

Refocusing SIDS research: Is butylcholinesterase a predictive biomarker?

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Unexpected infant and childhood deaths are defined as those where the child was not thought by the family or healthcare professionals to be at risk of death 24 hours before the death or the major collapse leading to the death.¹ Unexpected deaths include those subsequently shown to be explained by rapidly progressive natural causes e.g., previously unrecognised cardiac abnormalities, or infections, accidental and non-accidental trauma, drowning and suicide. They also include sudden infant death syndrome a term allocated to an infant death (< 1 year) when no sufficient explanation can be identified following a thorough investigation of the scene and circumstances of death, a post-mortem examination including microbiology and histopathology performed by a pathologist or medical examiner with paediatric training, and a multi-professional review of all available information.²

The devastation caused by a child's sudden and unexpected death, compounded by lack of explanation is hard to make tangible. The first time I ran an engagement day with bereaved parents I spoke to a man who told me about his son, Thomas*. After introducing himself he said "I'm Thomas' dad". This one small statement conveyed his loss and grief with such clarity it was palpable. Thomas is no longer here but he will always be his dad. Like every parent that day he was a parent looking for answers. How is it possible that his son died and no one could tell him why?

Many hypotheses have been postulated as to the cause of SIDS, but the prevailing view is that there is no single cause. Rather it is a phenomenon which occurs when risk factors combine, known best as the "triple risk model".³ This model proposes the convergence of three factors: a vulnerable infant, a critical developmental period and an exogenous stressor. Epidemiological research into the latter has arguably been the most successful to date with numerous circumstances e.g.

sleeping prone, parental smoking, recognised as increasing the risk of SIDS. Following public health campaigns, notably the advice to place babies to sleep on their back,⁴ the incidence of SIDS has reduced by up to 80% but it has not gone away. Incidence rates vary by ethnicity and country ranging from approximately 0.1 per 1000 live births in Japan and the Netherlands to 0.8 per 1000 in New Zealand.⁵

A period of critical development has brought attention to the autonomic system and the potential role of age dependent autonomic dysfunction in SIDS. The brainstem has often taken centre stage in previous studies as the master and commander of autonomic regulation particularly with regard to cardio-respiratory responses.⁶ Cardio-respiratory systems have similarly undergone investigation, with up to 5-10% of SIDS cases linked to cardiac ion channel gene variants and presumed cardiac arrhythmia.⁷ These and other gene disorders e.g. metabolic form much of the vulnerable infant category.

Harrington *et al* in a recent issue of *eBiomedicine*,⁸ focussed on the cholinergic system as an integral part of the autonomic system. Acetylcholine, the major neurotransmitter (NT) at nicotinic synapses within the CNS and the neuromuscular junction is hydrolysed by two enzymes acetylcholinesterase (AChE) and butylcholinesterase (BChE), although AChE predominates. Despite its role as a major neuronal NT, Acetylcholine, BChE and AChE are expressed in most tissues including many non-neuronal cell types. Recently both enzymes have attracted attention in the fields of inflammatory disease, multiple sclerosis and Alzheimers disease.⁹ Genetic polymorphisms are of particular interest as they regulate enzyme activity levels and response to cholinesterase inhibitor therapy.¹⁰

Harrington *et al* collected 722 dried blood spots (DBS), taken 2-3 days after birth from infants born between 2016 and 2020 in New South Wales.⁸ Forensic pathology records were used to identify individuals born within this time-frame who had died of SUDI (Sudden Unexpected Death in Infancy). They aimed to measure AChE and BChE activity from the DBS but due to technical limitations measurements were restricted to BChE specific activity. Ultimately the analysis of DBS BChE activity from 26 infants who subsequently died of SIDS, and 30 non-SIDS sudden deaths was included. Each case sample was analysed alongside 10 DBS samples taken on

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the same post-natal day, from surviving infants of the same gender and born on the same day as the index case. This is an impressive and robust control data set. The authors show that BChE specific activity levels were significantly lower in the SIDS cases compared to controls and to the non-SIDS deaths. There were no significant differences between non-SIDS deaths and controls. Normative values for BChE activity analysed in this way from DBS outside of this study are not known. This means that although BChE activity levels are lower in the SIDS cases than the control samples, we cannot determine for certain if they are below a physiological norm.

Can we extrapolate BChE activity taken from DBS to what may be happening at neuronal synapses? AChE is the predominant enzyme in the cholinergic system so what effect could reduced BChE activity have? Will results be replicated in other cohorts? These questions need to be answered and a functional model is required to understand the system effect but the findings are undeniably intriguing. They potentially show a measurable vulnerability in the autonomic system before death occurs. The authors have re-focused SIDS research with a new target in sight. A target that could unify central nervous, cardiac and respiratory, including respiratory muscle systems, that have all been implicated in SIDS.⁵

*Name has been changed for privacy.

Contributors

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Declaration of interests

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