Artifactual Hypoglycaemia Associated With Cyanotic Congenital Heart Disease: a New Perspective towards Understanding

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Abstract: Hypoglycemia remains an infrequently and potentially dangerous complication in all patients. Patients who are suspected of having hypoglycemia should be questionable until confirmed by appropriate tests. Herein, we report clinical findings of three cyanotic congenital heart disease cases diagnosed artifactual hypoglycaemia, including an updated review of literature of artifactual hypoglycaemia. The cyanotic congenital heart disease led to secondary erythrocytosis, which provided the high levels of erythrocytes that we believe caused the artifactual hypoglycemia in combination with delayed processing of the sample. Currently, there are few specific studies on cyanotic congenital heart disease cases diagnosed artifactual hypoglycaemia. The report of our cases and the literature review underline the unnecessary of a detailed work-up for artifactual hypoglycaemia can be avoided if it is suspected in patients with cyanotic congenital heart disease. Clinicians should consider potential discrepancy in asymptomatic individuals before initiating costly examination. Our paper may represent the tip of the iceberg and raises concerns about the proper management of individuals with artifactual hypoglycaemia in cyanotic congenital heart disease.

Keywords: Hypoglycaemia, Artifactual, Cyanotic, Congenital heart disease.

INTRODUCTION

Hypoglycaemia remains an uncommon and potentially dangerous complication in cardiac surgery. As hypoglycaemia is often asymptomatic, clinical methods are required to screen for the condition. Formal laboratory measurement of the plasma glucose concentration is the best method of identifying patients with hypoglycaemia [1].

In patients without diabetes, hypoglycemia is a clinical syndrome with diverse causes, such as infectious, tumor, or other reason. Low plasma glucose concentrations lead to symptoms, and there should be immediate therapy aimed at restoring blood glucose to normal levels [2, 3]. So, it is important to distinguish artifactual hypoglycaemia from real hypoglycemia.

Artifactual hypoglycemia has been reported in infants with cyanotic congenital heart disease [4]. Now we report a series of cases with cyanotic congenital heart disease, were found of hypoglycaemia, but in good condition and no hypoglycemia appropriate clinical manifestations.

Review of electronic medical records of three patients admitted to the cardiac surgery at affiliated hospital of Guilin Medical University. Literature review was also performed. A review of literature for artifactual hypoglycaemia associated with cyanotic congenital heart disease was performed using the articles cited in Google Scholar and PubMed.

Case 1

A 29-year-old Chinese woman with double outlet right ventricle with pulmonary stenosis was hospitalized for operation. Laboratory tests revealed secondary erythrocytosis with microcytosis and hypochromia (erythrocyte count, 9.89×10^{12} /L; hemoglobin level, 198 g/L, hematocrit, 74.7%). Leukocyte and platelet counts were in normal range. Liver and kidney function test results were in normal range. Insulin, adrenocorticotropic hormone, thyroid hormones levels were all within normal ranges. On physical examination, we found cyanosis (resting SaO2, 78%), blood pressure of 118/70 mm Hg, heart rate of 78 beats/min, and temperature of 36.6 °C. Her venous serum glucose level was reported to be very low (3.01 mmol/L]). Two consecutive finger-stick values of 3.3 mmol/L and 3.5 mmol/L confirmed hypoglycemia. Her medical history did not include diabetes mellitus, and he did not report taking oral antidiabetic agents, insulin, or drugs that may cause hypoglycemic unawareness. Because she did not report symptoms of hypoglycemia despite having low glucose values, we suspected artifactual hypoglycaemia and measured a glucose level immediately after taking another venous sample. In the next morning, blood glucose level was normal, with a value of 4.6 mmol/L. The patient underwent double outlet right ventricle corrective surgery, and the clinical outcome was favorable. In addition to the index patient, other two patients with cyanotic congenital heart disease were studied.

Case 2

Case two was a 33 year-old Chinese man with an established diagnosis of Tetralogy of Fallot. Laboratory test results indicated anemia (erythrocyte count 7.31×10^{12}/L, hemoglobin 179 g/L, hematocrit 71.7%). Liver and kidney function test results were in normal range. Insulin, adrenocorticotropic hormone, thyroid hormones levels were all within normal ranges. On physical examination, we found cyanosis, blood pressure of 120/77 mm Hg, heart rate of 78 beats/min, and temperature of 36.4 °C. Liver and renal function tests were normal. Pulse oximetry was 82.9%. Venous plasma glucose was 2.34mmmol/L (at 10:30AM). Glucose concentrations were measured simultaneously on blood from the fingertips was 4.1mmol/L. The next day morning venous plasma (at 7:00AM) was 5.1mmol/L.

