a pediatric intensive care unit. Since a few days she complained of nausea and vomiting. The diagnosis of gastroenteritis was made by an ambulance doctor. Already in the week before the girl was weak and tired and could not attend school. In an ambulance diagnosis of viral gastroenteritis. During renewed admission to an ambulance she suddenly lost consciousness, and suffered an cardiac arrest. Immediately resuscitation measures were started. During resuscitation diagnosis of metabolic disorder and suspected diabetes mellitus.

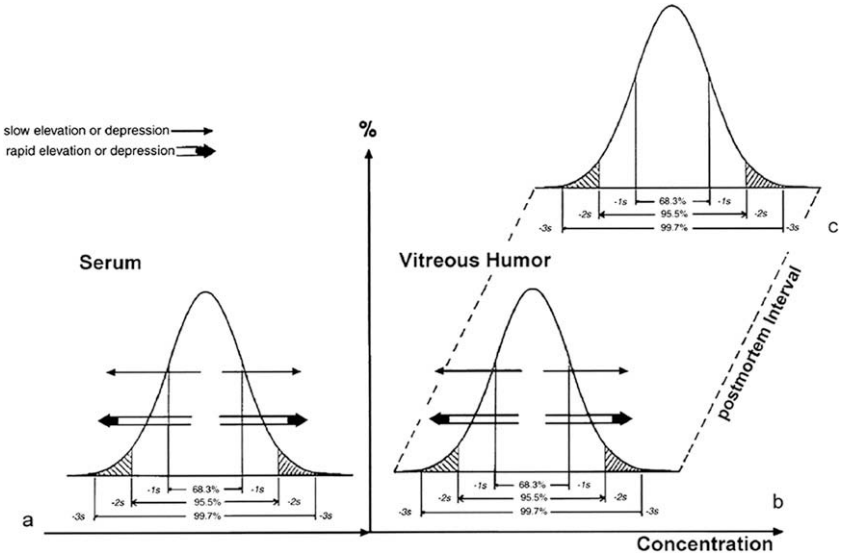

Fig. 1. To use vitreous humor as a mirror of antemortem serum values the following requirements must be fulfilled: frequency distribution of antemortem serum (a) and postmortem vitreous values (b) on "normal individuals" must be calculated and compared. Do the antemortem serum and the postmortem vitreous values have the same frequency distribution? Are elevations or depressions equilibrated in vitreous humor? Are the postmortem vitreous values stable (b and c: stability of the frequency distribution over the postmortem interval) (from [15]).