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Review

Stress and sudden death ☆

Claire M. Lathers [a,*], Paul L. Schraeder [b]

[a] Office of the Director, Center for Veterinary Medicine, U.S. Food and Drug Administration, Rockville, MD 20855, USA
[b] Department of Neurology, Drexel University College of Medicine, Philadelphia, PA 19102, USA

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Abstract

Cardiac patients, psychiatric patients, and certain ethnic groups experiencing acute stressful circumstances are at risk for unexpected sudden death. Although stress is associated with changes in autonomic neural function, its role as a potential risk factor for sudden unexpected death in epilepsy (SUDEP) is not known. The association of epilepsy with cardiac abnormalities, such as neurogenic arrhythmias and microscopic perivascular and interstitial fibrosis, and with depression and anxiety indicates that emotional stress should be evaluated as a potential risk factor for SUDEP. The impact of adverse emotional states on the autonomic control of cardiac rhythm is a known important factor leading to cardiac dysrhythmias in humans and other species. The interaction between emotional factors and the arrythmogenic potential of epileptiform discharges and the possibility of benefit from stress management intervention need to be investigated.

Keywords: Sudden death; Sudden unexpected death in epilepsy; Epilepsy; Cardiac disease; Psychiatric disorders; Stress; Depression

1. Introduction

Sudden deaths associated with stress have been reported since antiquity [1]. The *Acts of the Apostles* 5:1–11 [2] describe how Ananias was charged by Peter to have "lied not to man but to God." Ananias fell to the ground dead. His wife Sapphira met a similar fate when told that those who had buried her husband were at the door and planning to "carry thee out." In 1942, Walter Cannon [3] cited examples from the anthropology literature of death from fright and entitled his article: "Voodoo Death." Cannon discussed the role of the sympathico-adrenal system. Engle [4] collected 160 different accounts of sudden deaths due to emotional stress, finding that in most cases the circumstances were associated with extreme excitation, resignation, or despondency. Even if it is only in the form of a mental image of pain, psychological stress can cause asystole [5]. Cardiac pathological changes reported in victims of stress-related deaths [6] have been designated *myofibrillar degeneration* or *myocytolysis*. This microscopic entity has been found to be identical to that identified in the hearts of patients who died of subarachnoid hemorrhage and other acute strokes.

2. Sudden death in certain ethnic populations

Although Lown [7] noted that sudden cardiac death is the major challenge in cardiology, sudden death is also a recognized risk in certain ethnic populations [8]. For example, healthy Filipino men may experience *Bangungut*, an unexpected death during sleep. *Bangungut* means "to rise and moan during sleep." *Pokkuri* is the term used to describe sudden cardiac deaths among apparently healthy Japanese soldiers during World War II [9]. In the case of the soldiers, warfare could produce major stresses including personal danger, mourning, extreme excitation, resignation, and despondency. Engle [4] described eight precipitating circumstances that precede sudden death: (1)

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* Corresponding author. Present address: 115 South Manning Boulevard, Albany, NY 12203, USA. Fax: +1 518 482 6732.
E-mail address: lathers@attglobal.net (C.M. Lathers).

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illness or death of a close person, (2) acute grief, (3) threat of loss of a close person, (4) mourning or anniversary of a death, (5) loss of status or self-esteem, (6) personal danger or threat of injury, (7) relief from danger, and (8) reunion, triumph, or happy ending. The precipitating event was one that was impossible for the victim to ignore because it was abrupt, unexpected, or dramatic or because of its intensity, irreversibility, or persistence.

Retrospective investigation of 51 cases of sudden unexplained death in non-East Asian subjects, including indigenous Saudis, between January 1995 and June 1997, revealed that most victims were subcontinent Indians (43%) [10]. Autopsies were done on 22 victims. Seven exhibited mild to moderate cardiac hypertrophy, with two of these seven also having mild to moderate coronary stenosis. Four other victims exhibited a similar degree of coronary narrowing, but had no evidence of myocardial hypertrophy. Severe pulmonary congestion and alveolar hemorrhage were detected in 18 of the 22 victims autopsied.