The patient underwent Tetralogy of corrective surgery and the clinical outcome was favorable.

Case 3

Case two was an 8 year-old girl was also diagnosis of Tetralogy of Fallot. Laboratory test results indicated anemia (erythrocyte count 7.83×10^{12}/L, hemoglobin 185 g/L, hematocrit 68.2%). Liver and renal function tests were normal. Pulse oximetry was 79%. Venous plasma glucose was 2.81 mmmol/L (at 10:30AM.). Glucose concentrations were measured simultaneously on blood from the fingertips was 4.5mmol/L. The next day venous plasma (at 7:00 AM) was 5.1mmol/L. The patient underwent Tetralogy corrective surgery and the clinical outcome was favorable.

DISCUSSION

Usually, glucose in blood plays a critical role in providing energy to the central nervous system. Hypoglycemia is when blood glucose decreases to below normal levels. This may result in a variety of symptoms including clumsiness, trouble talking, loss of consciousness, seizures, or even death. Symptoms typically come on quickly [5]. A feeling of hunger, sweating, shakiness, and weakness may also be present. Hypoglycemia always indicates an emergency because it implies an inability of the central nervous system to meet its energy needs. Resultant mental status impairment places the patients at risk for accidents and brain injury. Left untreated, hypoglycemia can result in permanent neurologic damage and even death.

We use the term "artifactual hypoglycemia" for patients with discrepancy between different laboratory measurements and actual blood glucose, regardless of symptoms that present with similar symptoms without low plasma glucose [6]. Artifactual hypoglycemia is a phenomenon wherein the readings value of blood glucose measured is significantly lower than real blood glucose level. To make certain of the diagnosis of hypoglycemia, documentation of plasma

glucose below the normal range is necessary [7]. Despite a wide range of plasma glucose concentrations being used by different authors to define hypoglycaemia, most clinicians accept a range of 2.5-7.5mmol/l as the limits of normoglycaemia [8]. Nonetheless, an alert value can be defined that draws the attention of both patients and clinicians to the potential harm associated with hypoglycemia. The guideline suggests that patients at risk for hypoglycemia should be alert to the possibility of developing hypoglycemia at a self-monitored plasma glucose continuous glucose monitoring subcutaneous glucose concentration of ≤70mg/dL(≤3.9mmol/L). The glucose level that defines hypoglycemia is a plasma concentration of ≤3.9mmol/L in the classification of hypoglycemia [9]. For clinical purposes, hypoglycemia may be defined as (1) blood glucose level at or below3.9mmol/L, (2) the presence of transient symptoms, such as sweating, tremulousness, anxiety, palpitations, weakness and huger, and (3) prompt response of symptoms to ingestion of glucose injection of glucose.

In cyanotic congenital heart disease cases, the most notable symptom is often bluish discoloration of the mucous membranes and skin (cyanosis). Individuals with cyanotic congenital heart disease typically develop intensification of cyanosis, particularly of the lips, fingernails and toenails. Secondary erythrocytosis was occurred in our cases. The levels of erythrocytes that transport oxygen to body cells are elevated because of increasingly inadequate oxygen supply to body tissues. Additional signs may include increasing dyspnea, lethargy, fatigue, or additional findings. The degree of cyanosis and polycythemia varies, depending upon the duration and severity of hypoxia. Chronic hypoxia is associated with decreased serum glucose and insulin concentrations. Secondary erythrocytosis was occurred in our cases. Hypoxia is a cause of glucose intolerance because a hypoxia-induced decrease in ATP levels and adrenergic input could open these K+ channels, thereby decreasing muscle glucose uptake. The further mechanisms of hypoxia-induced glucose intolerance need further clarification.

