Diabetic Ketoacidosis in Children with Type One Diabetes Mellitus: Risk Factors, Outcome and Complications

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Abstract: Background: Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children with type one diabetes mellitus (T1DM). Mortality is predominantly related to the occurrence of cerebral edema. Objective: The aim of the study is to identify the risk factors leading to the development of DKA and to increase awareness of both physicians and general population. Materials and methods: Data was collected from 99 patients admitted with the diagnosis of DKA to the pediatric ward at Al-Numan Teaching Hospital from January 2018 to December 2020. Diagnosis was based on both clinical and biochemical criteria. Information was taken regarding risk factors, outcome and complications. Results: Risk factors differ in patients with new onset diabetes from those with established T1DM. In new onset cases young age (less than 5 years) was the most important factor (42.8% were in the age group 2 – 6 years). Regarding established cases insulin omission and poor metabolic control were the most important risk factors (65.3% had poor control with omission of insulin doses). Regarding recurrent episodes of DKA adolescent females with behavioral problems or family problems were the highest risk group (85.7%). There were no deaths in our study, 9% developed complications related to hypoglycemia and electrolyte disturbances. One patient developed cerebral edema and one patient developed acute renal failure. Conclusion: like other studies, our study showed that risk factors differ depending on whether the patient had new onset or established T1DM. Young age was the most important risk factor for new onset cases while insulin omission and poor metabolic control was the most important risk factor in established cases. Regarding recurrent episodes of DKA peri pubertal and adolescent females with behavioral problems were the highest risk group. Awareness of these and other contributing factors will help in reduction of the number of DKA episodes. Most of the complications related to DKA or its treatment were due to electrolyte disturbances (hyponatremia and hypokalemia) and hypoglycemia. Cerebral edema although occurring in less than 1% of patients remains a devastating complication and the main cause of death in DKA.

Keywords: Type one diabetes mellitus, diabetic ketoacidosis, cerebral edema, hypoglycemia and electrolyte disturbances

1. Introduction

Diabetic ketoacidosis (DKA) is the leading cause of morbidity and mortality in children with type one diabetes mellitus (T1DM). It is a metabolic derangement caused by the absolute or relative deficiency of insulin leading to intracellular starvation and stimulating the release of counter regular hormones (glucagon, catecholamines, cortisol and growth hormone). The combined effect of these two factors lead to the development of hyperglycemia, hyperosmolality, ketonemia, ketonuria and metabolic acidosis. (1). Clinical features of DKA include dehydration, rapid deep sighing respiration (Kussmaul breathing), vomiting, abdominal pain, progressive obtundation and loss of consciousness and fever if there is infection.

The biochemical criteria for diagnosis include
1) Hyperglycemia (blood glucose >11 mmol/L or 200mg/dl)
2) Venous pH< 7.3 or bicarbonate < 15 mmol/L
3) Ketonemia and ketonuria

Treatment is with exogenous insulin, fluid and electrolyte replacement, this is done according to DKA treatment protocols. (2)

Diabetic Ketoacidosis Treatment Protocol

<table>
<thead>
<tr>
<th>TIME</th>
<th>THERAPY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st hr</td>
<td>10-20 mL/kg IV bolus 0.9% NaCl or LR</td>
<td>Quick volume expansion; may be repeated. NPO. Monitor I/O, neurologic status. Use flow sheet. Have mannitol at bedside; 1 g/kg IV push for cerebral edema</td>
</tr>
<tr>
<td>2nd hr until DKA resolution</td>
<td>0.45% NaCl plus continuous insulin drip 20 mEq/L K+ and 20 mEq/L Ca + 5% glucose if blood sugar &lt; 250 mg/dl (14 mmol/L)</td>
<td>IV rate 85 mL/kg + maintenance bolus 23 hr</td>
</tr>
<tr>
<td>Variable</td>
<td>Oral intake with subcutaneous insulin</td>
<td>If K &lt; 3 mEq/L, give 0.1-10 mEq/kg as oral K solution or increase IV K to 80 mEq/L</td>
</tr>
</tbody>
</table>

Frequency and risk factors of DKA
1) DKA with new onset T1DM
   There is a wide geographic variation in the frequency of DKA at diabetic onset, and rates correlate inversely with regional incidence of T1DM and therefore the level of awareness in the community of pediatric diabetes. The range is from 15% - 67%. Risk factors include young
age, low socioeconomic level, no family history of diabetes and misdiagnosis.(3)