A leading cause of death of young men in several East Asian populations is sudden and unexplained death in sleep [11]. A review of autopsy records from 1948 to 1982 in Manila was used to classify these types of deaths. A nested case–control study of death certificates examined birthplace as an indicator of risk of sudden, unexplained death in sleep. There were 722 sudden, unexpected deaths in sleep during this time. Characteristics of victims in each group were similar: 96% were male, mean age was 33, and modal time of death was 3:00 AM. The deaths were seasonal, peaking in December and January. The death rate for mean ages 25–44 increased from 10.8 to 26.3 per 100,000 person-years from 1948 to 1982, possibly because of more accurate classification of cause of death. Because the deaths appeared to be a regional phenomenon in Southeast Asia it was speculated that environmental factors were likely, as the deaths were seasonal, increased over the time span studied, and were more common among migrants to Manila than among people born there.

Owada et al. [12] reported on autopsies of sudden death cases in Japan from May 1994 to February 1998. The medical records for 91 cases were reviewed, and interviews were conducted with the victims' close family members. Of 271 cases, 176 patients 20 to 59 years old were classified as cases of sudden death in the working generation. Of the sudden death cases, 29 were due to coronary artery disease (31.9%), 18 to acute cardiac dysfunction (19.8%), 6 to other cardiac diseases (6.6%), 4 to acute aortic dissection (4.4%), 4 to cerebrovascular disease (4.4%), and 30 to other diseases (32.9%). Risk factors identified included long-term stress, history of heart disease, hypertension, chest symptoms, autonomic disturbance, short-term stress, and a smoking habit. Short-term stress, autonomic disturbance, and a smoking habit increased the risk of sudden death due to coronary artery disease. Long-term stress was associated with increased risk of sudden death due to acute cardiac dysfunction. Autonomic disturbance and stress were related to the occurrence of sudden death. The authors recommend that it would be helpful to identify subjective symptoms so one can intervene to relieve such stress and presumably reduce the risk of sudden death.

Basso et al. [13] reported on 200 cases of sudden death in persons less than 35 years of age in the Veneto region in Italy. Fifteen cases (7.5%) were due to cerebral, 10 to respiratory (5%), and 163 to cardiovascular (81.5%) etiologies. Twelve deaths (6%) were unexplained. For cardiovascular sudden death, obstructive coronary atherosclerosis was found in 23% of the cases and arrhythmogenic right ventricular cardiomyopathy in 12.5%. Mitral valve prolapse occurred in 10%, conduction system abnormalities in 10%, and congenital coronary artery anomalies in 8.5%. Myocarditis was reported for 7.5%, hypertrophic cardiomyopathy for 5.5%, aortic rupture for 5.5%, and dilated cardiomyopathy for 5%. Nonatherosclerotic acquired coronary artery disease was reported in 3.5%, postoperative congenital heart disease in 13%, aortic stenosis in 2%, pulmonary embolism in 2%, and other causes in 2%. Sudden death was unexplained in 6% of the cases. Thus, even though a large spectrum of cardiovascular disorders appeared to be the most common organic substrate for most sudden deaths in this population, more than 1 in 20 cases of sudden death in this young adult population were not explained by structural risk factors.

3. Non-SIDS pediatric sudden unexplained death in the United States

Sudden unexplained death claims more than 4000 persons between the ages of 1 and 22 each year in the United States. Almost half of the pediatric sudden death victims have a normal structural autopsy. Therefore, identification of children at risk for cardiac arrhythmias as a cause of seizurelike events and optimal seizure control measures in those at risk for seizure-related cardiac arrhythmias are possible approaches to risk reduction [14]. Many studies suggest that assessment of medical histories, in combination with cardiovascular and EEG evaluation of surviving family members, may help to clarify possible risks for various categories of sudden unexplained death [15–20]. The genetic basis for potentially fatal arrhythmia associated with the inherited long-QT syndrome (LQTS) may be a factor. For example, a 17-year-old sudden death victim's mother was challenged with epinephrine and a potential defect in the phase 3 potassium current encoded by the gene *KVLQT1* was identified. A 5-bp deletion was identified in the genetic material recovered from the decedent's paraffin-embedded heart tissue [15]. Such isolated cases indicate that the ability to perform molecular autopsies on achieved necropsy material may transform the forensic evaluation of sudden death. The combination of catecholamine provocative testing in surviving family members and postmortem LQTS gene analysis may unmask families with "concealed" LQTS and establish the cause of previously unexplained sudden death, including, presumably, sudden