

Dead in Bed: A Rare Complication of Type 1 Diabetes Mellitus

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ABSTRACT

Introduction: Type 1 diabetes or juvenile diabetes or insulin-dependent diabetes, is a chronic condition of autoimmune destruction of the beta cells in the pancreas due to which the pancreas makes little or no insulin. Treatment requires insulin supplementation, which has its own side effects. Dead in bed syndrome is the name given for fatal outcome seen in young diabetic patients who are found dead in morning in a clearly undisturbed surrounding. In most of the cases there is no history of diabetes related complication, and the post-mortem examination is ordinarily negative.

Case description: We described a case of sudden death of a Type 1 Diabetic young female brought for post-mortem examination along with a short commentary on "Death in Bed Syndrome" seen in such diabetic individuals. At post-mortem examination the cause of death was not apparent. The biochemical and histopathological examination as well as the chemical analysis of viscera were inconclusive. No definite opinion was given regarding cause of death. However, the police insisted that death be declared natural or unnatural.

Conclusion: To reduce premature mortality in people with childhood-onset diabetes focus should be on prevention of acute complications. Medicolegal experts should be careful in giving opinion in such cases and such opinion should be based on exclusion.

Keywords: [Diabetes Mellitus, Sudden death, Hypoglycaemia, nocturnal]

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic diseases, with an increasing incidence and prevalence worldwide. [1]

It is a chronic disorder of anomalous metabolism, in which abnormally elevated levels of blood glucose, lead to a multitude of effects on various organ systems of the body. The most common type is Type 2 DM, in which the body becomes resistant to insulin or doesn't make enough insulin, and is commonly referred to as "adult-onset DM. Another less common type is the Type 1 DM, earlier referred to as the juvenile DM or the insulin dependent DM, where the pancreas produces little or no insulin by itself, attributable to the autoimmune destruction of insulin producing beta cells in the pancreas.

As per the diabetes country profile by the WHO, deaths attributable to DM, constitute 2% of all the deaths reported in India. People with type 1 diabetes need lifelong insulin replacement therapy. Type 1 diabetes is associated with high morbidity and mortality. In the Diabetes Control and Complications Trial, intensive therapy was associated with a threefold increase in the

risk of severe hypoglycaemia [2] and severe hypoglycaemia occurred more often during sleep. It has recently been demonstrated that hypoglycaemic episodes precede the development of hypoglycaemic unawareness. Hypoglycaemic unawareness is defined as hypoglycaemic episode without warning symptoms of the decreasing blood glucose level. Concerns are being raised about this phenomenon. [3] Although many cases have been reported worldwide, there is still a need to raise awareness about this condition, especially in developing nations. We are reporting on a case that was brought to a tertiary care centre for autopsy.

CASE REPORT

A young girl, aged 22 years, was brought to the emergency department of our institute by her parents. The girl was in an unconscious state on her arrival to emergency. As per the parents, the patient had been suffering from type 1 diabetes for quite some time. On examination blood pressure and Pulse were unrecordable. CPR (cardiopulmonary resuscitation) was started as per the latest ACLS (advanced cardiovascular life support) guidelines. However, she could not be revived and was declared dead on arrival. As per the history given by her parents, the deceased was diagnosed with type 1 diabetes around 5 years ago. She had been receiving insulin injections on a regular basis for the previous year. Blood sugar was apparently well under control, as per history. During the entire course of disease progression, no apparent organ dysfunction was detected. The medical record provided by the parents also revealed no major organ involvement. The reports of biochemical tests done a few days prior to the incidents were within normal limits. There was no history of change in the brand or dosage of insulin. The deceased had no complaints and was reportedly healthy the night before her death. She had her last meal late at night. In the morning, she did not wake even after repeated efforts. Fearing something was wrong, she was

taken to the emergency wing where she was declared dead on arrival.

