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Introduction

Diabetic ketoacidosis (DKA) is a metabolic derangement caused by the absolute or relative deficiency of the anabolic hormone insulin. Together with the major complication of cerebral edema, diabetic ketoacidosis is the most important cause of mortality and severe morbidity in children with diabetes, particularly at the time of first diagnosis ***(Wolfsdorf et al., 2007)***.

Consensus statements from the European Society for Pediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society (ESPE/LWPES) in 2004, the American Diabetes Association (ADA) in 2006, and the International Society for Pediatric and Adolescent Diabetes (ISPAD) in 2007 defined the following biochemical criteria for the diagnosis of DKA:

1. Hyperglycemia, defined as a blood glucose of >200 mg/dl (11 mmol/l) **AND,**

2. Metabolic acidosis, defined as a venous pH <7.3 and/or a plasma bicarbonate <15 mmol/l ***(Mallare et al., 2003)***.

The adage “A child is not a miniature adult” is most appropriate when considering diabetic ketoacidosis (DKA). The fundamental pathophysiology of this potentially life-

threatening complication is the same as in adults. However, the child differs from the adult in a number of characteristics:

1) The younger the child, the more difficult it is to obtain the classical history of polyuria, polydipsia, and weight loss. Infants and toddlers in DKA may be misdiagnosed as having pneumonia, reactive airways disease (asthma), or bronchiolitis and therefore treated with glucocorticoids and/or sympathomimetic agents that only compound and exacerbate the metabolic derangements. Because the diagnosis of diabetes is not suspected as it evolves, the duration of symptoms may be longer, leading to more severe dehydration and acidosis and ultimately to coma. Even in developed countries, some 15–70% of all newly diagnosed infants and children with diabetes present with DKA ***(Roche et al., 2005)***. Generally, the rates of DKA are inversely proportional to rates of diabetes in that community, but throughout the U.S., the overall rates of DKA at diagnosis have remained fairly constant at approximately 25% ***(Rewers et al., 2005)***. DKA, defined by blood bicarbonate < 15 mmol/l and/or pH < 7.3 was present in 23.3% of a carefully analyzed cohort. However,

the prevalence of DKA decreased significantly with age from 36% in children < 5 years of age to 16% in those > 14 years but did not differ significantly by sex or ethnicity ***(Rewers et al., 2005)***.

2) The higher basal metabolic rate and large surface area relative to total body mass in children requires greater precision in delivering fluids and electrolytes. The degree of dehydration is expressed as a function of body weight, i.e., 10% dehydration implies 10% loss of total body weight as water. However, the calculation of basal requirements, although a constant per unit of surface area, must be carefully adjusted when calculating per unit mass because the amount of fluid per kilogram declines as the infant or child grows ***(Wolfsdorf et al., 2006)***.
3) Cerebral and other autoregulatory mechanisms may not be as well developed in younger children. Hence, greater severity at presentation in younger children together with less maturity of autoregulatory systems combine to predispose children to cerebral edema, which occurs in approximately 0.5–1% of all episodes of DKA in children and is the most common cause of mortality in children with DKA ***(Lawrence et al., 2005)***. Only a minority of deaths in DKA are attributable to other causes, such as sepsis,

other infections (including mucormycosis), aspiration pneumonia, pulmonary edema, acute respiratory distress syndrome, pneumomediastinum, hypo- or hyperkalemia, cardiac arrhythmias, central nervous system (CNS) hematoma or thrombosis, and rhabdomyolysis. Currently, the etiology, pathophysiology, and ideal treatment are poorly understood, but these are areas of intense investigation. Because cerebral edema occurs in the context of DKA, reduction of the incidence of DKA should be a major goal of treating children with diabetes. The reported mortality rates in children with DKA are constant in national population based studies varying from approximately 0.15 to 0.3%. Once cerebral edema develops, death occurs in some 20-25%, and significant morbidity, including pituitary insufficiency, occurs in 10-25% of survivors. Where medical services are less well developed, the risk of dying from DKA is greater, and children may die before receiving treatment. Overall, cerebral edema accounts for approximately 60-90% of all DKA-related deaths in children ***(Wolfsdorf et al., 2006)***.

4) Whereas delay in diagnosis is the major cause of DKA in previously unrecognized disease in younger

children, omission of insulin is the leading cause of recurrent DKA, most prevalent among adolescents. In this group, some 5% of patients account for > 25% of all admission for DKA ***(Edge et al., 2001)***.

These important differences between children and adults require careful attention to issues of management. The aim of this work is to briefly review the pathophysiology of DKA in childhood and discuss recommended treatment protocols, with recommendations and strategies for the prediction and prevention of DKA and, hence, its complications in infants and children.

Epidemiology

Diabetic ketoacidosis is characteristically associated with type 1 diabetes. It also occurs in type 2 diabetes under conditions of extreme stress such as serious infection, trauma, cardiovascular or other emergencies, and, less often, as a presenting manifestation of type 2 diabetes, a disorder called ketosis-prone diabetes mellitus.

DKA is frequently the initial presentation of children with new onset type 1 diabetes mellitus. In a surveillance study of almost 3000 episodes of DKA in the United Kingdom, 38 % occurred in patients at the time of initial diagnosis of diabetes mellitus ***(Edge et al., 2001)***. In other studies from Europe and North America, the frequency of DKA as the initial presentation for type 1 diabetes mellitus is approximately 25 % (range from 15 to 67 %) ***(Wolfsdorf et al., 2006)***.

