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Paediatric Diabetic Ketoacidosis in Newly-Diagnosed Type1 Diabetes: Delayed Diagnosis and Unexpected Development of Systemic Hypertension During Therapy

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Abstract

***Background:** Delayed diagnosis of paediatric diabetic ketoacidosis (DKA) is known to be common but development of systemic hypertension during therapy is unexpected. The aim of the report is to increase awareness among physicians that systemic hypertension could develop during therapy even if the blood pressure was normal at presentation.*

***Case presentation:** A case of a 17-year-old girl who presented in our Children's Emergency Department with in newly-diagnosed type 1 diabetes complicated by ketoacidosis. The patient was earlier seen in two different hospitals within 72 hours where diagnoses of malaria and sickle cell anaemia crisis were made, respectively. She had severe dehydration but no hypotension. Intravenous fluid was administered to her in a referral hospital for suspected sickle cell anaemia with vaso-occlusive crisis. Laboratory findings included hyperglycaemia (random blood glucose 20.8mmo/L; 347mg/dl), acidosis (serum bicarbonate 5mmol/L), ketonuria 2+; glycosuria 2+, and urine specific gravity of 1.015. At admission, the blood pressure was 100/60mmHg (< 50th percentile for both systolic and diastolic blood pressure) but progressively rose to 140-180/80-100mmHg (> 99th percentile) by the third day on admission.*

***Conclusion:** In adolescents with DKA, a more frequent measurement of blood pressure is justified throughout the period of hospital admission, even when admission blood pressure is normal.*

Keywords: *Adolescence, delayed diagnosis, diabetic ketoacidosis, type 1 diabetes, hypertension.*

Introduction

Diabetic ketoacidosis (DKA) is a life-threatening but potentially preventable acute complication of newly-diagnosed type 1 diabetes (T1D) in children. It is characterized by reduced intravascular volume and dehydration. Several factors contribute to such dehydration and these include osmotic diuresis due glycosuria, decreased oral intake due to anorexia and vomiting and increased insensible water loss due to hyperventilation [1,2]. Typically, severe dehydration will lead to hypovolaemia and systemic hypotension. Blood pressure (BP) may be elevated due to cerebral oedema with resultant increased intracranial pressure [3,4]. In literature, recognized complications of DKA include deep vein thrombosis, cerebral oedema, cerebralvenousthrombosis,haemorrhagicorischaemic stroke, rhabdomyolysis, pneumomediastinum (Hamman syndrome), pulmonary oedema, pulmonary embolism, pancreatitis, gastrointestinal bleeds, gastroparesis, acute kidney injury and memory dysfunction [1,4,5]. Some complications associated with therapy include inadequate or excessive fluid replacement, hypokalaemia, hypoglycaemia, and relapse of ketoacidosis [4]. Hypertension is not a known complication of therapy.

In literature, reports of delayed/missed diagnosis of DKA are common, both in developed and developing countries. Within this context, results of several studies indicate that 15% to 86% of children with DKA are not diagnosed as diabetic at first physician consultation [6-10]. It has been documented that parents and physicians have difficulty recognizing signs and symptoms of diabetes mellitus in children [11,12], a factor that contributes to delayed/missed diagnosis.

The National Heart, Lung and Blood Institute (NHLBI) charts defined hypertension when either systolic or diastolic blood pressures is equal or greater than the 95th percentile for age, height and gender [13]. For descriptive purposes, cerebral oedema was defined by clinical evaluation which included alteration in mental status and vital signs that led attending physician (Consultant paediatrician) to administer hyperosmolar therapy (mannitol) [3]. In this paper, delayed/missed diagnosis refers to failure to consider DKA following one or more physician consultation in an episode of illness.

The purpose of this paper is to report a case of severe paediatric DKA with delayed diagnosis and unexpected development of systemic hypertension during therapy.

Case Report

We report a case of a 17-year-old girl who presented in our Children's Emergency Unit with new-onset type 1 diabetes complicated by ketoacidosis. The presenting complaints were excessive urination for 2 weeks, vomiting for 4 days, difficulty in breathing for one day and unresponsiveness to calls for 3 hours. The patient was noticed to be losing weight despite increased appetite and consumption of food, even late at night. She had a positive history of polydipsia but no enuresis. Fever and vomiting were present. At the onset of symptoms, she was taken to a Public Secondary Healthcare Hospital where she was treated for malaria on outpatient basis because of lack of bed space. She was later taken to another Public Secondary Healthcare Hospital where she was admitted and treated with intravenous fluid and some injections. Following worsening of symptoms, the patient was referred to University of Benin Teaching Hospital (UBTH) as a case of Sickle cell anaemia in vaso-occlusive crisis with peptic ulcer disease as a differential diagnosis. There was no history of convulsion or irrational behaviour. She was not previously known to have diabetes mellitus or systemic hypertension. Family history of diabetes mellitus and hypertension was negative. On arrival in the emergency department, physical examination revealed an acutely ill-looking adolescent girl with altered level of consciousness and a Glasgow coma score of 11/15. She was restless and severely dehydrated. The pupils were of normal size and reactive to light. She had normal findings on fundoscopy. She had Kussmaul respiratory pattern with a respiratory rate of 36 cycles/minute. The lung fields were clear on auscultation. Oxygen saturation was 99%. The pulse rate was 120 beats/minute and blood pressure was 100/60mmHg (< 50th percentile for both systolic and diastolic BP, respectively). Other cardiovascular examination findings were normal. Her body temperature was 37^{0}C, weight 37kg (< 5th percentile), length 158cm (25th percentile) and BMI 15.6kg/m^{2} (<5th percentile). The laboratory findings at point of admission are summarized in Table 1.

