A case of hypoglycemia-induced QT prolongation leading to torsade de pointes and a review of pathophysiological mechanisms

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Abstract

Torsades de pointes is a life-threatening cardiac arrhythmia. Occurrence of this arrhythmia as a result of hypoglycemia has not been reported in the literature. We describe an interesting case of an insulin-dependent diabetic patient presenting with torsades de pointes resulting from hypoglycemia. A 62-year-old male was admitted to the hospital following an episode of severe insulin-induced hypoglycemia and a cardiac arrest. He was found to unresponsive at home after taking insulin. His serum glucose was found to be 18. He was given juice initially to normalize his glucose and was then transferred by EMS to ER where he was given 5% dextrose infusion. Analysis of the LifeVest rhythm recording showed torsades de pointes that was terminated by defibrillation of the LifeVest. Several mechanisms are responsible for torsade, including QT interval prolongation, adrenalin secretion and calcium overload leading to intracellular calcium oscillations. These mechanisms are a trigger to torsade de pointes. Predisposing factors were present leading torsade to occur.

Introduction

Torsades de pointes is a polymorphous arrhythmia characterized by sinusoidal variations in QRS axis, irregular RR interval and a ventricular rate ranging between 160-250 beats per minute. The causes are categorized into congenital and acquired.[1] Acquired causes include metabolic disturbances, medications, heart disease, autoimmune diseases, hypothermia and many others.[2] We report a case of hypoglycemia-induced torsade de pointes, which has not been previously described in the literature before. We also review the mechanisms that could have contributed to the incidence of this arrhythmia.

Case Report

A 62-year-old male patient was admitted to the hospital following an episode of severe hypoglycemia, reduced responsiveness and defibrillation by a LifeVest (Figure 1). The patient took 8 units of the short acting insulin Aspart prior to dinner. Five hours later, his wife found the patient in his room diaphoretic and not very responsive. She checked his serum glucose and found it to be 18 mg/dL. She proceeded to give him juice with sugar in it and rechecked it, showing an increase to 27 mg/dL. The patient's LifeVest was observed to defibrillate by the wife. He began to improve and was then transferred by EMS to ER where he was given 5% dextrose infusion.

The patient is an insulin dependent type 2 diabetic with a prior admission for DKA. His past medical history is significant for ischemic heart disease, non-ST elevation myocardial infarction for which he had a stent placed in the left anterior descending artery (LAD) 5 weeks prior, and multiple previous stents in the circumflex and LAD. His other comorbidities included congestive heart failure NYHA 2-3, peripheral arterial disease, type 2 diabetes, hypothyroidism, hypertension, hyperlipidemia, GERD, chronic kidney disease stage 3A, gout, anemia and a diabetic foot ulcer. His medications included baby aspirin, clopidogrel, atorvastatin, carvedilol, isosorbide mononitrate, lisinopril, levothyroxine, aspart insulin, glargine insulin and pantoprazole.

The patient's ejection fraction was 20-25% on echocardiogram. He was given a LifeVest for an increased risk of life-threatening cardiac arrhythmias. In addition, the patient was until recently a smoker. He does not have significant alcohol intake and denies illicit drug use.

The patient's vital signs on admission to ER were heart rate 90, blood pressure 132/82 mmHg, respiratory rate 20, oxygen saturation 97% on 2 liters oxygen and temperature 97.8 F. His initial blood test is shown in Table 1.

Analysis of the recorded cardiac rhythm by the LifeVest showed the presence of torsades that was terminated following defibrillation by the LifeVest (Figure 1). The patient had an EKG taken while in hospital following the episode of torsade showing a corrected QT (QTc) interval of 533. This is significantly increased from an EKG that was performed a month earlier that showed a QTc of 483 (Figure 2). The patient's magnesium was replaced to a level of 2.2 mg/dL. He was placed on amiodarone and an implantable cardioverter defibrillator (ICD) was inserted for secondary prophylaxis.

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Dedication: I dedicate this article to my parents who have worked tirelessly to give me the best life they can. I also want to dedicate this article to the Wayne State Internal Medicine program director Dr Khalid Zakaria who has made every effort possible to make the program a great success and an amazing learning environment for residents.

