Unexplained to Unexpected: Cytokine Levels Unravel the Mystery and Help Attain Closure in Sudden Unexpected Death in Children

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Unexpected death occurring in an apparently healthy child is called ‘sudden unexpected natural death’ (SUD). Availability of sophisticated tests like brainstem studies, genetic analysis, and neuropathologic research has led to the diagnosis of infections, undetected developmental anomalies, genetic/metabolic disorders, vascular events, and occult malignancy [1]. Unexplained deaths are those where etiology could not be established even after a thorough investigation, including child’s medical history, circumstances of death, complete autopsy, and ancillary testing [2]. Campaigning for safe sleep practices, avoidance of tobacco smoke exposure, and creating awareness have reduced the rates of sudden infant deaths in most countries [3]. Infections affecting the respiratory, cardiovascular, or neurological system leading to SUD have been reported [4]. Mild fever, unwitnessed seizure, apnea, and sudden cardiac rhythm abnormalities may go unnoticed and unreported.

Morichi et al. have reported 4 children who were brought in cardiac arrest and tested positive for various viruses during postmortem infectious diseases’ work up [5]. Cytokine profiling was done in cerebrospinal fluid (CSF) samples obtained at arrival. The levels were compared with CSF samples of 4 children with noninfectious causes of accidental death and 11 controls with non-central nervous system illnesses without fatal episodes. The authors found a significantly high level of inflammatory cytokines, namely interleukin-1 receptor antagonist (IL-1ra), IL-6 and tumor necrosis factor (TNF- α), chemokines, namely IL-8, granulocyte-colony stimulating factor (G-CSF) and monocyte chemoattractant protein-1/chemokine ligand 2 (MCAF/CCL2) and platelet-derived growth factor (PDGF) in the infectious group in comparison with noninfectious and control group.

Despite clinical suspicion of infection in more than half of the SUD cases, confirmation of etiological agent remains low [4]. Common viruses identified include respiratory syncytial virus, herpes simplex virus, cytomegalovirus, adenovirus, influenza, parainfluenza, enterovirus, and rotavirus [5, 6]. Appropriate body fluid or tissue and inclusion of the implicated virus in the panel used for testing may not be possible at all times if clinical manifestations were nonspecific. Measurement of cytokines as surrogate markers to differentiate infectious and noninfectious causes may be beneficial.

Hypercytokinemia, chemokine-induced enhancement of blood brain barrier permeability, neuroendocrine pathway diurnal variations, rapid induction of systemic inflammatory response syndrome with paucity of compensatory anti-inflammatory response syndrome, and vascular tone abnormalities are proposed mechanisms leading to sudden death [7]. Elevated cytokine levels may help differentiate severe systemic manifestations causing death from incidental viral infections. Cytokine gene polymorphisms may alter their expression, and underlying immunodeficiency can complicate the picture [8]. The study children were detected in a state of cardiopulmonary arrest during sleep; the authors have not provided the time interval from the event to sampling. There may have been postmortem changes in these levels, and also, comparisons in only a small number of children hinders us from deriving definitive conclusions [5].

Testing facilities for multiple viruses, multiple cytokines and growth factors are not readily available in all centers. However, considering the emotional trauma of parents of such children, genetic basis for many of these illnesses, and hesitancy for complete autopsy, this study highlights the need to ensure storage of appropriate timely samples for analysis.

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Declarations

Conflict of Interest None.