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TECHNICAL NOTE

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Schizophrenia as a Cause of Death

ABSTRACT: Schizophrenia is a chronic disorder that is associated with increased mortality. Although traumatic deaths account for most of this increase, there is also an increased rate of natural deaths in this population. Altered autonomic physiology in this group might contribute to death. To determine if there are schizophrenics in whom, after a complete autopsy, no recognizable cause of death other than schizophrenia is established, the records of the Office of Chief Medical Examiner of the City of New York were reviewed for deaths associated with schizophrenia and a natural manner of death. Six such decedents were identified, and their histories and autopsy results are described. We believe that schizophrenia per se is a potentially lethal disorder. Autonomic irregularities and their interactions with psychotropic drugs deserve further attention.

KEYWORDS: forensic science, schizophrenia, sudden death, mortality, autonomic dysfunction, psychotropic drugs, long QT syndrome

Schizophrenia is a disorder characterized by delusions, hallucinations, disorganized speech and grossly disorganized behavior. Onset of schizophrenia typically occurs between the late teens and the mid-thirties and has been observed globally with prevalence among adults reported to be in the range of 0.5 to 1.5%. The course and outcome of the disease is unpredictable; some individuals have exacerbations and remissions, while others remain chronically ill (1).

Studies have shown an increased incidence of mortality among schizophrenics. To represent excess mortality, standard mortality ratios (SMRs) correspond to the ratio of observed to expected mortality. Expected mortality is generally calculated on the basis of official death rates. A SMR greater than 1.0 implies that the number of observed deaths exceeds the number of expected deaths. In a ten-year follow-up study carried out by Allenbeck and Wistedt (1986) that described the incidence of mortality among 1190 patients with schizophrenia hospitalized in Stockholm County during 1971, both male and female patients had twice (SMR = 2.4) the mortality rate of the general population (2). A 1989 review of nine studies in which schizophrenic patients were followed for at least five years found that their overall mortality is approximately twice that of the general population (3).

Tsuang and Woolson (1977) conducted a four-year follow-up study that compared excess mortality using standard mortality ratios. Their results generally showed schizophrenics subject to an increased mortality. Standard mortality ratios for male participants ranged from 4.69 (1935–44), 3.4 (1945–54), 0.86 (1955–64), and 1.44 (1965–74). Similar results were found for female subjects as well; their standard mortality ratios ranged from 3.30 (1935–44), 1.3 (1945–54), 2.06 (1955–64), and 1.8 (1965–74) (4).

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A 29-year follow-up study conducted in a Danish hospital by Mortensen and Juel (1990) described mortality rates of 6178 patients diagnosed with schizophrenia consistent with previous findings. They observed an overall increased mortality rate (SMR of 1.20 between 1957–1986) compared to the general Danish population (5).

In 1987, Black and Fischer assessed the mortality risk in 356 DSM-IIIR schizophrenic patients. They observed a nearly threefold (SMR = 2.96) increase in mortality compared to the general population in the state of Iowa (6). Other studies also support this observation (7–9). Several authors have demonstrated that suicide accounts for most of this excess mortality (2,3,6,8,9).

Beyond the scope of violent manners of death such as suicide, homicide, and accident, natural deaths of schizophrenics are commonly related to cardiovascular disease (2,3,5,7,10). In this article, we present the histories of six decedents who were subjects of a complete autopsy that subsequently established no recognizable cause of death other than schizophrenia.

Methods

Approximately 45,000 autopsies performed by the Office of Chief Medical Examiner between 1993 and 2001 were searched by computer for all deaths with schizophrenia as a final diagnosis and a natural manner of death. A total of 214 files from Manhattan (74), Brooklyn (42), Queens (55), the Bronx (35), and Staten Island (8) were identified and then examined manually. Two additional cases from 1988 also came to our attention during our review.