2) DKA in established T1DM

The incidence of DKA is 1-10% per patient per year. Risk factors include

- Insulin omission and poor adherence to treatment
- Poor metabolic control
- Previous episodes of DKA
- Age (peri pubertal and adolescent girls have the highest risk )
- Low socioeconomic level and personal behavioral problems
- Limited access to outpatient diabetic care.(3)

Morbidity and mortality

In national population studies the mortality rate from DKA is 0.15 – 0.30 %. Cerebral edema accounts for 60 – 90 % of deaths, it is a devastating and unpredictable complication of DKA and it’s treatment. It’s occurrence is about 7/1000 episodes of DKA and it’s pathophysiology is not well understood.

Risk factors include young age, new onset T1DM, more severe acidosis at presentation, administration of large amounts of fluid in the first 4 hours of treatment and administration of bicarbonate. Early signs of cerebral edema that should be looked for include headache, irritability, unexplained decrease in heart rate and increase in blood pressure.

Other complications of DKA include hypokalemia, hypoglycemia, hyponatremia, peripheral venous thrombosis, sepsis, acute renal failure and acute pancreatitis.(4)

2. Methods and Materials

This is a retrospective study done at Al-Numan Teaching Hospital from January 2018 to December 2020, 99 patients with DKA admitted to the pediatriac ward were included. Diagnosis of DKA was made according to both clinical and biochemical criteria other investigations were done according to comorbidities.

Patients were divided into two groups those with new onset T1DM and those with established T1DM, data was taken from their medical records regarding

1) Risk factors contributing to DKA development including:
   a) Age
   b) Sex
   c) Compliance with treatment and metabolic control
   d) (compliance and metabolic control was considered good if the patient had regular check of his blood sugar at home and regular visits to the diabetic care outpatients )
   e) Socioeconomic level (based on educational level of the parents)
   f) Low if illiterate or primary school education, medium if secondary school education and high level if university graduate)
   g) Personal behavioral problems and family problems

   h) Inter current infection

2) Outcome and complications of DKA episode

3. Results

The total number of patients included in the study was 99, 39 (39.3%) males and 60 (60.6%) females. patients with new onset T1DM were 21 (21.2%) and those with established T1DM were 78 (78.7%).

Table 1: New or established T1DM and sex distribution

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>New onset</td>
<td>15(15.1%)</td>
<td>6(6.1%)</td>
<td>21(21.2%)</td>
</tr>
<tr>
<td>Established</td>
<td>24(24.2%)</td>
<td>54(54.5%)</td>
<td>78(78.7%)</td>
</tr>
<tr>
<td>Total</td>
<td>39(39.3%)</td>
<td>60(60.6%)</td>
<td>99(100%)</td>
</tr>
</tbody>
</table>

Patients with new onset T1DM and DKA

Total number of patients was 21, 15 (71%) males and 6 (28.5%) females.

Risk factors for the development of DKA in this group included:

1) Age of patient

Table 2: Age and sex distribution

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 – 6 years</td>
<td>6(28.5%)</td>
<td>3(14.2%)</td>
<td>9(42.8%)</td>
</tr>
<tr>
<td>7 – 10 years</td>
<td>3(14.2%)</td>
<td>3(14.2%)</td>
<td>6(31.6%)</td>
</tr>
<tr>
<td>11 – 14 years</td>
<td>6(28.5%)</td>
<td>3(14.2%)</td>
<td>9(42.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>15(71%)</td>
<td>6(28.5%)</td>
<td>21(100%)</td>
</tr>
</tbody>
</table>

2) Family history of diabetes mellitus

Table 3: Family history of Diabetes mellitus

<table>
<thead>
<tr>
<th>Diabetes Mellitus</th>
<th>Present</th>
<th>Absent</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3(14.2%)</td>
<td>18(85.7%)</td>
<td>21(100%)</td>
</tr>
</tbody>
</table>

3) Socioeconomic state of family

Table 4: Socioeconomic level of family

<table>
<thead>
<tr>
<th>Socioeconomic level</th>
<th>Low</th>
<th>Medium</th>
<th>High</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9(42.8%)</td>
<td>12(57.1%)</td>
<td>12(57.1%)</td>
<td>21(100%)</td>
</tr>
</tbody>
</table>

4) Misdiagnosis of the condition

If the child was diagnosed as having an acute illness before reaching the diagnosis of diabetes and DKA

Table 5: Misdiagnosis of DKA

<table>
<thead>
<tr>
<th>Misdiagnosis</th>
<th>Correct diagnosis from the beginning</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>9(42%)</td>
<td>12(57%)</td>
</tr>
</tbody>
</table>

Patients with established T1DM and DKA

Total number of patients was 78, 24 (30.7%) males and 54 (69.2%) females.

