Two Cases of Sudden Death in Obese Psychiatric Patients with Microscopic Cardiopulmonary Abnormalities

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Abstract  We present 2 cases of sudden death in obese psychiatric patients who had microscopic cardiopulmonary abnormalities. Postmortem analysis of the bloods from both patients detected several kinds of psychiatric drugs, however their levels were below the lethal level.  Case 1 was a 33-year-old woman and her heart showed severe fatty infiltration in the atrioventricular (AV) node and left-sided His which was compressed by hypertrophic septal myocardium and hypertensive pulmonary arteriopathy with endocardial thickening of the right atrium and ventricle. Case 2 was a 37-year-old woman and her heart showed mild downward displacement of the tricuspid valve with severe stenosis of the AV node artery.  The cause of death in Case 1 was considered to be acute poisoning by three psychiatric drugs through their effect on the preceding cardiopulmonary abnormalities, while that in Case 2 was considered to be the fatal arrhythmia due to occlusion of the AV node artery resulting from the effect of three psychiatric drugs.  These 2 cases suggest that microscopic cardiopulmonary abnormalities may be significant findings in obese psychiatric patients and may help in investigations into the manner of death.  Further investigation may be needed for exploring the pathological mechanisms of these abnormal findings in obese and/or psychiatric patient.

Key words: Sudden unexpected death, Psychotropic drug, Obesity, Conduction system abnormality, Pulmonary hypertension

Introduction

Sudden unexpected death is occasionally seen in psychiatric patients, and various causes of death including cardiovascular insufficiency have been reported\(^9\). Toxicological analysis is important, but sometimes it is not possible to determine the cause of death because there are no criteria regarding lethal levels when several drugs are taken at once and/or when the patients has a preceding pathological condition. Obesity has been considered to be one of the risk factors of sudden unexpected death\(^9\) and sudden death occasionally occurs in obese psychiatric patients\(^9\). We present 2 cases of sudden death in obese psychiatric patients whose blood levels of psychiatric drugs were not high enough for us to conclude that the cause of death was simple poisoning.

Case history

Case 1
A 33-year-old woman was found dead in a tent at midnight. She had been camping
with her colleagues and had gone to sleep after enjoying an evening with them. Resuscitation was not successful. She had a history of depression and had been given several kinds of psychiatric drugs. However, it was not determined how much of the drugs she had taken before going to sleep. According to her family, she had a habit of snoring in her sleep.

Case 2
A 37-year-old woman was found dead in bed. She had been diagnosed as schizophrenic and had been given several kinds of psychiatric drugs. She had a history of sudden dyspnea and had been diagnosed as suffering from bronchial asthma.

Autopsy Findings

Case 1
The deceased was 161.5 cm tall and weighed 70 kg. Examination of the external surface of her body revealed no evidence of blunt force trauma. Severe livor mortis was seen over the dorsal aspect of the body. There was no petechial hemorrhage beneath the conjunctiva. Adipose tissue had developed within the subcutaneous tissue and around the internal organs. The heart weighed 337 g. The deposition of fat was conspicuously evident on the epicardium, and both atria were dilated. Transverse sections of the ventricles revealed mild hypertrophy of the left ventricle and dilatation of the right ventricle (Fig. 1A). There was no congenital anomaly or atherosclerosis of the coronary artery. Dilatation of the tricuspid ring with myxoid degeneration of the valve was evident (Fig. 1B). On microscopic examination, the myocytes of both ventricles showed mild hypertrophy with disarrangement of the myofibers and nuclear polymorphism. Diffuse interstitial fibrosis was also seen. The right atrium revealed endocardial thickening with an increase in elastic fibers as compared with age matched other heart (Fig. 2). On examination of the cardiac conduction system, severe fatty infiltration was seen in the sinoatrial (SA) node and artio-ventricular (AV) node. The left-sided bundle of His showed fibrosis, and was compressed by the hypertrophic right-sided ventricular myocardium. Occlusion of the intramyocardial small arteries was seen in the ventricular septum (Fig. 3). In the lung
parenchyma, hypertrophy of the medial and intimal cell proliferation of small arteries that were consistent with hypertensive pulmonary arteriopathy were seen (Fig. 4). No typical plexiform arteriopathy, which is suggestive of primary pulmonary hypertension, was observed. In the alveolar space, sparse type II pneumocytes could be seen. The liver revealed small foci of cholestasis. No other significant findings were noted in the other organs.