From these 216 files, six were identified with no competent cause of death other than schizophrenia. This assessment was made only after other potential etiologies were ruled out by a complete autopsy, including examination of the thoracic and abdominal viscera, neck organs, and brain. A complete postmortem investigation consists of a scene investigation, autopsy, microscopic examination of tissues, and extensive toxicology testing

that includes analysis for alcohol, other volatile substances, commonly abused illicit drugs, sedatives-hypnotics, opioids, and antipsychotics. In addition, any history or circumstance suggesting the availability of a drug not identified by our routine screening is specifically sought, either in our laboratory or an outside reference laboratory.

Case 1

A 41-year-old schizophrenic white man was found dead on his living room floor. The scene investigation indicated that he collapsed to the floor from a seated position. There were no illicit drugs or medications found at the scene, and his apartment was not in disarray. Interviews revealed that the decedent stopped taking medication and was described as "hyper" for two months before his death. Past medical history included a stab wound of the chest 13 years previously.

Autopsy disclosed a well-healed left thoracotomy scar and dense fibrous pleural and pericardial adhesions. An oblique one-inch line of sutures with visible pledget material was located over the right ventricle and had associated fibrosis. These findings were sequelae of the old stab wound.

The organs were otherwise unremarkable. The heart weighed 360 g. The right dominant coronary arterial system was free of atherosclerosis, and the myocardium exhibited moderate biventricular dilation. The aorta had mild atherosclerosis, and the lungs were congested.

Toxicological testing of blood and urine was negative. Histology and neuropathology were unremarkable.

We considered the possibility that an arrhythmia due to the fibrous scarring in the heart was the cause of death. However, the area of scarring was small and in the anterior right ventricle, far from the major branches of the conduction system. In addition, further history from the family disclosed that since the stabbing he had suffered no cardiac problems and had full exercise tolerance. In fact, he shoveled snow the week before his death. Therefore, we conclude that death was associated with schizophrenia and that neither physical nor chemical injury contributed to death.

Case 2

A 35-year-old black man with schizophrenia and mental retardation lived in a psychiatric facility. After becoming agitated and assaulting a staff member, he was administered 4 mg of lorazepam and restrained in his room. Four hours later, the decedent again became agitated, and an hour later he was given another 4 mg of lorazepam. Two hours after the second dose (and 7 h after the initial agitation event) a change of breathing occurred, and the decedent subsequently had cardiorespiratory arrest. He was brought to the emergency department unresponsive with fixed and dilated pupils. Prior medical history included Stevens-Johnson syndrome due to carbamazepine. His maintenance medications at the time were benztropine, clozapine, iron, and famotidine.

At autopsy, there were no physical injuries. The heart weighed 450 g (117-kg man) with slightly dilated cardiac chambers and no atherosclerosis. The liver weighed 2305 g and was moderately fatty. The remaining organs were unremarkable.

Toxicology detected clozapine (1.0 mg/L) in the blood. Imipramine (<0.1 mg/kg) and clozapine (40.1 mg/kg) were detected in the gastric contents. The liver was positive for clozapine (13.6 mg/kg), imipramine (<0.1 mg/kg), and benztropine (0.5 mg/kg). Clozapine and norclozapine were detected in the urine. Toxicological testing and re-testing did not detect lorazepam.

After a complete autopsy, the cause of death was schizophrenia with acute agitation.

Case 3

A 44-year-old schizophrenic black man, who resided at a psychiatric center, was evaluated for protracted constipation. Standard diagnostic procedures including colonoscopy ensued without complications. A small dose of meperidine was given during the procedure. Within hours following colonoscopy, the man had multiple psychotic outbursts and behaved oddly. Two attendants restrained him. While waiting for transport, the man became unresponsive and stopped breathing. His maintenance medications at the time were chlorpromazine, olanzapine, benztropine, valproic acid, clozapine, and lorazepam.

At autopsy, the external examination was unremarkable. The heart weighed 290 g with 60% atherosclerotic stenosis of the proximal and mid left anterior descending coronary artery. The aorta showed focal fatty streaks. The lungs were normal. Focal hemorrhages were present along the greater curvature of the gastric mucosa, and the descending colon was markedly dilated. All other internal organs were unremarkable.

