Diabetic Ketoacidosis in Children and Adolescents

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Diabetic ketoacidosis (DKA) represents an acute, severe complication of relative insulin deficiency and a common presentation of Type 1 Diabetes Mellitus (T1DM) primarily and, occasionally, Type 2 Diabetes Mellitus (T2DM) in children and adolescents. It is characterized by the biochemical triad of hyperglycaemia, ketonaemia and/or ketonuria, and acidaemia. Clinical symptoms include dehydration, tachypnoea, gastrointestinal symptoms, and reduced level of consciousness, precipitated by a variably long period of polyuria, polydipsia, and weight loss.

diabetic ketoacidosis | type 1 diabetes mellitus | pitfalls | children

1. Introduction

DKA represents the most common acute hyperglycaemic emergency in children and adolescents with diabetes mellitus [1]. Based on the *International Society for Pediatric and Adolescent Diabetes* (ISPAD) guidelines, it is characterized by the biochemical triad of hyperglycaemia (serum glucose > 11 mmol/L or >200 mg/dL), ketonemia (β-hydroxybutyrate concentrations > 3.0 mmol/L) and/or moderate or large ketonuria, and a high anion-gap metabolic acidaemia (venous pH < 7.3 and/or bicarbonate < 18 mmol/L) [2][3].

Clinically, DKA is characterized by dehydration, tachypnoea and Kussmaul breathing, smell of ketones in the breath, nausea, vomiting, abdominal pain, drowsiness, confusion, reduced level of consciousness and coma, which are precipitated by a variably long period of polyuria, polydipsia, and weight loss. Most children presenting with DKA are in a volume-depleted state, which, in its most severe form, results in acute tubular necrosis and potentially in acute kidney injury (AKI) [3].

DKA occurs primarily at the onset of type 1 diabetes mellitus (T1DM) as a result of absolute or relative insulin deficiency due to autoimmune destruction of the β-cells of the islet of Langerhans and concomitant elevation of counter-regulatory hormones induced by stress, such as glucagon, growth hormone, catecholamines, and cortisol. It may also occur due to uncontrolled T1DM. Lack of adequate insulin and increase in counter-regulatory hormones lead to increased glucose production by the liver and the kidney, through gluconeogenesis and glycogenolysis, and reduced peripheral glucose utilization. As a result, hyperglycaemia, hyperosmolarity, increased lipolysis, and ketogenesis occur. Hyperglycaemia and hyperketonaemia lead to osmotic diuresis, dehydration, and electrolyte loss. Acidosis is enhanced by lactic acidosis caused by hypoperfusion.

In children and adolescents, DKA commonly occurs at the initial diagnosis of T1DM, with the incidence varying from 13% to 80% in different populations [4][5][6]. It can also occur in the context of newly diagnosed T2DM, caused by impaired insulin secretion or action, or in children and adolescents with uncontrolled T2DM, also known as ketosis-prone T2DM [1].

DKA can be precipitated by any physiological stress, including infections, with urinary tract infections and gastroenteritis being the leading causes [7][8]. Poor adherence to insulin therapy and insulin pump issues, such as dislodgement or blockage of infusion sets, are also frequent causes of DKA [9]. Among children and adolescents with known T1DM, DKA mostly occurs due to insulin omission, particularly in the presence of gastrointestinal infections with vomiting [10]. Poor diabetes control, previous episodes of DKA, dysfunctional family relationships, limited access to medical care, history of psychiatric disorders, and adolescent age are also risk factors for DKA in children and adolescents [11][12].

The mortality rate of DKA in children is reported as <1% in developed countries [13], caused primarily by cerebral injuries and cerebral oedema [14]. Nonetheless, among children with T1DM, DKA is the leading cause of mortality accounting for >50% of all deaths [15].