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Coronary angiography showed the left main coronary artery is a large caliber vessel without stenosis. The circumflex is a large codominant system without significant stenosis in the proximal segment. The first obtuse marginal branch has no severe stenosis. The second obtuse marginal branch has 85% stenosis of the proximal segment, as noted on previous coronary angiography 5 weeks prior. The LAD is a large to moderate caliber vessel without restenosis of the site of prior angioplasty and stenting. Successful angioplasty and stenting of the second obtuse marginal branch was performed as part of a two-stage procedure following LAD stenting 5 weeks prior. The staging was chosen to avoid acute kidney injury from high volume contrast for two stents given patient has chronic kidney disease.

Discussion

Torsades de pointes is a polymorphous

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type of ventricular arrhythmia that can be caused by an acquired or congenital prolongation of the QT interval. Acquired causes include metabolic disturbances, medications, heart disease, autoimmune diseases, hypothermia and many others.[2] Our case is the first reported example in humans where torsade de pointes is caused by hypoglycemia as a result of insulin therapy.

A single episode of hypoglycemia that requires medical attention is reported to have a two-fold increase in mortality. Most of these deaths are of cardiac causes. Hypoglycemia has been shown to cause QT prolongation, an effect that precedes the occurrence of torsade de pointes.[3-8] Other proarrhythmogenic effects of hypoglycemia have also been described in the literature, which are the subject of this review.

The first mechanism that can lead to QT prolongation is mediated by the effect of low serum glucose on the Human ether-a-go-go-related gene (HERG) potassium channel. Hypoglycemia results in conduction blockade of HERG, a rapidly repolarizing potassium channel of cardiac ventricular myocytes.[9] The effect is prolongation of the action potential and therefore the QT interval (Figures 3 and 4).

The second mechanism of arrhythmia promotion occurs as a result of secretion of epinephrine from the adrenal medulla in response to hypoglycemia. Epinephrine is well-known to be arrhythmogenic, leading to beta adrenergic stimulation of cardiomyocytes and an an increase in heart rate. It also increases intracellular calcium and cyclic adenosine monophosphate (cAMP), which elevates the risk of arrhythmias.[10,11]

In addition to adrenalin secretion, hypoglycemia also causes insulin secretion, which in turn drives potassium into the cells, lowering serum potassium level. A low serum potassium in itself causes QT prolongation and increases the propensity for torsade de pointes to occur.[12] Further evidence of the effect of hypoglycemia through the action of insulin on QT interval change was demonstrated by the use of insulin shock therapy in the first half of the twentieth century.[13-15] The intention was to purposely induce hypoglycemia through administration of exogenous insulin, thereby putting the patient into a coma. This was used as a treatment of psychiatric diseases; however, it was later abandoned as a result of sudden death in some patients. It did, however, show several effects on the electrocardiogram, one of which was QT prolongation.[13]

In one study, continuous nocturnal EKG and glucose monitoring was performed in type I diabetic patients. The study found that in patients that had nocturnal hypo-

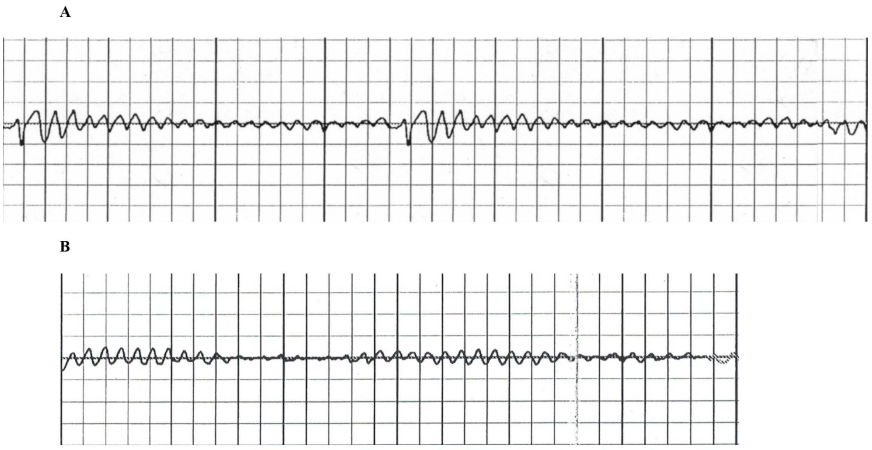


Figure 1. A) and B) show LifeVest recordings of torsade de pointes.