Although population-based studies are lacking, the incidence of DKA as the initial presentation in type 2 diabetes mellitus varies considerably. In a systematic review, factors associated with increased risk for having DKA at presentation are younger age (<5 years), ethnic minority status, diagnostic error, lack of health insurance, lower body mass index, and delayed treatment ***(Usher-Smith et al., 2011)***. In different studies, 4 % of Canadian aboriginal children, 25 % of Irish children, 30 % of Mexican-American children and more than 40 % of obese

African-American adolescents with type 2 diabetes mellitus initially present with DKA ***(Sapru, Gitelman et al., 2005)***.

In addition, DKA and its complications are the most common cause of hospitalization, mortality, and morbidity in children with established type 1 diabetes mellitus ***(Edge et al., 2001)***.

Initial presentation of type 1 diabetes mellitus:

Children who are young (<6 years of age) or from a low socioeconomic background are at increased risk for DKA at initial presentation ***(Rewers et al., 2008)***. The data supporting these conclusions are illustrated by the following observations:

- A retrospective study from Germany reviewed 2121 newly diagnosed children with type 1 diabetes mellitus, 558 of whom (26 %) presented in DKA ***(Neu et al., 2003)***. The incidence of DKA was higher (36 %) in children less than five years of age.
- The importance of socioeconomic status was illustrated in a review of 139 patients with newly diagnosed type 1 diabetes mellitus seen at a single center in the United States ***(Mallare et al., 2003)***. The investigators used the lack of private insurance as a proxy for low socioeconomic status. A disproportionate number of children having either Medicaid or no insurance presented in DKA compared to those with private insurance (62 versus 34 %). Children less than five years of age were also

at increased risk for DKA (relative risk 2.7 compared to older children).

In established type 1 diabetes mellitus:

The incidence of DKA in children who are known to have type 1 diabetes mellitus was 8 episodes per 100 person years in the largest reported prospective study in which 1243 American children were followed for five years ***(Rewers et al., 2002)***. Risk factors for recurrent DKA included:

- Higher A_1C values and higher reported insulin requirements
- Female adolescents, with the highest risk in female adolescents over 13 years of age
- Children over 13 years of age, regardless of gender, who are underinsured and/or have a history of psychiatric disorders
- Longer duration of diabetes mellitus

Almost 60 % of DKA episodes occurred in only 5 % of children. Similar findings were noted in the United Kingdom surveillance study cited above ***(Edge et al., 2001)***. Patients with known diabetes mellitus who had four or more episodes (4.8 percent of patients) accounted for 35 % of all episodes of DKA.

Thus, a small group of patients consume a disproportionate amount of healthcare resources and costs. The identification of these patients at high risk for recurrence of DKA and the

establishment of a comprehensive diabetes treatment program may reduce the rates of DKA and possibly healthcare costs ***(Rewers et al., 2002)***. Such a program should emphasize compliance with management recommendations, including adherence to the insulin regimen and the use of home glucose monitoring.

Type 2 diabetes mellitus:

Although less common, ketosis and DKA can occur in children with type 2 diabetes mellitus, particularly in African-American children ***(Sapru et al., 2005)***. In a retrospective review of 69 patients (between 9 and 18 years of age) who presented with DKA at a tertiary center, 13 percent had type 2 diabetes mellitus ***(Sapru et al., 2005)***. At presentation, there was no difference in the serum pH level but patients with type 2 diabetes mellitus compared to those with type 1 diabetes mellitus had higher blood glucose levels.

Precipitating factors:

Recurrent episodes of DKA with established type 1 diabetes mellitus are primarily the result of underlying poor metabolic control and frequently missed insulin injections ***(Rewers et al., 2002)***. Omission of insulin injections is particularly common among adolescents.

Stress is also an important precipitating factor. Stress increases the secretion of catecholamines, cortisol, and glucagon, which promote both glucose and ketoacid production. As an example,

infection can precede an episode of DKA ***(Flood and Chiang, 2001)***.

In addition, medications such as corticosteroids, atypical antipsychotics, diazoxide, and high dose thiazides, have precipitated DKA in individuals not previously diagnosed with type 1 diabetes mellitus.

Pathogenesis

Two hormonal abnormalities are largely responsible for the development of hyperglycemia and ketoacidosis in patients with uncontrolled diabetes ***(Rose and Post, 2001)***:

- Insulin deficiency and/or resistance.
- Glucagon excess, which may result from removal of the normal suppressive effect of insulin ***(Diamond et al., 1991)***. There is no evidence for defective pancreatic alpha cell function in diabetes, since there is a normal glucagon response to nonhypoglycemic stimuli, such as arginine ***(Palmer et al., 1976)***.

Although glucagon excess contributes to the development of DKA, it is not required. As an example, patients with complete pancreatectomies and who have no pancreatic glucagon will develop DKA if insulin is withheld; however, it takes longer for DKA to develop compared with patients with type 1 diabetes.

In addition to these primary factors, increased secretion of catecholamines and cortisol can contribute to the increases in glucose and ketoacid production.

Normal response to hyperglycemia:

The extracellular supply of glucose is primarily regulated by two hormones: insulin and glucagon. As the serum glucose concentration rises after a glucose meal, glucose enters the