Table 1. Summary of laboratory findings at the point of admission

Parameter	Result	Comments
Random blood glucose	20.8mmol/L	Hyperglycaemia
Serum sodium	124	Hyponatraemia
Serum potassium	4.8	Normokalaemia
Serum chloride	90	Hypochloridaemia
Serum bicarbonate	5	Severe acidosis
Serum urea	31	Normal
Serum creatinine	0.7	Normal
Urine ketone	2+	Ketonuria
Urine glucose	2+	Glycosuria

Urine specific gravity	1.015	Elevated
Blood in urine	Negative	No haematuria
Urine protein	Negative	No proteinuria
Urine culture	Yielded no growth	Sterile
Blood culture	Yielded no growth	Sterile
Total white blood cell	21.6 x 10^3/μL	Leucocytosis

A diagnosis a ketoacidosis in a newly-diagnosed type 1 diabetes mellitus was made. The patient was commenced on 0.9% saline infusion at 20mls/kg over the first one hour. In the second hour, she was commenced on continuous insulin infusion at 0.1IU/kg/hr. The rest of the fluid (deficit plus maintenance) was given over the next 48 hours. As a policy, intravenous antibiotics (ceftriaxone) was administered. On the 3rd day on admission, she was still ill looking with respiratory distress and BP ranged between systolic 140 to 170mmHg (> 99th percentile) and diastolic 80 to 100mmHg (90th-99th percentile). With deterioration in level of consciousness, a diagnosis of DKA complicated by cerebral oedema was made. Intravenous mannitol was commenced but this intervention did not help. All the blood pressure measurements were performed with the patient lying in supine position, using mercury sphygmomanometer with appropriately-sized arm cuffs and recorded in the patient's charts. The patient was subsequently transferred to the Intensive Care Unit of the hospital. Her clinical condition continued to deteriorate until her demise on the 5th day on admission.

Discussion

The pathway to recognition of DKA in this patient was prolonged, despite the presence of classical symptoms of type 1 diabetes mellitus complicated by ketoacidosis. The index patient had two physician consultations in two different hospitals before referral to our hospital. In the first hospital the diagnosis was malaria and in the second, the diagnosis was sickle cell anaemia in vaso-occlusive crisis. As a consequence, the type and quantity of intravenous fluid administered at the referral hospital was based on the diagnosis which may have been inappropriate for DKA treatment. The delay in diagnosis with the attendant delay in commencement of appropriate treatment may have contributed to the severe nature of the DKA (serum bicarbonate < 5mmol/L) at presentation in our hospital. Such delayed/missed diagnosis is common in clinical practice, both in developed and developing countries [6-10], representing a preventable health care failure. Therefore, there is a need to create more awareness among parents and physicians regarding clinical features of diabetes mellitus and DKA. One way of doing this is through establishing nation-wide diabetic awareness day. This view is supported by the report of a study in Australia [14]. Within this context, simple awareness programmes in schools and physicians office in the form of posters depicting clinical features of diabetes mellitus have helped over several years to reduce occurrence of DKA to zero in Parma, Italy [15]. In fact, the programme proved successful several years after it has been stopped [16]. The history of fever in the index patient suggests presence of sepsis. Data from developing countries indicate that sepsis not only precipitate DKA but also complicate fluid therapy, resulting in increased mortality [17]. Our patient most probably had inappropriate fluid therapy at the referral hospital, partly contributing to development of cerebral oedema.

At the point of admission, our patient had a normal blood pressure in association with severe dehydration. DKA being a hypovolaemic state is expected to be associated with hypotension rather than hypertension. Unexpectedly, on the third day of admission our patient developed systemic hypertension which persisted till her demise, despite efforts to control the cerebral oedema with mannitol administration. A similar observation has been reported previously in a study involving children below 18 years old conducted at Seattle Children's hospital, USA [3]. DKA may result in both dehydration and cerebral oedema. However, these two pathologic processes may have opposing effects on blood pressure [3]. Several mechanisms have been postulated to explain the occurrence of hypertension despite dehydration in patients with DKA. Cerebral oedema may lead to increase in intracranial pressure (ICP) and subsequent increase in systemic BP aimed at maintaining cerebral perfusion [5]. Another

mechanism for hypertension in DKA is stress response via increase in catecholamine levels following small increases in cerebral oedema and ICP [18]. In addition, the levels of other counter-regulatory hormones (such as glucagon, cortisol and growth hormone) and proinflammatory cytokines have been shown to be elevated in DKA. These chemical substances may have effect on BP acutely [19,20]. Hyperosmolality leads to release of anti-diuretic hormone which increases BP via V2 receptors [21]. Over-activity of the rennin-angiotensin system as well as arginine vasopressin (known to be highly activated in DKA) is also a possible cause of the observed hypertension [18,21,22].

We did not give any specific therapy for the hypertension. This was because of the uncertainty regarding the pathophysiological process involved in the development of cerebral oedema in DKA. If cerebral ischaemia is involved as the major causal pathway leading to cerebral oedema (cytotoxic), then hypertension may be a physiological response to maintaining cerebral perfusion and would be desirable and protective [3]. On the other hand, if cerebral re-perfusion is the main pathophysiological process, then treating the hypertension may be warranted as a therapy to limit vasogenic cerebral oedema [23,24]. In addition, the role of inflammatory-mediator release, glucotoxicity or acidosis in causing cerebral oedema is poorly understood. All these reflect the controversies surrounding the aetiopathogenesis of DKA-related cerebral oedema.

In conclusion, frequent measurement of blood pressure is justified throughout the period of hospital admission, even when admission blood pressure is normal.

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