Autopsy examination: The police were informed, and the dead body was shifted to the mortuary for an autopsy. It was the dead body of a moderately built and nourished female. Externally the dead body was thoroughly examined for any fresh injury, but external examination did not reveal any suspicious injuries. The body was opened according to standard procedure for internal examination. The internal examination was unremarkable. A sample of blood and visceral samples were collected for toxicological analysis. Samples were taken for histopathological examination. Further samples of blood and urine were taken for the biochemical profile. Subsequently, report of chemical analysis did not manifest any poison. The histopathological examination did not reveal any organ dysfunction. The biochemical profile was unremarkable. The cause of death was declared as undetermined. However, the police insisted that death be declared natural or unnatural. The board of doctors referenced the available literature and opined "possibility of death due to natural cause cannot be ruled out".

DISCUSSION

The cause of death in Type I DM has been attributed to acute diabetes complications (e.g., hypoglycaemia, diabetic ketoacidosis), chronic diabetes complications (e.g., cardiovascular disease, renal disease, infections), and non-diabetes (e.g., accidents, violence). In certain cases, the cause of death remains undetermined. A subset of these types of deaths where the cause of death remains undetermined is the "Dead-in-Bed Syndrome." This syndrome refers to a small subset of deaths in young (< age 50 years) people with Type 1 DM who are otherwise healthy (i.e., no diabetic complications) but are discovered dead in their beds without any evidence of struggle or sweating, which is usually associated with a hypoglycaemic event. [4]

Death in bed syndrome was first described in 1991. In July 1989, in a British inquest, an expert suggested that an increase in use of human insulin had caused an increase in sudden deaths of young people with Type 1 diabetes and attributed it to hypoglycaemia. This was followed by a telephone news programme in the September of same year which widely publicised the issue. This led the British Diabetic Association to conduct a survey. A total of 53 deaths were reported. Of these 34 cases were included in the study. The study implicated nocturnal hypoglycemia and recommending normoglycaemia or a normal HbA1c as the target in patients who sleep alone. [5]

Following this study Ian Campbell in his editorial while discussing the above survey coined the term "Dead in bed syndrome". He suggested that methods, both biochemical as well as neuropathological, be developed for the accurate diagnosis of hypoglycaemia after death. He suggested that pathological examination of brains in such deaths should not only be confined to excluding gross macro pathology, such as haemorrhage or thrombosis, but should incorporate findings attributable to hypoglycaemic brain damage such as laminar necrosis. [6]

Later, The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group, designed to examine whether aggressive treatment of blood glucose, lipids and blood pressure (BP) could lower the risk of cardiovascular disease (CVD) in 10,000 individuals with established type 2 diabetes. However, it prematurely terminated glucose control component of the ACCORD trial at the request of the independent data monitoring and safety committee due to an unexpected increase in the number of sudden cardiac deaths in those participants receiving [7] intensive glucose lowering treatment. However, investigators involved in a 5 year study, The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial, that tested a similar hypothesis in over 11,000

individuals with type 2 diabetes recruited worldwide, found no evidence of increased overall or cardiac mortality in their intensively treated population. [8] The incidence of "dead in bed syndrome" has been reported in 22–45% of sudden unexplained deaths among young people with Type 1 DM. [10] Historically, such deaths were attributed to hypoglycaemia. Recently, cardiac ion channelopathy has been put forward as a likely explanation. Weston and Gill in their paper suggest nocturnal hypoglycaemia as a likely prerequisite, but attribute sudden death to cardiac arrhythmia. [10] Clark, Best, and Fisher had suggested that nocturnal sympathoadrenal responses and relatively increased parasympathetic activity predispose to arrhythmia during a hypoglycaemic event. [11]

Parekh suggested that repeated episodes of hypoglycaemia cause orexin-A neurons to adapt which leads to defective awakening and hypotonia of upper airway muscles. Both these combine leading to intermittent hypoxia over a period of time. This intermittent hypoxia causes a combination of factors including depression of ventilation, increase in sympathetic tone, fluctuations in intrathoracic pressure and cardiac arrhythmias. These in conjunction with an underlying cardiovascular pathology cause cardio-respiratory failure and thus sudden death during sleep. [12]