Analysis of blood and urine was undertaken and no alcohol was detected. However, three psychiatric drugs, phenobarbital, chlorpromazine and promethazine, were detected. The phenobarbital concentration in the whole blood was 72.1 \( \mu \text{g/ml} \), a value between the toxic range (40-60 \( \mu \text{g/ml} \)) and the lethal level (> 80 \( \mu \text{g/ml} \)). The chlorpromazine concentration was 0.141 \( \mu \text{g/ml} \), a value within the therapeutic range (0.01-0.50 \( \mu \text{g/ml} \)). The promethazine concentration was 0.155 \( \mu \text{g/ml} \), a value between the therapeutic range (0.006-0.009 \( \mu \text{g/ml} \)) and the lethal range (2.4-12\( \mu \text{g/ml} \))

Case 2

The deceased was 165 cm tall and weighed 74 kg. External and internal examinations showed almost all the same findings as in Case 1. The heart weighed 295 g. There was no atherosclerosis of the coronary artery. Mild dilatation of the bilateral ventricles and mild downward displacement of the septal leaflet of the tricuspid valve.
Sudden death in obese psychiatric patient

Fig. 3 Microscopic appearance of the conduction system of Case 1.
A; Marked fatty infiltration in AV node (arrow). Interstitial fibrosis of superior ventricular septum. (TV; tricuspid valve) (Masson's trichrome, x10)
B; The bundle of His located on the left side of the superior ventricular septum is severely compressed by the right-sided ventricular myocardium. Severe interstitial fibrosis of the ventricular myocardium around the bundle. Arrowhead shows an occluded intramyocardial small artery. (Masson's trichrome, x5)
C; High power view of the intramyocardial small artery (Masson's trichrome, x50)

valve were seen. On microscopic examination, the histological findings of ordinary myocardium of bilateral ventricles were similar to those in Case 1. Severe interstitial fibrosis was evident in the superior ventricular septum and the AV node. A
significant findings were present in the other organs.

Analysis of blood was carried out and no alcohol was detected. The same three psychiatric drugs as detected in Case 1 were also detected in this case. The concentrations of phenobarbital, chlorpromazine and promethazine in the whole blood were 6.14 µg/ml, 0.01 µg/ml, and 0.008 µg/ml, respectively, values which were all within the therapeutic range.

Discussion

Obesity and mental illness are both considered high-risk factors for sudden death due to natural causes, and atherosclerotic heart disease has been considered to be major cause of the death in each condition91518. Our two cases did not have atherosclerosis in the coronary artery, however, had microscopic cardiopulmonary abnormalities that could cause sudden death in a few previous literatures201116). These abnormalities may not be specific findings in the obese and/or patients with psychiatric disorder. However, we propose that these abnormalities correlate the high incidence in the sudden death with obesity and/or mental illness, from detailed summary of our two cases.

Recently, sleeping apnea, which is considered to be a risk factor for sudden death39, occurs frequently in both obesity and psychiatric patients1314). Since sleeping apnea occasionally causes pulmonary hypertension10, and since we were not able to explain the pathogenesis of the pathological changes of the right–sided heart such as dilatation of the tricuspid ring, myxoid degeneration of the valve and endocardial thickening of the right atria with the exception of the sleeping apnea, we assume that Case 1 may have had a high probability of
subclinical pulmonary hypertension due to sleeping apnea.

Bharati et al. revealed that fatty infiltration of the conduction system appears in sudden death cases in obese young adults, and they assumed that fatty infiltration of the vital parts of the conduction system probably predispose people to the development of arrhythmias, and the tendency for arrhythmogenesis may be facilitated or accentuated by cardiac hypertrophy, focal myocardial disarray and infiltration of inflammatory cells, small artery disorder, and physiological disorders such as sleeping apnea. We consider that the infiltration of fat in Case 1 was more severe compared with Bharati's cases.

