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Risk factors for sudden cardiac death among patients with schizophrenia

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ABSTRACT

Introduction: Patients with schizophrenia suffer from excessive premature mortality, and sudden cardiac death (SCD) is receiving growing attention as a potential cause.
Aim: The present study investigated the incidence of SCD and its risk factors in a large schizophrenia cohort.
Methods: We enrolled a consecutive series of 8264 patients diagnosed with schizophrenia (according to DSM-III-R and DSM-IV criteria) who were admitted to a psychiatric center in northern Taiwan from January 1, 1985 through December 31, 2008. By linking with national mortality database, 64 cases of SCD were identified. The standardized mortality ratio (SMR) for SCD was estimated. The cases were matched with controls randomly selected using risk-set sampling in a 1:2 ratio. A standardized chart review process was used to collect socio-demographic and clinical characteristics and the prescribed drugs for each study subject. Multivariate conditional logistic regression analysis was used to identify correlates of SCD at the index admission and the latest admission.
Results: The SMR for SCD was 4.5. For the clinical profiles at the index admission, physical disease (adjusted risk ratio [aRR] = 2.91, $P < .01$) and aggressive behaviors (aRR = 3.99, $P < .01$) were associated with the risk of SCD. Regarding the latest admission, electrocardiographic abnormalities (aRR = 5.46, $P < .05$) and administration of first-generation antipsychotics (aRR = 5.13, $P < .01$) elevated the risk for SCD. Consistently, aggressive behaviors (aRR = 3.26, $P < .05$) were associated with increased risk as well.
Conclusions: Apart from cardiovascular profiles and antipsychotics, physical aggression is a crucial risk factor that deserves ongoing work for clarifying the mechanisms mediating SCD in schizophrenia.

1. Introduction

Schizophrenia is a debilitating disease that affects 1% of the world population and often leads a deteriorating course and premature mortality. The life expectancy of patients with schizophrenia is 10–25 years shorter than that of the general population, and it has not had improvements similar to the general population during the past decade (Crump et al., 2013). The standardized mortality ratios (SMRs) range from 2 to 4 for patients with schizophrenia depending on the cause of death. Additionally, the SMRs have escalated for all leading causes of death for the past 20 years (Saha et al., 2007). One possible explanation for their shorter life expectancy is a tendency toward unnatural deaths such as suicides, accidents, violence, and substance abuse (Crump et al., 2013; Saha et al., 2007; Sweeting et al., 2013). Nonetheless, two-thirds of the premature deaths among patients with schizophrenia are, in fact, accounted for by natural causes, with 40%–50% of them being due to cardiovascular diseases (Sweeting et al., 2013).

In the psychiatric care community, concerns are amplified regarding the possibility of increased risk of sudden cardiac death (SCD) in patients with schizophrenia. SCD is reported to be three times as likely among patients with schizophrenia as among individuals from the general population (Davidson, 2002), and myocardial infarction may account for over half of the cases (Ifteni et al., 2014). SCD is typically defined as death due to a cardiac cause within a short time (minutes to hours) after the symptoms initially appear. The symptoms often occur without warning, which inevitably triggers an inspection of the entire therapeutic process afterward, searching for preventable causes (Davidson, 2002; Laursen et al., 2011). Risk factors for SCD in the general population are not well established, but age, smoking, metabolic profile (e.g., hyperlipidemia, hypertension, glucose intolerance, obesity),

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cardiac conditions (e.g., tachycardia, left ventricular hypertrophy, intraventricular conduction block), and decreased pulmonary vital capacity are implicated (Straus et al., 2004a).

It is well known that patients with schizophrenia are predisposed to cardiovascular diseases, and antipsychotics may aggravate such risk (Newcomer, 2007; Scigliano and Ronchetti, 2013), setting the stage for lethal arrhythmia or myocardial infarction to occur. The most established risk factor of SCD in schizophrenia is antipsychotic exposure. Patients receiving antipsychotics have a greater risk than non-users to die prematurely of SCD (Girardin et al., 2013; Sweeting et al., 2013), and the association is dose-dependent (Ray et al., 2001). First-generation and low-potency antipsychotics appear to carry an unusually higher liability, whereas second-generation antipsychotics may ameliorate such risk (Kiviniemi et al., 2013).

Apart from antipsychotic exposure, prior research shows that the risk factors for SCD in schizophrenia are mostly related to cardiac arrhythmia (e.g., prolonged QTc interval and Torsade de Pointes) (Glassman and Bigger, 2001; Suvisaari et al., 2010). Intriguingly, a comprehensive exploration of potential risk factors, including demographic characteristics, cardiovascular diseases, psychopathology, and laboratory markers, is rarely performed. Accordingly, we explored the incidence and risk factors for SCD in a large, hospital-based schizophrenia cohort. Potential correlates of multiples dimensions were being assessed, including demographics, psychopathology, physical illnesses, laboratory markers, and electrocardiography findings.

