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Hippocampal abnormalities and sudden childhood death

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Do postmortem structural changes in the hippocampal formation explain the still mysterious mechanism of premature mortality in otherwise normal children? Could clinically unrecognized seizures provide a missing link between two syndromes featuring sudden unexpected death in children, SUDC, and individuals with a history of epilepsy, SUDEP?

Two recent reports [1, 2] highlight unexpected patterns of epileptiform pathology in the forebrain of infantile SUDC cases. The novelty involves the region where the structural changes were discovered, and their striking overlap with those described in pediatric febrile seizure cohorts that often evolve into hippocampal sclerosis and temporal lobe epilepsy [3]. In a pilot forensic study of 153 SUDC cases, the three most common morphological features identified were focal dentate granule cell bilamination, asymmetry, and malrotation, seen in 47.8 % (33/69) of SUDC cases compared to 13.3 % (3/23) of explained cases. Nearly half (59/121) of the cases had a personal or family history of febrile seizures, and a fever around the time of death. A further compelling similarity was that 93 % of the victims were found prone during a sleep period; SUDEP shows a similar nocturnal and positional predisposition. Exome testing found 1 of 3 genotyped cases was positive for a de novo KVLQT1 cardiac LQT mutation, a proven cause of SUDEP [4]. Such mutations of ion channel genes co-expressed in heart and brain are a recent and important risk factor for SUDEP, where they cause seizures, arrhythmias, and premature death [4]. Interestingly, SUDEP genes lead to hippocampal and dentate gyrus abnormalities in mouse models, and seizures themselves are a well established cause of further structural deformation in immature brain. Therefore the hippocampal lesions represent a newly forming seizure focus with a high probability of progression to epilepsy, warranting a new term, ‘epilepsy in situ’.

Since the hippocampus lies far from the lower brainstem where the forensic SIDS lamppost has shone for several decades, what makes this lesion lethal? Long focused on pontine and medullary centers where microcircuits regulate cardiorespiratory pacemaking, the search for causative abnormalities has moved to higher levels of central autonomic pathways mediating arousal and auto resuscitation [5]. Forebrain control over cardiorespiratory nuclei resides in the rostral limbic system, including amygdalo-hippocampal circuitry and insula, loci well known for their low focal seizure thresholds. Hyperexcitability and seizures confined to these circuits may be clinically subtle, and even in the absence of a seizure, SUDEP genes lower the threshold for brainstem spreading depression, a lethal event [6].

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Ultimately, sudden death risk depends upon a diverse combination of structural, physiological, and genetic features. The etiology in an individual case may be unclear, and whether inherited or acquired, how early the biological risk begins (in utero, perinatal, or thereafter) will vary. Given the spectrum of anatomical pathways and excitability molecules that promote their normal connectivity, the risk of sudden unexpected death depends upon the collective status of scores of causal gene variants that unleash autonomic instability and seizures; such ‘pre-epilepsy’ cases may present either with or without structural pathology or clinically manifest seizure activity.

Indeed, as the authors point out, the visible lesion they define as ‘hippocampal malformation associated with sudden death’ (HMASD), was present in almost 50 % of the total cases of SUDC, leaving the remaining 50 % unexplained. In both groups, cardiac LQT gene testing deserves to become an integral element of the forensic workup. Going forward, special stains for activity-dependent cell markers that seizures leave in their wake [7] could provide further evidence to establish a forensic diagnosis of “epilepsy in situ”, a new term that may be usefully applied to a microscopic epileptiform lesion with or without evidence of actual seizures.

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