Some authors have reported that the left-sided bundle of His may be an abnormal finding and could result in fatal arrhythmia. The bundle of His in Case 1 was not only located at the left side of the ventricular septum, but was also clearly pressed by the surrounding hypertrophic right-sided septal myocardium, and longitudinally compressed compared with normal subjects. Some authors have considered that this lesion is itself a normal variant, however, we assume that this lesion seen in Case 1 may provide arrhythmogenic potential in patients with other specific backgrounds such as obesity and/or hypertensive pulmonary arteriopathy as noted in Case 1.

Stenosis of the AV node artery is known

Fig. 5 Microscopic appearance of the conduction system of Case 2.
A: Downward displacement of the tricuspid attachment. Interstitial fibrosis is evident in the superior ventricular septum. Arrowhead shows AV node artery. (Masson's trichrome, x2.5)
B: High-power view of AV node artery. Severe stenosis due to intimal thickening. (Elastica von Gieson, x50)
to appear in various pathological conditions, and is considered to be a cause of sudden cardiac death. Accordingly the AV node artery in Case 2, which showed at least 75% stenosis, may be significant. In one of our earlier reported cases, acute ischemic changes were not evident in the conduction system, but were evident in the working myocytes of the superior ventricular septum near the node. In addition, one of the 7 obese patients in Bharati's report showed stenosis of the AV node artery with mild downward displacement of the tricuspid valve, which has been termed mild Ebstein's anomaly by some authors. We can therefore assume that mild downward displacement of the septal leaflet of the tricuspid valve, which is located near the AV conduction system, may be a significant finding. It is interesting to note that occlusion of the AV node artery occasionally occurs in cases of mitral valve prolapse. The posterior leaflet of the mitral valve, which is located near the AV conduction system, as is the septal leaflet of the tricuspid valve, is a favorable site of occurrence of mitral valve prolapse. We can therefore assume that mild but long-standing hemodynamic alteration near the AV node due to this anomaly would cause occlusion of the AV node artery, similar to mitral valve prolapse.

Physiological study has shown that some phenothiazines, including chlorpromazine and promethazine, are associated with the development of ventricular and atrial tachycardia, bigeminal rhythm, premature atrial beat, varying degrees of heart block, and ventricular fibrillation. We should therefore consider that these psychiatric drugs became triggering factors for arrhythmogenic events in our two obese psychiatric patients who had preceding congenital and/or acquired microscopic cardiopulmonary abnormalities.

To conclude, with regard to Case 1, the cause of death is considered to have been acute poisoning by three psychiatric drugs through their effect on preceding cardiovascular abnormalities. On the other hand, we consider that the cause of death in Case 2 was fatal arrhythmia due to occlusion of the AV node artery probably resulting from the effect of three psychiatric drugs. However, further investigation of large number of cases may be needed for exploring the pathological mechanisms of these cardiopulmonary abnormalities in obese and/or psychiatric patients. These 2 cases suggest that detailed morphological and functional evaluation of the cardiovascular system may help on investigations into the manner of death in obese psychiatric patients. The circumstances of death, and the results of toxicological and pathological examinations should be carefully considered when determining the manner of death.

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心肺に病理組織学的異常を伴う肥満精神病患者の突然死の2例

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病理組織学的に心刺激伝導系や肺に異常所見を認めた肥満を伴う精神病患者の突然死の2例を報告する。剖検後の中毒学的検査では、その薬物所見の高度は致死濃度に達していないかった。症例1は33才の女性で、聴取した病歴からは睡眠時無呼吸であった可能性がある。右心房の内膜肥厚、右室壁への骨格的高度の脂肪浸潤、His束の左方変位と右側壁心筋からの高度圧排が認められ、肺には、肺高血圧症の存在を示唆する多数の小動脈の狭窄像が認められた。症例2は37才の女性で、三尖弁中隔尖の軽度の落ち込み、球室結動脈の高度狭窄を認めた。この2例は高血圧によるペリフェリアル血管の異常が突然死の発症に関与したことが示唆され、従来の検査で未発見の肥満を伴う精神科患者の突然死の一つの原因になっていることが推察された。