



Sudden unexpected death in schizophrenia: Autopsy findings in psychiatric inpatients



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ABSTRACT

Schizophrenia is associated with premature mortality and a high rate of sudden, unexpected deaths. Autopsy data are scant, and in studies using death certificates or root cause assessments, a majority of sudden deaths remained unexplained. In the community, post-mortem data indicate that the most common cause of sudden “natural” death is coronary artery disease. In this study, we used autopsy findings to determine the cause of sudden death in a consecutive cohort of 7189 schizophrenia patients admitted to a free-standing, psychiatric teaching hospital from 1989 to 2013. Medical record review identified 57 patients (0.79%) who died suddenly and unexpectedly during hospitalization. Autopsies were performed in 51 (89.5%) patients (55.9 ± 9.4 years, male = 56.9%). Autopsy-based causes of sudden death were most commonly cardiovascular disorders (62.8%). Specific causes included myocardial infarction (52.9%), pneumonia (11.8%), airway obstruction (7.8%), myocarditis (5.9%), and dilated cardiomyopathy, hemopericardium, pulmonary embolus, hemorrhagic stroke and brain tumor (2.0% each). The sudden death remained unexplained in 6 (11.8%) patients, 3 of whom had evidence of coronary arteriosclerosis on autopsy. Patients with and without myocardial infarction were similar regarding age, gender, smoking, body mass index and psychotropic treatment (*p* values ≥ 0.10). In conclusion, sudden cardiac death occurs at a 0.8% rate in a psychiatric hospital, well above general population rates. Autopsy findings indicate that sudden death in schizophrenia is caused by structural cardiovascular, respiratory and neurological abnormalities, with most cases due to acute myocardial infarction. Early recognition and treatment of coronary artery disease must become a clinical priority for all adults with schizophrenia.

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1. Introduction

The physical health of patients with schizophrenia is poor (De Hert et al., 2011a) and a large body of evidence has documented their shortened life expectancy (Osby et al., 2000; Rasanen et al., 2005; Colton and Manderscheid, 2006; Bushe et al., 2010). Suicides, accidents and cardiovascular disorders are considered the main reasons for the excess of premature, sudden and unexpected deaths in this population (Ruschena et al., 1998; Appleby et al., 2000; Colton and Manderscheid, 2006; Loas et al., 2008; Bushe et al., 2010; Manu et al., 2011). In patients treated with antipsychotic drugs, which include a large number of

individuals receiving psychiatric care for schizophrenia, sudden cardiac death has been the focus of large epidemiological studies in the United States (Ray et al., 2001; Ray et al., 2009). Using death certificates and complex algorithms to exclude patients who died from previously known noncardiac conditions and to adjust for co-morbid somatic disorders, the investigators established that the incidence-rate ratio of sudden cardiac death was doubled in individuals prescribed first- or second-generation antipsychotics in the last month of life (Ray et al., 2009). The findings were thought to reflect the dose-dependent antipsychotic drugs' inhibitory effect on phase 3 of the myocardial cell repolarization, which may lead to *torsades de pointes*, an arrhythmia that may lead to ventricular fibrillation and sudden death. However, the findings were disputed by the American Psychiatric Association's Council on Research, which has stated that “a retrospective analysis of death certificates to evaluate mortality by SCD [sudden cardiac death], ... may overestimate SCD incidence” (Lieberman et al., 2012). The American Psychiatric Association's position is supported by the methodology used to ascertain the sudden arrhythmic death syndrome

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(Behr et al., 2007). This diagnosis is made in cases of sudden death with no history of cardiac disease, no identifiable macroscopic cause of death at a complete autopsy, and no abnormal findings on microscopic examination of the heart by a cardiac pathologist.

Autopsy findings in patients with schizophrenia who died suddenly have been reported only a few times in the past two decades. In a study of 66 cases presented to the medical examiner in Maryland from 1994 through 1996, the majority of deaths not due to accidents or suicides were caused by atherosclerotic heart disease (Chute et al., 1999). In a 10-year review of 683 autopsies performed in people with a history of schizophrenia by the Department of Forensic Medicine in Sydney, Australia, the main cause of natural death was cardiovascular disease, present in 23% of a cohort in which 37% of deaths were attributed to suicide or voluntary overdose with prescribed or illicit drugs (Sweeting et al., 2013). In this Australian series, 72 (11%) of cases remained unexplained, and 30 of these patients were presumed to have primary arrhythmogenic disorders which may have been discoverable at a “molecular autopsy” (Semsarian and Hamilton, 2012). A study limited to 10 cases of clozapine-induced myocarditis diagnosed at autopsy included 3 patients with sudden and unexpected death (Ronaldson et al., 2011). The significance of these observations is limited by selection bias and incomplete clinical data.