Toxicology detected chlorpromazine (1.1 mg/L), benztropine (<0.1 mg/L), haloperidol (<0.1 mg/L), and valproic acid (32 μg/mL) in the blood. Chlorpromazine (305.7 mg/kg) and benztropine (1.3 mg/kg) were detected in the gastric contents. The liver was positive for chlorpromazine (16.3 mg/kg), haloperidol (2.4 mg/kg), and olanzapine (2.3 mg/kg). Histology revealed thickened leptomeninges, mild chronic colitis, slight thickening of cardiac vessels without inflammation, and focal glomerulorsclerosis.

The cause of death was certified descriptively as sudden death following colonoscopy for fecal impaction due to multiple anticholinergic medications for treatment of schizophrenia.

Case 4

A 40-year-old schizophrenic white woman lived with her brother, who last saw her alive at 6:30 a.m. At 9:30 a.m., he called 911 after finding her unresponsive on the floor of their apartment. There were no illicit drugs or medications found at the scene, and the apartment was not in disarray.

At autopsy, external examination revealed a 1.5 by 1 in. red-blue contusion of the left forehead with soft tissue hemorrhage and no underlying skull fracture. The heart weighed 320 g with no atherosclerosis, but slight hooding of the mitral valve leaflets. The lungs were normal. All other internal organs were unremarkable.

Toxicology detected mesoridazine (2.0 mg/L), sulforidazine (1.2 mg/L), and thioridazine (0.6 mg/L) in the blood. Thioridazine (2.3 mg/kg), mesoridazine (12.0 mg/kg), and sulforidazine (3.5 mg/kg) were detected in the gastric contents (<0.1 mg thioridazine in 15 g stomach contents, 0.2 mg mesoridazine in 15 g stomach contents, and <0.1 mg sulforidazine in 15 g stomach contents). The liver was positive for thioridazine (9.3 mg/kg), mesoridazine (0.3 mg/kg), and sulforidazine (3.5 mg/kg). Thioridazine, sulforidazine, and mesoridazine were detected in the urine. Histology revealed a small papillary carcinoma of the thyroid and marked vascular congestion of the lung, liver, and kidney. Neuropathology was unremarkable.

After complete autopsy, the cause of death was signed as a cardiac arrhythmia of unknown etiology with chronic schizophrenia included as a contributory condition. After review we believe this death resulted from a cardiac arrhythmia associated with schizophrenia.

Case 5

A 37-year-old schizophrenic black man resided at a psychiatric facility. After becoming agitated and assaulting another patient, he was physically restrained and secluded. Ten minutes later, he was found unresponsive. His history included intravenous drug use and hypertensive cardiovascular disease. His maintenance medications at the time were haloperidol, imipramine, and benztropine.

The external examination revealed no trauma other than soft tissue swelling of the left eye with small areas of hemorrhage. Scars of intravenous drug abuse were found on the left forearm. There was no hypertensive disease. The heart weighed 310 g (82 kg man), the coronary arteries were unremarkable, and the kidneys were smooth. All other internal organs were unremarkable.

Toxicology detected desipramine (0.1 mg/L) in the blood and (0.9 mg/kg) in the liver. Histology revealed non-specific mononuclear lymphocytic infiltration of the periportal connective tissue of the liver. The lungs were edematous and congested. The heart and brain were unremarkable.

After complete autopsy, the cause of death was cardiorespiratory arrest after a restraint procedure for schizophrenia with acute agitation.

Case 6

A 54-year-old woman with schizophrenia who lived for the last 30 years in a supervised residence was found dead in her unlocked room. She was fully clothed and was lying supine on the floor next to her bed. She had been seen alive in her usual state of good health 4 h earlier.

At autopsy she had a small contusion on the left side of her head without associated skull fracture, hemorrhage, or brain injury. She had slight pulmonary emphysema, and her heart weighed 300 g and was free of atherosclerosis. Histology was unremarkable.

Toxicology revealed benztropine (<0.1 mg/L) and olanzapine (0.1 mg/L) in the blood. Postmortem electrolytes were within normal range.