Emily Tu et al. conducted a retrospective review of autopsy reports of Australians with Type 1 DM, who died at the age of 40 or younger. They found that cardiovascular disease accounted for 51% of deaths, followed by acute complications of diabetes, unnatural deaths, and sudden unexpected deaths, which accounted for 27%, 28%, and 22 % of deaths in such individuals. Of the sudden, unexpected deaths, 10 people were found dead in bed undisturbed with no cause of death found at autopsy ("dead-in-bed" syndrome; mean age (SD), 30.2 (9.4) years; males: females, 4: 1; [13] Thordarson and Sovik, over a 10 year period, studied such deaths in Norwegian diabetic patients,

and found an increasing incidence of unexplained deaths, in addition, 75% of all cases reported frequent episodes of hypoglycaemia, with 62.5% experiencing nocturnal episodes. [14]

Nocturnal hypoglycaemia seems to be the precipitating factor, but why some patients should succumb to such a common occurrence remains unclear. Two related theories predominate. First, patients who are at risk for "dead in bed syndrome" have subtle and undetected abnormalities in cardiovascular autoregulation. These subtle changes may be due to previous episodes of hypoglycaemia, leading to a transient metabolic autonomic dysfunction. These changes lead to a relatively increased sympathetic nervous system activity that, during hypoglycaemic episodes, predisposes the patient to fatal ventricular arrhythmias. Second, is the theory that QTc (lengthening associated with hypoglycaemia (driven by the sympathoadrenal response) predisposes the patient to fatal ventricular arrhythmias. A national or international database of such patients should be created, and during the procedure of autopsy, appropriate tissue for genetic samples should be taken from any patient with Type 1 diabetes who has a sudden, unexplained death. This will enable us to start identifying at-risk individuals. [15] Taneberg et al. describe a 23-year-old man with type 1 DM, who suffers from recurrent episodes of severe hypoglycaemia. They attached a continuous glucose monitoring system to the patient. The patient was found dead in his undisturbed bed, and the data demonstrated a glucose level of 30 mg/dL around the time of his death. An autopsy on the said patient revealed no major organ abnormalities. [16] A diabetes control and complications trial, conducted over a period of 30 years laid emphasis on reducing night time hypoglycaemia to reduce such deaths. [17]

Sudden, unexplained deaths in children are a source of concern for family members, law enforcement, and forensic medicine experts alike. A complete post-mortem report in such cases should document a

detailed history of past illnesses, including medications for those illnesses. A post-mortem examination should rule out poisoning and significant organ disease. Apart from routine chemical and histopathological examinations, Palmiere suggests post-mortem biochemical investigations should be systematically performed in both diagnosed and undiagnosed individuals in order to identify fatal complications of DM [18] Simon Heller suggested that cause of death can be attributed to hypoglycemia in only those case where it leads to characteristic pathological changes, for example, in hypoglycaemia-induced cerebral damage. A fatal cardiac dysrhythmia caused by hypoglycaemia leaves no histopathological clues. [19] Establishing hypoglycemia at post-mortem examination is problematic as glucose levels tend to decrease in matter of several hours, making its estimation in post-mortem blood and vitreous fluid unreliable. Use of Insulin and C peptide may be beneficial in post-mortem examinations in such unexplained deaths but require endorsement through scientific validation studies.

CONCLUSION

Review of literature shows that nocturnal hypoglycaemia and arrhythmia are the most probable cause of sudden death in type I diabetic patients. Other factors are also studied by researchers from time to time. Prevention of cute complications needed to be focused to reduce premature mortality in childhood diabetic patients. Medicolegal experts should be careful in giving opinion in such cases and such an opinion should be based on exclusion.

Abbreviations: DM- Diabetes Mellitus, WHO- World Health Organization, CPR- cardiopulmonary resuscitation, ACLS- advanced cardiovascular life support, SD- Standard Deviation, QTc- Corrected QT interval

Declaration by Authors

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