Reported rates of sudden cardiac death in the general population range from 0.1 to 0.2% (Zipes and Wellens, 1998). In contrast with the limited data regarding the etiology of sudden death in patients with schizophrenia, autopsies have established that the majority of sudden and unexpected fatalities in the community are due to coronary artery disease. In a prospective study involving 692 individuals without history of cardiac disease autopsied in 83 coroner's jurisdictions in England, death was ascribed to coronary artery disease in 82.4% of cases, with acute ischemic changes in more than half of the subjects (Bowker et al., 2003). The proportion of coronary artery disease as the cause of sudden death was 63% in Ireland (Downes et al., 2010), and 80% in Hennepin County, Minnesota (Adabag et al., 2010). Similar findings have been reported in autopsies of adult hospital patients in Pittsburgh, Pennsylvania, who were presumed to have died of cardiac arrhythmia, but of whom 62% had >75% coronary artery stenosis and 53% had histological evidence of myocardial infarction (Nichols and Chew, 2012).

In this study, we present analyses of a consecutive cohort of patients treated for schizophrenia who died suddenly and unexpectedly in Romania, a country in which the public health legislation mandates autopsies for all patients dying during a hospital stay. We adopted a null hypothesis and postulated that the main cause of death in patients with schizophrenia is no different than in the general population, i.e., coronary artery disease with evidence of acute myocardial infarction.

2. Materials and methods

2.1. Setting

The patients described in this report were admitted to a 120-bed, free standing, public psychiatric hospital located in Brasov, Romania (population 277,000). The clinical care is provided by board certified psychiatrists affiliated with the local medical school. Patients deemed by their treating psychiatrist to have a significant medical deterioration are transferred the same day to the county hospital. The retrospective review of medical records was approved by the hospital's Ethics in Research Committee.

2.2. Patient population

From January 1, 1989 through December 31, 2011, the hospital admitted 7189 adult patients diagnosed with schizophrenia according to the contemporaneous version of the *Diagnostic and Statistical Manual* of the American Psychiatric Association. Public health legislation

requires a forensic evaluation of all inpatient deaths. The post-mortem examinations are carried out by board certified pathologists employed by the government at the local Institute for Legal Medicine. Autopsies are performed in all cases and the pathology report must include a summary of the findings. Exceptions from autopsy are granted only for narrowly defined religious or personal preference reasons.

2.3. Definition of sudden death

Hospital records over the 25-year period of the study identified 57 patients who died suddenly and unexpectedly. All of these patients died while being asymptomatic or within 1 h of new symptom(s) onset. None of these patients died of physical trauma, homicide, suicide or accidental drug overdose.

2.4. Data collection

Autopsies were performed in 51 (89.5%) of the 57 patients with schizophrenia who died suddenly and unexpectedly. Data extracted from their medical records and the post-mortem examination report included demographic information, duration of psychiatric disorder, length of stay prior to death, past medical history, medication regimen at the time of death, and autopsy findings. The chlorpromazine equivalent of the antipsychotic drugs received in 24 h preceding the sudden death was calculated according to published guidelines (American Psychiatric Association, 1997; Woods, 2003) and as previously used (Correll et al., 2009).

2.5. Statistical analyses

The autopsy findings were used to divide the sample into two groups of patients with or without myocardial infarction at autopsy. The significance of the differences between groups was assessed with χ^2 or Fisher's Exact tests for proportions and *t* test for continuous variables. All data were analyzed with JMP 5.0.1, 1989–2003, SAS Institute, Inc, Cary, North Carolina. All tests were two-sided, and alpha was set at <0.05.

3. Results

The study group comprised 29 males (56.9%) and 22 females (43.1%) with a mean age of 55.9 ± 9.4 years (Table 1). Patients had been diagnosed with schizophrenia for an average of 27.7 ± 10.3 years prior to their sudden death. The admitting diagnosis for the last hospitalization was paranoid subtype in 47 patients (92.2%), and catatonic and undifferentiated in 2 patients (3.9%) each. With the exception of one patient with pneumonia in whom the antipsychotic was stopped 2 days prior to death, all patients had received antipsychotic drugs in 24 h preceding their death, which had occurred after an average length of stay of 11.7 ± 7.6 days. The past medical history, as recorded by the admitting psychiatrists, was remarkable for congestive heart failure (4 patients, 7.8%), arterial hypertension (4 patients, 7.8%), bronchial asthma or chronic obstructive pulmonary disease (3 patients, 5.9%), diabetes mellitus (1 patient, 2.0%) and dyslipidemia (1 patient).

3.1. Causes of death

Cardiovascular disorders, identified in 32 (62.8%) of the cases, were the most common cause of sudden death in this cohort of inpatients with schizophrenia. The cardiovascular disorders included 27 patients (52.9%) with acute myocardial infarction, and 3 patients (5.9%) with myocarditis. None of the cases of myocarditis had been treated with clozapine. One patient (2.0%) had dilated cardiomyopathy and acutely decompensated heart failure with pulmonary edema. The cause of death was identified in one patient (2%) as cardiac tamponade due to hemopericardium. This patient was the only one restrained just before

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