After complete autopsy, we conclude that this death was associated with schizophrenia and that neither physical nor chemical injury contributed.

Discussion

The increased mortality among schizophrenics is partly due to the increased incidence of violent death (2,3,6,8,9). In addition, the medical management of these patients is often complicated, requiring many different drugs. Complications of therapy must also account for part of this increased mortality. The third possibility is that the altered physiology of schizophrenia, in and of itself or in combination with medications, can be a cause of death.

In five of the six subjects, toxicological testing revealed the presence of neuroleptic drugs. This is expected due to the chronic nature of schizophrenia and the necessary long-term treatment of the disease. We evaluated the symptoms and concentrations of these medications in order to exclude them from contributing to the cause of death. Two common toxic manifestations in individuals receiving neuroleptic drugs are tardive dyskinesia and neuroleptic malignant syndrome. These are rarely fatal or abrupt in onset. There is nothing in the five decedent histories that reveals behavior resembling the involuntary dyskinetic movements of tardive dyskinesia or the catatonic rigidity, stupor, fever, profuse sweating, and incontinence of neuroleptic malignant syndrome (11).

Toxicological testing of Subject 2 detected 1.0 mg/L of clozapine in his plasma. Clozapine is used to treat severely ill schizophrenic patients who do not respond to the standard antipsychotic course of therapy. Plasma clozapine concentrations after the standard clinical dose range from 0.06 to 1.0 mg/L. In addition, it is recommended to parallel treatment with weekly hematological testing due to the risk of developing agranulocytosis. In this case, there is no evidence of lesions of the throat or other mucous membranes consistent with agranululocytosis. Seizures and tardive dyskinesia are other adverse reactions to chronic therapy and were absent in this decedent's history. Therefore, we conclude that clozapine intoxication did not contribute to the agitation and ultimately the death of Subject 2 (11).

Toxicological testing of Subject 3 detected 1.1 mg/L of chlorpromazine in his plasma. Mental patients typically receive up to 2400 mg daily for the maintenance of their medical condition. Chronic high-dose therapy often reaches serum concentrations (1 to 44 mg/L) similar to those in fatal cases; however, assessing liver concentration can differentiate fatal and therapeutic levels. Side effects of chlorpromazine, in addition to tardive dyskinesia and neuroleptic malignant syndrome, include drowsiness, fainting, hypotension, tachycardia, tremor, dizziness, coma, and convulsions. Subject 3 was on a 1600-mg chlorpromazine regimen. An interview with Subject 3's doctor did not reveal any such circumstance or adverse reaction consistent with chlorpromazine overdose. In addition, Subject 3's liver chlorpromazine concentration of 16.3 mg/kg was significantly below the potentially fatal concentration range of 34 to 90 mg/kg. Therefore, we conclude that chlorpromazine intoxication did not contribute to the psychotic outbursts and ultimately the death of Subject 3. The three other serum toxicology findings, benztropine (<0.1 mg/L), haloperidol (<0.1 mg/L), and valproic acid (32 μg/mL), were all within therapeutic range (11).

Psychotropic drugs can cause prolongation of the QT interval. Thioridazine has been associated with sudden death through this mechanism (12,13). Prolongation of the QT interval is thought to be dose related. Subject 4 was on thioridazine. The blood concentration of this drug was within therapeutic range. No EKG was available, but would be of obvious interest to rule out prolongation of the QT interval as the mechanism of death.

Toxicological testing of Subject 5's serum detected 0.1 mg/L of the antidepressant desipramine. Standard steady-state blood levels in patients receiving chronic daily doses of desipramine have ranged from 0.010 to 0.280 mg/L. Subject 5 is within the therapeutic range (11). Similarly, benztropine and olanzapine levels of Subject 6 are within therapeutic range.

After considering the toxicological findings and demonstrating that the subjects did not exhibit any anatomic cause of death, we investigated possible mechanisms of sudden death in schizophrenics.

