SEVERE KETOACIDOSIS AT ONSET OF TYPE 1 DIABETES IN CHILDREN DUE TO LATE DIAGNOSIS

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SUMMARY

A case is reported of a young patient who presented to University Department of Pediatrics in Prishtina with a newly diagnosed diabetes in December 2006. On admission, the patient showed severe ketoacidosis due to the late diagnosis, in spite of two prior visits to a general practitioner. Biochemistry results on admission included serum glucose 35 mmol/L, venous pH 6.9, bicarbonates 4.8 mmol/L, Na 138 mmol/L, K 3.5 mmol/L, L 12,000, urea 6.5 mmol/L, creatinine 50 µmol/L and ketonuria ++++. Treatment consisted of fluid replacement over 48 hours and careful monitoring of electrolytes and glycemia, based on the protocol issued by ESPE and American Diabetes Association. Children aged less than five years are more likely to present with diabetic ketoacidosis, partly as the result of their clinical presentation not having been recognized by health professionals as being compatible with diabetes, leading to a delay in the diagnosis and referral to hospital. We highlight the need for increased vigilance among general practitioners and pediatricians for the early presenting symptoms of diabetes in this vulnerable age group (0-4 years) in order to prevent diabetic ketoacidosis in new-onset diabetes and reduce its fatal complications, which could theoretically be achieved through a physician awareness campaign.

INTRODUCTION

Diabetic ketoacidosis (DKA) is an acute serious complication of type 1 diabetes mellitus (type 1 DM) and it is still a major contributor to the morbidity and mortality in children. The biochemical criteria for DKA diagnosis include hyperglycemia >11 mmol/L, venous pH <7.3 mmol/L, bicarbonates <15 mmol/L and ketonuria (1). Late diagnosis can contribute to the manifestation of a severe form of DKA based on the following classification: mild DKA when venous pH <7.3 and/or bicarbonates <15 mmol/L; moderate DKA when pH <7.2 mmol/L and/or bicarbonates <10 mmol/L; and severe DKA when pH <7.1 and/or bicarbonates <5 mmol/L (2,3).

We examined data on the children and adolescents presenting with DKA over a recent 1-year period. In a total number of 15 new type 1 DM cases, there were two patients aged <5 years admitted with severe DKA.
as a new onset diabetes. The new cases of diabetes were almost equally recorded in female (8 cases) and in male (7 cases) children. Two cases with severe DKA were from a rural area, with low socioeconomic status; however, new cases of type 1 DM showed an almost equal distribution in rural (8 cases) and urban (7 cases) areas. There were three cases with DKA in adolescents, two female and one male, due to eating disorders, infection and omission of insulin treatment. Here we report on a recent newly diagnosed case of severe DKA due to the late diagnosis, and on appropriate management strategies.

CASE REPORT

An 18-month-old girl from a rural area presented to the Department with depressed consciousness, comatose state, pale skin with peripheral cyanosis and tachypnea. Her initial assessment revealed a heart rate of 155/min with thread pulse, respiratory rate of 60/min with Kussmaul breathing, dry mucous membranes, sunken eyes, poor capillary return, and cold fingers and toes. She weighted 11 kg, had no adenopathy, with normal findings on lung and heart auscultation.

Three days before admission, the child was agitated, noncontactible, with rare vomiting, elevated temperature, anorexic and complaining of abdominal pain. Her mother sent her to the doctor, a general practitioner, who supposed that the patient had urinary tract infection. The doctor put her on treatment with cotrimoxazole and paracetamol. One day after the visit, the child started vomiting more often and her parents transferred her to a hospital closest to their village for the second time to get help from doctors for the sick child. On that occasion, the child was rehydrated with dextrose and saline infusion, laboratory testing was not performed, and they turned back home. During that night, the child started to vomit ever more frequently and was drowsy. The parents took the child to the hospital again, now for the third time, and the doctors tested her for glycemia, which was 35 mmol/L. Now the patient was referred to our Department.

Laboratory testing: serum glucose 35 mmol/L, venous pH 6.9, bicarbonates 4.8 mmol/L, Na 138 mmol/L, K 3.5 mmol/L, L 12,000, urea 6.5 mmol/L, creatinine 50 µmol/L and ketonuria ++++. Serum osmolarity was calculated and it was 311 mmol/kg.