2. Pitfalls Related to the Diagnosis of DKA

DKA is more frequent in children with T1DM, but it also occurs in adolescents with T2DM [4]. Among those with T1DM, DKA is more frequent in newly diagnosed children less than 5 years old and in populations with limited access to medical care due to economic or social reasons [16][17]. In those with T2DM, a genetic predisposition for ketosis-prone T2DM is suggested by the increased incidence observed in people of African or Hispanic origin. Children and adolescents with ketosis-prone T2DM also have a strong family history of insulin resistance and T2DM, and frequently have obesity [8]. They present with decreased insulin concentrations and autoimmune markers of T1DM, such as islet cells, insulin, glutamic acid decarboxylase, and protein tyrosine phosphatase autoantibodies, at similar concentrations as those with hyperosmolar hyperglycaemic state (HHS); however, their β-cell function recovers and insulin secretion is restored soon after treatment [8]. Thus, insulin treatment is not required in the long term and oral glucose-lowering medications are appropriate. Diagnosing the type of diabetes in children and adolescents presenting with DKA can be challenging given the increased rates of obesity in the general paediatric population [18] and the positive autoimmune markers present in children and adolescents with ketosis-prone T2DM.

Differentiating between DKA and HHS, is yet another pitfall in the diagnosis of DKA. The two conditions are hyperglycaemic emergencies, although, with distinct pathophysiologies. HHS, which is rare in children with T1DM and more common in adults with T2DM, is characterized by marked hyperglycaemia and absence of ketosis. Specifically, HHS is characterized by severe hyperglycaemia (glucose > 30 mmol/L or 540 mg/dL), increased serum osmolality (>320 mOsmol/L) due to electrolyte and glucose concentrations, and circulatory volume depletion due to osmotic diuresis, in the absence of ketosis (β-hydroxybutyrate concentrations < 3.0 mmol/L) and acidosis (pH > 7.3 and HCO_3^- > 15 mmol/L) [19]. Insulin concentrations are adequate to inhibit ketogenesis but not sufficient

to ensure adequate cellular glucose uptake. Although HHS is less frequent than DKA, it is associated with higher mortality, of up to 20% [20][21]. As with DKA, concurrent illness or physiological stress may precipitate HHS, as a result of an increase in counter-regulatory hormones. The differentiation between the two conditions is necessary as circulatory volume depletion is more severe in HHS compared to DKA; therefore, management of HHS mainly involves more aggressive fluid resuscitation to restore fluid and potassium deficits and reduce hyperosmolality.

In addition, lack of prompt recognition of new-onset T1DM by health-care providers is another pitfall that may increase the risk of DKA [22]. Missed or delayed diagnosis is mainly caused by the presence of clinical symptoms that overlap between T1DM and other, usually more common, medical conditions. Specifically, in children, the clinical symptoms precipitating DKA include: (i) polyuria, i.e., excessive urination, due to osmotic glycosuria with water and electrolyte loss, leading in some cases to enuresis, (ii) polydipsia, i.e., excessive thirst, secondary to polyuria, (iii) polyphagia, i.e., excessive hunger, and (iv) weight loss [23]. Recognizing the hyperglycaemia-induced nature of these symptoms is crucial for a timely diagnosis of a new presentation of diabetes, avoidance of misdiagnosis and prevention of DKA and its associated risks. Frequent misdiagnosis errors include diagnosing a urinary tract infection, attributing increased thirst to heat or increased physical exercise, particularly during the summer, and attributing weight loss to accelerated height gain, particularly during adolescence. Obtaining a thorough medical history can allow distinguishing diabetes-related polyuria from frequent urination caused by a urinary tract infection, which is also characterized by a small urine volume and the urge to urinate. A detailed medical history can also reveal progressively deteriorating, and otherwise unexplained, polydipsia, polyuria, and weight loss. Weight loss and gradually worsening fatigue, which are caused by insulin deficiency and the increase in counter-regulatory hormones that result in lipolysis and muscle lysis in the effort to compensate for intracellular glucopenia and lack of energy, are frequently attributed by parents or children to exercise and increased learning activities.

Once ketosis and acidosis begin to develop, gastrointestinal symptoms are added, including nausea, vomiting and abdominal pain, in more than 60% of patients [7][24]. These symptoms are often misperceived as gastroenteritis, especially in the context of a relatively short history. Therefore, increased index of suspicion is required by the clinician in order to not be misguided. However, the possibility of DKA being triggered by a gastrointestinal tract infection should not be ignored, and this is yet another diagnostic pitfall. Furthermore, in severe metabolic acidosis, abdominal pain may mimic an acute abdomen leading in some cases to the false diagnosis of appendicitis and/or peritonitis. Again, a thorough medical history may reveal pre-existing polyuria, polydipsia, and weight loss; whereas, a careful clinical examination may reveal severe dehydration and circulatory volume depletion presenting as dry mucous membranes, delayed capillary refill time, and tachycardia. Also, measurement of capillary and/or blood glucose concentrations in the presence of such symptoms is of particular importance.