In addressing the issue of natural death in schizophrenics, a logical area to evaluate is the autonomic nervous system (ANS) because schizophrenics exhibit dysfunction in autonomic nervous system activation (14). Three tests of autonomic activity have been evaluated: Skin conductance levels (SCL), nonspecific skin conductance responses (NS-SCRs), and rate of skin conductance response-habituation. The premise behind this electrodermal response system is that the electrical conductivity of the skin can be measured by applying a small constant voltage across a pair of electrodes positioned on the surface of the skin. Measurements are taken by a continuous polygraphic tracing of the tonic skin conductance level (SCL), and phasic increases in skin conductance (skin conductance responses, SCRs) are superimposed. Because the eccrine sweat glands are mediating these electrodermal events,

the above three experimental parameters are useful for assessing autonomic, or specifically, sympathetic arousal (15).

Several experiments have described, with some exceptions, not only autonomic aberrations, but also cardiac deviations in schizophrenics after a drug-free period. These experiments detail, in comparison to the general population, the higher tonic levels of autonomic arousal under resting conditions, a reduced ANS response to stress, a slow habituation of electrodermal orienting responses (ORs) to stimulation, and an increased resting heart rate (14).

Over the decades, Zahn et al. have documented electrodermal skin data for a diverse range of schizophrenics. In his 1981 study, Zahn evaluated 46 acute schizophrenics against a control group of 118 subjects. Detailing resting base levels of interest, Zahn concluded, "The schizophrenic group had a significantly higher resting HR (83.9 vs. 76.0) and lower HR variability (3.61 vs. 4.47) than the controls—suggestive of mild tachycardia. Schizophrenics also showed a higher frequency of spontaneous SCRs (2.98 vs. 1.73)." However, it is worth noting that base SCLs of the control group (19.95 vs. 17.60) were greater than the schizophrenic group. In assessing habituation, Zahn took the relative measure of responsivity for each subject and concluded "schizophrenic women showed a marked deficit in habituation, while the evidence for the men is more equivocal." Zahn thus asserts that the results of his 1981 study "provide evidence that acute schizophrenic patients exhibit marked difference in ANS functioning compared with normal controls" (14).

In subsequent studies, Zahn et al. (1997) evaluated autonomic abnormalities in 21 childhood-onset schizophrenic patients using similar indicators as in 1981 and showed similar results (16).

In a comprehensive review, Dawson and Nuecheterlein (1984) presented the outcome of ten previous electrodermal studies and observed that six/ten studies resulted in a higher skin conductance level among schizophrenic patients, suggesting an increased basal sympathetic arousal (17). Later Dawson et al. (1994) also compared electrodermal data among 20 schizophrenic patients to 20 controls. Dawson concluded "tonic electrodermal activation became abnormally high during a psychotic state, which suggests that schizophrenic psychotic states are accompanied by elevated sympathetic nervous system activation" (17).

In his 1977 article, Zahn reviews the link between autonomic functioning and individuals with a genetic risk for developing schizophrenia. Although some studies cite electrodermal data that are consistent with autonomic dysfunction, these findings were not reliably replicated. Therefore, Zahn concludes that no characteristic of ANS functioning is firmly involved in a predisposition for schizophrenia (18).

In 1998, Jansen et al. compared the cortisol response to a psychosocial stressor in schizophrenic and control populations. Their findings support the idea that schizophrenics have altered psychological and biological adaptation mechanisms (19). Other studies also support the finding that schizophrenics exhibit altered autonomic functioning (20–22).

The autonomic irregularities in schizophrenics provide a mechanism by which schizophrenia can produce sudden death. The etiology of such mechanisms in a given instance can be inferred by the autopsy exclusion of other physical and toxicological causes, but no functional derangement can be measured directly by a structurally based procedure on a dead patient. Therefore, our contention that schizophrenia per se is a potentially lethal disorder rests upon the evaluation of fatalities with a positive medical history of schizophrenia and the exclusion of other causes. The interaction of these autonomic irregularities with psychotropic medications may be of great importance and must be further evaluated.

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