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ORIGINAL ARTICLE

Does Sudden Unexplained Nocturnal Death Syndrome Remain the Autopsy-Negative Disorder: A Gross, Microscopic, and Molecular Autopsy Investigation in Southern China

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Abstract

Objective: To look for previously unrecognized cardiac structural abnormalities and address the genetic cause for sudden unexplained nocturnal death syndrome (SUNDS).

Methods: Data for 148 SUNDS victims and 444 controls (matched 1:3 on sex, race, and age of death within 1 year) were collected from Sun Yat-sen University from January 1, 1998, to December 31, 2014, to search morphological changes. An additional 17 patients with Brugada syndrome (BrS) collected from January 1, 2006, to December 31, 2014, served as a comparative disease cohort. Target-captured next-generation sequencing for 80 genes associated with arrhythmia/cardiomyopathy was performed in 44 SUNDS victims and 17 patients with BrS to characterize the molecular spectrum. The SUNDS victims had slight but statistically significant increased heart weight and valve circumference compared with controls.

Results: Twelve of 44 SUNDS victims (*SCN5A*, *SCN1B*, *CACNB2*, *CACNA1C*, *AKAP9*, *KCNQ1*, *KCNH2*, *KCNJ5*, *GATA4*, *NUP155*, *ABCC9*) and 6 of 17 patients with BrS (*SCN5A*, *CACNA1C*; $P>.05$) carried rare variants in primary arrhythmia-susceptibility genes. Only 2 of 44 SUNDS cases compared with 5 of 17 patients with BrS hosted a rare variant in the most common BrS-causing gene, *SCN5A* ($P=.01$). Using the strict American College of Medical Genetics guideline-based definition, it was found that only 2 of 44 (*KCNQ1*) SUNDS and 3 of 17 (*SCN5A*) patients with BrS hosted a "(likely) pathogenic" variant. Fourteen of 44 SUNDS cases with cardiomyopathy-related variants had a subtle but significantly decreased circumference of cardiac valves, and tended to die on average 5 to 6 years younger compared with the remaining 30 cases ($P=.02$).

Conclusion: We present the first comprehensive autopsy evidence that SUNDS victims may have concealed cardiac morphological changes. SUNDS and BrS may result from different molecular pathological underpinnings. The distinct association between cardiomyopathy-related rare variants and SUNDS warrants further investigation.

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Since the initial report in 1917, sudden unexplained nocturnal death syndrome (SUNDS) has been considered an autopsy-negative disorder with unknown etiology and describes a distinct subgroup of individuals with idiopathic sudden death.[1] Sudden unexplained nocturnal death syndrome prevails preponderantly in Southeast Asia and has multiple academic terms in different nations such as bangungut in the Philippines,[1] lai-tai in Thailand,[2] pokkuri in Japan,[3] and sudden manhood death syndrome in China.[4] The incidence of SUNDS (per 100,000 people-years) has been reported to be as high as 43 in the Philippines[5] and 38 in Thailand.[6] Kampuchea, Laos, and Hmong

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refugees in the United States were also reported to have a high incidence (59, 82, and 92 per 100,000 people-years, respectively) of SUNDS.[7,8] The annual incidence of SUNDS is approximately 1 to 3 per 100,000 people in Southern China.[4,9]

The definition of SUNDS describes a perplexing entity with a special clinic phenotype[1-9]: (1) predominantly occurs in Southeast Asia or immigrants from Southeast Asia without a marked disease history; (2) prevails preponderantly in apparently healthy males (>90%); (3) more than 80% of victims are between 20 and 40 years of age; (4) occurs during nocturnal sleep with typical symptoms such as moaning and tachypnea, which last for just a few minutes before death; (5) there are no pathological changes to identify the cause of death; (6) most victims were sporadic; and (7) death most frequently occurred out of hospital without any clinical record, giving first access to forensic pathologists rather than clinicians.

Various hypotheses, such as bacterial infection,[10] potassium deficiency,[11] structural or functional abnormalities of the coronary arteries,[3] and nocturnal sleep respiratory disorders,[7] have been postulated by epidemiological studies on SUNDS but need further confirmation.[4,9] Although structural diseases such as cardiac conduction system (CCS) abnormalities and acute hemorrhagic pancreatitis account rarely for the death of a SUNDS victim,[1-3,5-9] the vast majority of cases reported were defined as autopsy-negative.[1,3,4,7-9,12-15]

As a special idiopathic sudden cardiac death (SCD), it differs significantly in clinical phenotype from other primary electric disorders such as long QT syndrome (LQTS) or short QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT). Brugada syndrome (BrS) and SUNDS have been considered to be phenotypically, genetically, and functionally the same allelic disorder.[16] We have previously reported postmortem genetic screening for SUNDS,[4,12-15] but these studies were limited by small autopsy numbers or a relative paucity of candidate genes screened. Thus, further studies for the morphological and molecular pathological characterizations of SUNDS are justified.

To address whether SUNDS is truly morphologically negative, we performed a case-control study on gross and microscopic findings in the largest number of Chinese SUNDS autopsy cases reported to date. In addition, we conducted a next-generation sequencing–based 80 genes targeted analysis on 44 consecutive SUNDS victims and 17 patients with BrS to characterize the molecular pathological spectrum of Chinese SUNDS compared with BrS.

METHODS

Study Population

Data for 148 consecutive SUNDS cases were collected from January 1, 1998, to December 31, 2014, at the National Center for Medicolegal Expertise at Sun Yat-sen University. The inclusion criteria for SUNDS were as previously reported[4,9,12-15]: (1) an apparently healthy individual older than 15 years and without a history of important disease; (2) who died of a sudden unexpected death during nocturnal sleep; (3) and had a negative autopsy, toxicology, histology, and death-scene investigation that resulted in their death being unexplained. Cases with (1) obvious disease or pathological changes to explain the death or (2) a nonnatural manner of death (such as suicide, homicide, and accident) were excluded.

Data for an additional 444 non-SUNDS death cases were collected from the same autopsy case database and served as the control group. These controls represented individuals with an acute nondisease death within 24 hours caused by traffic accident, mechanical asphyxia, electric shock, and carbon monoxide poisoning and were previously healthy, without any marked disease or pathological changes identified by postmortem examinations. The controls were matched 3:1 with the SUNDS cases. The matching criteria were as follows: (1) sex and race identical to the paired case; (2) age of death within 1 year; and (3) interval of death date within 3 months.

Seventeen consecutive patients with BrS during the period January 1, 2006, to December 31, 2014, were collected from the Department of Cardiology at the First Affiliated Hospital of Sun Yat-Sen University and designed as a comparative disease cohort for