Figure 2. A) EKG one month prior to occurrence of torsade, QTc 483; B) EKG after occurrence of torsade, QTc 533.

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glycemia had a mean increase in QT duration of 30 milliseconds, with one patient having a QTc of 560 milliseconds. Other arrhythmias, including ventricular ectopics, sinus bradycardia, atrial ectopics and P wave abnormalities were also observed.[15]

One final mechanism relevant to our case is a phenomenon called intracellular calcium oscillation.[16] This mechanism of action is a result of a flux in calcium between the myoplasm and sarcoplasmic reticulum, leading to oscillations in membrane potential. Should these oscillations exceed the threshold for membrane depolarization, a resultant nondriven action potential will occur.[14] This phenomenon is facilitated through the sodium-calcium exchanger on the plasma membrane and sarcoplasmic reticulum. A prerequisite to the occurrence of intracellular calcium oscillations is calcium overload. The risk also increases if action potential prolongation occurs. Hypoglycemia can cause both prolongation of action potential and calcium overload, both of which can result in tachycardia leading to torsade de pointe.[16,17]

The mechanisms discussed above are all potential inducers of torsade, but given the lack of any case reports in the literature, it is likely that predisposing conditions must exist for the occurrence of such ventricular arrhythmias. In our case, they were the trigger for torsade since our patient was already at risk of having these arrhythmias given a prolonged QT interval, low ventricular ejection fraction and magnesium level on the lower end of normal. The main learning point in our case is to avoid tight glycemic control in patients that have ischemic heart disease with a prolonged QT interval. This is supported by the evidence presented in the ACCORD trial, which demonstrated an increase in mortality in patients with tight glycemic control.[8]

Table 1. Initial blood test results.

Glucose	72	GFR	51
Sodium	147	Magnesium	1.7
Potassium	4.5	Albumin	2.7
Chloride	105	Lactate	2.7
Bicarbonate	27.7	White blood cell	9.5
Anion gap	14.3	Hemoglobin	9.9
Blood urea nitrogen	25		
Creatinine	1.4		

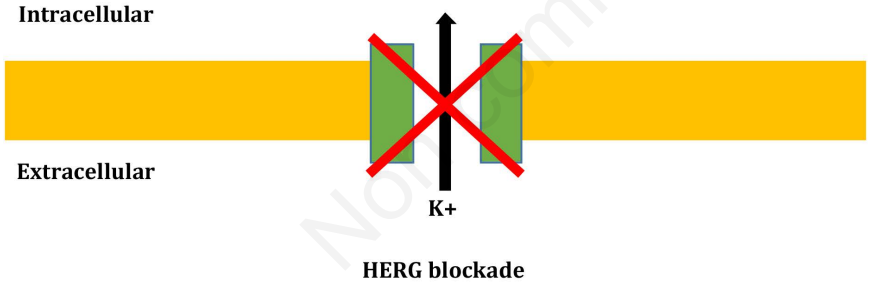


Figure 3. Showing blockade of conductance of rapidly repolarizing Human ether-a-go-go-related gene (HERG) potassium channel.

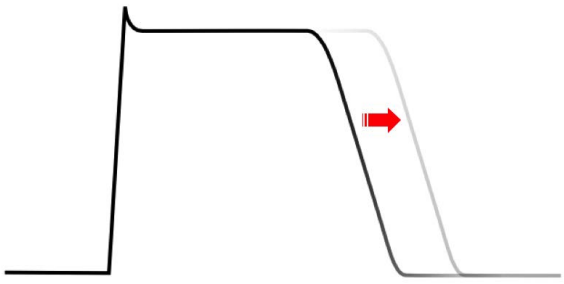


Figure 4. Showing prolongation of the action potential in a cardiac myocyte.

Conclusions

To conclude, we highly recommend against tight glycemic control in patients with predisposing factors for torsade de pointes. Patients with ischemic heart disease and prolonged QT interval are at a high risk for occurrence of torsades and should follow a less intense insulin therapy.

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