In addition, with the progression of DKA, Kussmaul breathing pattern is observed as a compensatory mechanism for hyperketonaemia and metabolic acidosis, characterized by tachypnoea, deep and laboured breathing. These symptoms may falsely be attributed to a respiratory tract infection or pneumonia. A careful physical examination can differentiate between the two conditions. Notably, DKA is not characterized by symptoms such as cough and fever, or by signs of respiratory distress, with the exception of tachypnoea. In contrast, children with DKA are either

normothermic or hypothermic. Also, a fruity odour due to acetone exhalation is typical of DKA. Caution should be raised about the likelihood of DKA being precipitated by a respiratory tract infection.

Finally, if DKA remains undiagnosed, mental status is impaired due to deteriorating dehydration and acidosis, resulting in lethargy or even coma. Excluding CNS infection, such as meningitis or encephalitis, is necessary.

3. Pitfalls Related to DKA Complications

Paediatric DKA is associated with a wide range of complications, with cerebral oedema being the most feared. Cerebral oedema is clinically apparent in 1% of diagnoses of DKA and is associated with a mortality rate of 40–90% [25][26]. It usually develops within the first few hours of initiation of fluid resuscitation, i.e., 7–8 h in approximately 2 out of 3 cases [27]; whereas, in the remaining cases it occurs up to 28–30 h after fluid resuscitation and initiation of insulin treatment [28]. It has been reported, however, that cerebral oedema may rarely occur prior to or up to 60 h after treatment initiation, which highlights the need for vigilance and continuous monitoring of the patients' mental status [28]. Risk factors for cerebral oedema include severe acidosis, severe dehydration, elevated blood pressure and markedly elevated BUN [3]. As already mentioned, rapid IV fluid resuscitation is discouraged, however no difference was found in the neurological outcomes between different rates of IV fluid administration in a recent study [27]. Warning clinical symptoms and signs include altered mental status, such as lethargy, irritability and confusion, onset of headache, progressively worsening vomiting or vomiting after beginning of treatment, urinary incontinence, specific neurological signs, i.e., cranial nerve palsies, and Cushing Triad (bradycardia, irregular respirations, hypertension). New headache, recurrence of vomiting should raise suspicion, particularly in the presence of severe ketoacidosis and hypertension [29].

Clinical identification of cerebral oedema is confounded due to similar clinical presentations caused by other medical conditions; alterations in mental status could be attributed to severe dehydration and acidosis, vomiting could be attributed to acidosis and ketosis, and urinary incontinence to polyuria [30][31].

Another pitfall is that cerebral oedema may not initially be visible on CT scan of the brain; therefore, if suspicion is high, treatment should be started [32].

4. Acute Kidney Injury (AKI)

Among the most common complications of DKA in children and adolescents is AKI, which occurs in 43% to 64% of DKA episodes in children [33][34]. In one-fourth of DKA episodes, AKI is severe, suggesting severe volume depletion [35] and highlighting the need for a delicate balance between treating severe hypovolaemia but also avoiding excessive fluid replacement that may increase the risk for cerebral injury [36]. Awareness about this complication and early recognition of AKI are important also because potassium repletion should not be started if renal function is impaired and should be withheld until urine output is documented [37].

Moreover, AKI has been associated with a substantially increased hazard rate for development of microalbuminuria and contributes to the development of diabetic kidney disease [38]. Therefore, timely fluid resuscitation is important for the prevention of AKI and for ameliorating the associated short- and long-term consequences.

Additional complications of DKA include hypokalaemia, hypoglycaemia, venous thrombosis, pancreatic enzyme elevations, rhabdomyolysis, pulmonary oedema, and cardiac arrhythmias. Prevention of all DKA-related complications, involves primarily prevention of DKA itself.

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