2. Methods

2.1. Study population

We enrolled patients with schizophrenia who were consecutively admitted to a psychiatric service center in northern Taiwan from January 1, 1985 to December 31, 2008. The methodology used is described extensively elsewhere (Kuo et al., 2011). In short, we included patients who at each discharge received a consistent principal diagnosis of schizophrenia (ICD-9 code 295.**) which was made after a diagnostic interview during admission and reconfirmed by a board-certified psychiatrist in charge. Some 8264 patients met the inclusion criteria and comprised the study cohort. In the present study, information regarding both the index admission and the latest admission prior to SCD were included. This study was approved by the Institutional Review Board of the Committee on Human Subjects of Taipei City Hospital, Taipei, Taiwan.

2.2. Case ascertainment

Each cohort member was electronically linked, by using the national identification number as an identifier, with the Department of Health Death Certification System in Taiwan from January 1, 1985 through December 31, 2008. Subsequently, we identified 867 deaths along with the cause of death (Fig. 1). Of those 867 patients who died, 64 died of SCD. SCD was defined as a death reported as occurring out of hospital or in the emergency room or as "dead on arrival" with an underlying cause of death reported as cardiac disease. The underlying cause of death included ICD-9 codes 390 to 398, 402, and 404 to 429, consistent with the criteria adopted in prior studies (Chugh et al., 2004; Zheng et al., 2001). Of SCD, coronary artery diseases (ICD-9 codes) included acute myocardial infarction (410), other acute and subacute forms of ischemic heart disease (411), old myocardial infarction (412), angina pectoris (413), and other forms of chronic ischemic heart disease (414). We then calculated SMRs for all causes of death.

2.3. Nested case–control study

Derived from the study cohort (N = 8264), we conducted a nested case–control study to explore potential risk factors associated with SCD by means of a time-consuming and comprehensive chart review process. This study was conducted within a cohort in which further information (perhaps from expensive or time-consuming tests) was obtained on most or all the case subjects, but for economy, was obtained from only a fraction of the remaining cohort subjects as the controls (Greenland, 2008). Typically, case–control studies involve a cumulative design in which controls are selected from non-cases at the end of a follow-up period (Greenland, 2008). However, the strategy of risk-set sampling for obtaining controls has an advantage, in which has potentially much less sensitivity to bias from exposure-related loss-to-follow-up, as noted by epidemiologists (Greenland and Thomas, 1982; Miettinen, 1976). We used this methodology to select controls in previous studies (Kuo et al., 2011, 2012; Pan et al., 2014). Based on risk-set sampling, this study selected two or fewer controls randomly for each case participant, matched for age (±5 years), gender, and the year of index admission. The index admission was defined as the earliest hospitalization during the study period. Additionally, controls were selected from cohort patients who were alive at the time of death of the corresponding case. Thus, cases that were identified later during the study period were eligible to serve as controls for earlier cases. Consequently, 53 cases were successfully paired with 103 controls; controls were unavailable or had incomplete information for 11 cases. In 50 case–control pairs, two controls were selected for each case. One control was chosen for each case in three pairs.

2.4. Data collection

A semi-structured form was used for any inpatient who was admitted to the Taipei City Psychiatric Center since 1980 (Kuo et al., 2011). The form collected clinical information and contained over 95 items including sociodemographic information and a detailed psychiatric evaluation, including the diagnosis, mental state examination, family history, and physical diseases. We used this form to collate clinical information in prior studies (Kuo et al., 2011). For each inpatient, a resident psychiatrist and a board-certified psychiatrist conducted semi-structured interviews for obtaining relevant clinical information during hospitalization. In addition, a fasting venous blood sample was routinely drawn for biochemical and serological analyses on the first morning after hospitalization. After hospitalization, a 12-lead electrocardiography (ECG) examination was immediately performed on each subject.

By means of a combined chart review process by two trained clinical psychologists and double checking by a senior psychiatrist (CJK), detailed information on each subject was obtained. We developed a structured concept form comprising 115 items for helping the review process. Typically, for each patient, 40 min were required to obtain the information regarding demographic status, social support, employment history, psychiatric comorbidity, the prescription of psychotropics (antipsychotics and antidepressants), symptom profile, other clinical features (e.g., suicide attempt, aggressive behaviors, physical diseases), and laboratory data related to the index and latest (most recent) hospital admissions, respectively. We measured the defined daily dose (DDD) of antipsychotics use based on the dosage information obtained from the Anatomical Therapeutic Chemical Classification system (ATC/DDD Index 2009. http://www.whocc.no/atc_ddd_index/ [accessed May 1, 2009]) (WHO Collaborating Centre for Drug Statistic Methodology, 2009). For example, 8 mg of haloperidol used daily was equal to one DDD.

The chart reviewers were blinded to the mortality status. All reviewers participated in a reliability study (Kuo et al., 2011), rating information for four cases and eight controls independently, with kappa values greater than 0.7 for all key variables, including symptom profiles, comorbidity, and suicide attempt.

2.5. Statistical analyses

First, we estimated the SMRs. The survival time for each subject was calculated from the index discharge to the end of the study. SMRs for