In cyanotic congenital heart disease, artifactual hypoglycemia in venous and finger-stick blood are caused by two different mechanisms. In venous blood, it is caused by in vitro consumption of glucose by high levels of blood cells after the sample is drawn and before it is tested. Serum glucose concentrations can drop significantly within 2 hours after sample collection, and longer intervals of time are associated with greater reductions in glucose levels. In cyanotic congenital heart disease cases, such as Tetralogy of Fallot, secondary erythrocytosis, which provided the high levels of erythrocytes that we believe caused the artifactual hypoglycemia in combination with delayed processing of the sample. When the blood sample was kept at 4 °C, the hourly change in glucose concentration

was insignificant. It is therefore recommended that blood samples should be collected in tubes containing glycolysis inhibitor and transported to the laboratory room as soon as possible to obtain accurate blood sugar measurement. In our cases, glycaemia was measured in the routine conditions for our laboratory, without addition of glycolysis inhibitor and with a delay of 3 or even more hours between the collection and analysis of the blood sample. Moreover, artifactual hypoglycemia also has been reported in patients with high levels of other types of blood cells, including leukocytes due to leukemia or a leukemoid reaction [10]. Artifactual hypoglycemia has been reported to occur in polycythemia vera and is caused by in vitro autoglycolysis due to an exaggerated consumption of glucose by increased leukocytes. For example, in polycythemia vera, this phenomenon may be due to both increased red and leukocytes induced enhanced glycolysis [11, 12]. Patients with polycythemia vera may have falsely low blood glucose values reported if blood specimens are not processed immediately after venipuncture. The artifactual hypoglycemia may be severe, producing blood glucose values in the range normally thought to be "significant" hypoglycemia. Cases of hyperleukocytosis-related hypoglycemia have been reported with blood diseases, especially myeloproliferative syndromes. In those situation the in vitro consumption of glucose was attributable to the leukocyte concentration but did not depend on its type [13]. In our cases, leukocyte counts were in normal range. The hypoglycemia phenomenon was due to secondary erythrocytosis.

We wish to make two points. First, in our hands, the cyanotic congenital heart disease led to secondary erythrocytosis, which provided the increased erythrocytes that we believe caused the artifactual hypoglycemia in combination with delayed processing of the sample. Hypoxic respiratory diseases are frequently accompanied by glucose intolerance. Oltmanns examined whether hypoxia is a cause of blood glucose intolerance in healthy subjects [14]. In his study, hypoxia is a cause of blood glucose intolerance because a hypoxia-induced decrease in ATP levels and adrenergic input could open these K+ channels, thereby decreasing muscle glucose uptake. The further mechanisms of hypoxia-induced glucose intolerance need further clarification.

The artifact hypoglycemia due to in vitro consumption of glucose in cases of erythrocytosis requires early recognition to avoid unnecessary and unproductive investigations [15].This process can be minimized by cooling samples promptly or by using inhibitors of anaerobic glycolysis. In finger-stick blood, artifactual hypoglycaemia is caused by impaired blood flow in the digital microcirculation, which leads to a local increase in glucose consumption. Because the severe cyanotic congenital heart disease has been connected with vascular and intravascular disorders of the microcirculation, we believe that this process explains why our first case had low glucose values in finger-stick blood. Acrocyanosis induces hypoglycaemia, likely through impaired blood flow in the local microcirculation, which leads to local increase in glucose consumption. This process also has been described in patients with the Raynaud phenomenon, peripheral vascular disease and shock [16]. Fingertips are the preferred site for blood glucose monitoring. Measurement at less painful sites, such as the forearm or the thigh has been proposed, but because of poor blood flow, equilibration with the venous blood glucose is slower at these sites, possibly leading to false value of glycemia [17].Thus, measurements at the fingertip are not accurate in states of rapid blood glucose fluctuations, so our cases emphasize that this site can be unreliable in cases of suspected microcirculatory changes. So, venous blood glucose testing may be preferred.

CONCLUSION

To our knowledge, there are a few reports of artifactual hypoglycaemia in both venous and finger-stick blood in the adult patient with cyanotic congenital heart disease. Although artifactual hypoglycaemia secondary to erythrocytosis stimulation of hypoxic is a major event, we suggest that it must be recognized by the clinician in order to avoid inappropriate reporting of adverse effects, performance of unnecessary evaluations and inadequate monitoring of cyanotic congenital heart disease cases diagnosed artifactual hypoglycaemia.

CONFLICT OF INTERESTS

None declared.

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