Resuscitation in this case was medical emergency and it followed ABC pattern. The child was given 100% oxygen, rehydration via central intravenous cannula was started with 20 mL/kg/h of normal saline initially and another intravenous cannula was inserted after one hour for infusion 0.1 UI/ kg/h of short-acting insulin. Since clinical estimation of fluid deficit is subjective and inaccurate, the American Diabetes Association suggests the use of 10% dehydration in severe DKA. The child was too ill to weigh and her weight was estimated from the equation: weight = 2x (age in years + 4). Fluid requirements were calculated for 48 hours as follows:

\[
\text{fluid requirements} = (\text{fluid maintenance} + \text{fluid deficit}) - \text{fluid used for resuscitation}
\]

\[
\text{fluid deficit} = \% \text{ dehydration} \times \text{ body weight (kg)}
\]

After 2 hours of rehydration, venous pH was 6.88 and upon consultation of a senior doctor, bicarbonates were added to the infusion. On admission, the level of potassium was 3.5 mmol/L and potassium was added in the second hour of treatment in infusion at a dose of 40 mmol/L.

After 4 hours, venous pH and bicarbonates started to improve gradually, blood glucose decreased to 4 mmol/L/h, her neurological status was improving and after 24 hours the child started breastfeeding. On the next day, the child started receiving subcutaneously premixed insulin 0.5 UI/kg Mixtard 30 subcutaneously (30% short-acting and 70% intermediate-acting insulin) and fluid replacement from time to time.

Two days after glycemia and acidosis improvement, the child was irritable and her abdomen was distended; native radiography showed paralytic ileus. Replacement of fluids and electrolytes corrected this disorder. After two days, the child recovered with no neurological sequels.
Three weeks of presentation and upon completion of parents’ education, the child was discharged and parents were instructed to continue insulin regimen twice daily with 0.4 UI/kg of Mixtard insulin with a biphasic mixture of 30% short-acting and 70% intermediate-acting insulin. Two thirds of the daily dose are given before breakfast and the remaining one third of the daily dose is given before dinner.

The child is living with her parents who are healthy and showed no impairment on glucose tolerance test, but her grandmother has type 2 diabetes.

DISCUSSION

Diabetic ketoacidosis is a life-threatening event and therefore early recognition of diabetes in children by health professionals is very important. Delay in the diagnosis by a health professional, especially in young age group of <4 years may lead to a severe form of DKA, coma and even death.

The younger the child, the more difficult it is to obtain classical history of polyuria, polydipsia and weight loss. Bearing in mind that “the child is not a small adult” is most appropriate when considering DKA (2). Infection is the most common precipitating cause of DKA worldwide, occurring in 30%-50% of cases. Urinary tract infection and pneumonia account for the majority of infections. Tachypnea and hyperventilation in DKA may lead to erroneous diagnosis of pneumonia, but the lack of cough and wheeze and the absence of abnormal findings on auscultation along with normal chest radiography should raise suspicion of diabetes as an alternative diagnosis (1).

Some infants and toddlers with DKA may also be misdiagnosed as having reactive airway disease (asthma) or bronchiolitis, and therefore treated with glucocorticoids and/or sympathomimetic agents that only compound and exacerbate the metabolic derangement (2). Inaccurate diagnosis of urinary tract infection or any other viral infection that characteristically evolves so rapidly in young children will prolong the period of exposure to DKA, thus leading to ever more severe dehydration and acidosis, impairment of consciousness and coma.

The symptom of bedwetting in a child who is usually “dry” can occur long before the diagnosis of type 1 DM. Unusual bedwetting was reported by 89% of parents as the first symptom of diabetes, and nine patients with diabetes sought medical attention because of nocturnal enuresis, but the pediatrician failed to recognize the symptom as secondary to hyperglycemia (4).

Although most schoolchildren will report polyuria and polydipsia, these symptoms may be less obvious in a very young child who may be relatively asymptomatic (e.g., polyuria will be less obvious in an infant in nappies) and in whom the other less characteristic symptoms may predominate (1). Symptoms like polyuria, polydipsia, weight loss, anorexia or hyperphagia, lethargy, constipation, infection (especially candidal skin infections), blurred vision and hypoglycemia (rare but it represents islet cell instability in the early stages of diabetes) may have been present for one week to six months before the diagnosis (1).

In any child presenting with impaired consciousness and/or acidosis, DM should be considered on differential diagnosis. Vomiting, abdominal pain and acidosis are the three major signs that are present in DKA (1). For this reason, it is suggested that all doctors “think of diabetes mellitus in any sick child whose cause of illness is not clear”.

There is a wide geographic variation in the frequency of DKA at diabetes onset, the rates showing inverse correlation with the regional incidence of type 1 DM. Approximately 25% of new patients with diabetes will present with DKA, and this rate of DKA at diagnosis is still constant throughout the United States (1,5).

Risk factors

DKA at onset of TIDM is more common in younger children (<4 years of age), children without a first-degree relative with type 1 DM and those from families of lower socioeconomic status (6,7).
Children under 5 years of age and girls face an increased risk of developing DKA, and the shorter duration of symptoms in patients presenting with DKA may indicate that DKA primarily results from a particularly aggressive course of the disease (8).

Children from families with low parenteral education level had ketoacidosis more often than those from families with high parenteral education level (9).

There are some ongoing and persistent problems like an increased incidence and severity of DKA at presentation among uninsured children with newly diagnosed type 1 DM (10). The rate of uninsured children in the United States is currently 12% (9.3 million), an unacceptably high number put at a life-threatening risk (10). Also, a tendency to recommend high carbohydrate containing drinks to children who are ill and vomiting may worsen the degree of hyperosmolality and hypernatremia (11). Even in places where healthcare is broadly available 25% of children with newly diagnosed DM can present with DKA because limited physician awareness as to the common recognizable symptoms of DM remains a major factor (12,13).

**Pathophysiology, management and treatment**

The triad of uncontrolled hyperglycemia, metabolic acidosis and increased total body ketone concentration characterizes DKA. These metabolic derangements result from the combination of absolute or relative insulin deficiency and increased levels of counter-regulatory hormones (glucagon, catecholamines, cortisol and growth hormone). A combination of these two hormonal abnormalities leads to impaired carbohydrate utilization and ketonemia, which in turn results in metabolic acidosis with loss of water through acidic breaths, rise in plasma lipids, hyperglycemia and glycosuria leading to osmotic diuresis and further loss of water, excretion of partly neutralized ketoacids via kidneys with loss of cations (Na⁺ and K⁺).

Successful treatment of DKA requires frequent monitoring of patients, correction of hypovolemia and hyperglycemia, replacement of electrolyte losses, and careful search for the precipitating cause. A wide consensus exists on the need to use small doses of regular insulin for continuous intravenous administration as therapy of choice for pediatric DKA (0.1-0.05 U/kg/h). The success of treatment is tightly connected to the correct management of rehydration, metabolic acidosis and electrolyte deficit replacement rather than insulin therapy, aimed at avoiding cerebral edema as the most dangerous complication of DKA.

All doctors when treating DKA in children should bear in mind that children are not small adults and that they have specific needs. There also are differences in the metabolic rate and surface area between children and adults, warranting greater precision in managing fluid and electrolytes.

Particular attention should be paid to the management of insulin, potassium, phosphate and acid base status. Adequate hydration and insulin therapy will reverse even a severe acidosis and any lactic acidosis, which may account for 25% of acidemia due to poor perfusion of tissue and renal function (1). Bicarbonates should only be considered to improve cardiac contractility in patients who are severely acidotic (pH <6.9) and with circulatory failure despite adequate replacement (1,3).

There is no evidence that adjunctive bicarbonates improved clinical outcome in children with severe DKA. The rates of metabolic recovery and complications were similar in patients treated with and without bicarbonates, and prolonged hospitalizations were noted in the bicarbonate group (14). The conclusion is that adjunctive bicarbonate is unnecessary and potentially disadvantageous in severe pediatric DKA (14). There is also evidence for an association between bicarbonate treatment for correction of acidosis and an increased risk of cerebral edema. Bicarbonate therapy may cause paradoxical acidosis of the central nervous system; rapid correction of acidosis caused by bicarbonates will result in hypokalemia, which may accentuate sodium load and contribute to serum hipertonicity (15). In addition, alkali therapy may increase hepatic ketone production, thus slowing the rate of recovery from ketosis (3). Increased serum urea nitrogen at presentation of DKA is associated with an increased risk of cerebral edema and this association may reflect in greater dehydration in these patients (1).
Because cerebral and other autoregulatory mechanisms may not be well developed in younger children, cerebral edema is a special concern (3).

In children with signs of severe DKA and those who are at an increased risk of cerebral edema, e.g., children aged <5 years, a new onset of type 1 DM should be immediately considered for treatment at an intensive care unit.

Although the mechanisms of cerebral edema are incompletely understood, evidence suggests that delay in the diagnosis contributes significantly. The longer the duration of symptoms before the diagnosis, the more severe are the clinical and biochemical disturbances and the greater are the chances of developing cerebral edema, especially in younger children.

During DKA, there is invariably a large depletion of total potassium even though the initial serum potassium concentration may be normal or even high. Early addition of potassium to the fluid is essential even if serum potassium is normal, because insulin will drive glucose and potassium into the cells producing rapid fall of serum potassium (1).

It is very important that insulin infusions should not be stopped before the acidosis is corrected, as insulin is required to switch off ketone production (1).

The most common cause of mortality in children with DKA is cerebral edema, which occurs in 0.3%-1% of pediatric DKA episodes and leaves one quarter of the survivors with permanent neurological injury (3). In places with less developed medical facilities, the risk of dying from DKA is greater, and children may die before receiving treatment (3).

Factors that are associated with an increased risk of cerebral edema include presentation with new onset type 1 DM, younger age and longer duration of symptoms.

Treatment with premixed insulin is easier to perform than mixing separate insulins, which is time consuming and requires manual dexterity, but adjustments of insulin doses based on home blood glucose monitoring are not possible with premixed insulins. Mixing of separate insulins allows for greater flexibility and probably better glycemic control than that which can be achieved using premixed insulin. An example is the situation of dawn phenomenon combined with waning of insulin action from the prior evening dose of intermediate-acting insulin producing pre-breakfast hyperglycemia; an appropriate response in this situation is to increase the dose of evening intermediate-acting insulin, but the ability to increase only intermediate-acting insulin is not possible in premixed insulins. Sometimes increasing the dose of intermediate insulin may be limited by the occurrence of hypoglycemia in the middle of the night and at the time of the peak activity of the intermediate-acting insulin. If this occurs, a change in timing of the evening dose of intermediate-acting insulin from dinner time to bed time may provide the needed duration of action, which is also not possible with premixed insulins. The insulin regimen of two fixed doses of insulin requires that the size and timing of meals be kept relatively constant from day to day, because a larger than typical meal will cause hyperglycemia and delay or decrease in the size of meal will risk hypoglycemia. The two dose split mix regimen with two fixed doses of insulin a day can often maintain the desired degree of control in newly diagnosed patients during the time that they continue to have some degree of endogenous insulin secretion.

Education of parents regarding nutrition and mixing separate insulins will have to be another importance in our setting to achieve better glycemic control in their children.

Prevention

Type 1 DM is growing at an alarming rate of 5% among preschool children and 3% in children and adolescents each year. The mortality rate of DKA has not changed since the 1970s, and remains between 3.4% and 4.6% (16). Therefore, prevention of DKA remains the most important goal to be achieved by early diagnosis and optimal management (17). The frequency of ketoacidosis at DM onset needs to be reduced through increased public and medical awareness of the presenting characteristics of childhood diabetes. These findings should serve as a call to arms for all physicians who care for children.
and particularly those who care for children with DM (12,17). Education of general physicians and medical students on the common presenting features of DM needs to be reinforced. Dipstick testing of urine for glucose and ketones is widely available and should be a routine in any sick child for whom another cause is not apparent or even if it is. Hyperglycemia should be confirmed if the urine is positive for glucose. Education and information about DM in children should be widely distributed and targeted at teachers of children in all schools, and availability and accessibility of medical care for all children must be a universal goal (12).

School and physician awareness campaign can successfully prevent DKA in children. The incidence of ketoacidosis in newly diagnosed diabetic children aged 6-14 years, in the area of Parma in Italy, was reduced from 78% to almost 0% after 6 years of information program that addressed teachers, students and parents with colorful posters with practical messages about diabetes, and pediatricians were instructed in the use of glucose meters (4). Increased public awareness of signs and symptoms of diabetes should lead to earlier diagnosis, particularly in children under age 5, where checking urine or blood for glucose may prevent misdiagnosis. In addition, high levels of awareness related to the existence of other members of families with type 1 DM can reduce the risk of DKA (4).

DKA can be prevented by shortening the period of carbohydrate intolerance that usually precedes the diagnosis of type 1 DM. Yet, the incidence of DKA among newly diagnosed patients remains unacceptably high, even in nations with highly developed system of medical care. We must say that recognizing the symptoms of diabetes early and treating it before metabolic decompensation sets in is feasible, so schools, kindergartens, nurses, teachers and the public at large should become aware of the increasing incidence of type 1 DM and refer such cases to a doctor promptly. It is concluded that “doctors must have diabetes high on their list as a possible diagnosis”.

CONCLUSION

We conclude that late diagnosis by the physician at initial patient encounter is especially prevalent in young children. The most severe changes of the acid-base balance parameters can be observed in youngest children (aged 1-4 years) living in rural areas (pH 6.9, HCO$_3^-$ 4.8 mmol/L); this should suggest that those children be watchfully observed and type 1 DM should always be considered as a possible cause of any alarming symptoms that may occur.

Recommendations issued by the American Diabetes Association for the management of children with DKA are useful to resolve even a severe DKA without any neurological sequels in a very young child with many risk factors to develop cerebral edema.

It is appropriate to begin to develop a national approach to eradicating DKA. This would require widespread public and professional education programs aimed at detecting new-onset type 1 DM patients prior to the onset of DKA. It would involve promoting diabetes screening programs aimed at detecting patients before the onset of symptomatic disease, and these would most appropriately be centered in the pediatrician’s office.

We suggest a program design and implementation of education to increase public awareness and greater medical alertness, which are necessary in our region to reduce DKA in new-onset type 1 diabetic children.

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REFERENCES