Risk factors for the development of DKA include:

1) Age and sex
Risk factors differ between DKA at the time of diabetes diagnosis and episodes occurring in patients with established diabetes.

At disease onset young age was found to be the most common factor associated with increased risk of DKA especially in children younger than 5 years this was consistent with our study that showed 42.8% of the patients were in the age group 2-6 years and with other multiple published studies (3), (5), (6). The causes are multiple including awareness of the general population of childhood diabetes (in our study 85.7% of the patients did not have family history of diabetes and therefore had little or no knowledge) lower index of suspicion by physicians as the signs and symptoms are similar to many of the acute illnesses of childhood and this was consistent with our study 57% of patients had another diagnosis before reaching the correct diagnosis and was found in other published papers (1) and finally low socioeconomic level as found in multiple published studies (3), (4), (6), in our study both low (42.8%) and medium (57.1%) socioeconomic levels were high risk factors.

In established diabetic cases regarding gender and age our study showed it is more common in females (69.2%) in comparison with males (30.7%). Peri pubertal and adolescent girls are the most common group (38.4%) especially in cases of recurrent DKA (85.7%), this was consistent with many published studies (1), (3), (4), (6), (7).

Insulin omission, either inadvertently or deliberately is the main cause in most of the cases. There are many causes for that:

1) No adult supervision and the child forgets to take insulin this is seen more in families with low socioeconomic level and this is in consistent with our study (61.5%) and other published studies (1), (3), (5).
2) Clinical depression
3) A means of escaping intolerable home situation
4) Attempt to lose weight in an adolescent girl

The last 3 causes are mostly seen in adolescent females especially in those with recurrent episodes of DKA. (3)

Inter current infection is another cause to precipitate an episode of DKA in our study (23%) of patients had an infection as the cause, urinary tract infection was found in 50% of those patients this was also found in other published studies (8).

Outcome and complications: There are many guidelines for treatment of DKA, in our hospital the guideline used was that from Nelson textbook of Paediatrics.

Regardless the guideline used the most important thing is correct replacement of insulin, fluid and electrolytes and close monitoring of the patient for early detection of any complications especially cerebral edema.

In our study there was no death, we had one case of cerebral edema (1%) who improved after receiving mannitol. In most studies the incidence of cerebral edema was between

2) Insulin omission and poor adherence to treatment 51 (65.3%) had poor adherence to treatment, the majority were females 36 (46.1%).

Table 7: Adherence to treatment in patients with T1DM and DKA

<table>
<thead>
<tr>
<th>Type of adherence</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good adherence</td>
<td>18(23%)</td>
<td>30(38.4%)</td>
<td>48(61.5%)</td>
</tr>
<tr>
<td>Bad adherence</td>
<td>6(7.69%)</td>
<td>24(30.7%)</td>
<td>30(38.4%)</td>
</tr>
</tbody>
</table>

3) Socioeconomic level, personal and family problems

Table 8: Socioeconomic level and sex distribution

<table>
<thead>
<tr>
<th>Socioeconomic level</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>30(38.4%)</td>
<td>18(23%)</td>
<td>48(61.5%)</td>
</tr>
<tr>
<td>Medium</td>
<td>30(38.4%)</td>
<td>30(38.4%)</td>
<td>60(76.9%)</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

4) Previous episodes of DKA

16 (20.5%) patients of the total 78 had more than one episode of DKA during the studied period, 2 (12.5%) were males and 14 (87.5%) were females 12 (85.7%) of the females were in the adolescent age group.

5) Inter current infection precipitating the DKA episode

18 (23%) patients of the total 78 patients had an infection as a precipitating factor to their DKA episode

From these 18 patients

9 (50%) patients had urinary tract infection
5 (27.7%) patients had gastroenteritis
4 (22.2%) patients had pneumonia

Outcome and complications of DKA episodes

In our study there were no deaths due to a DKA episode. The complications were as follows:

1) 1 (1%) patient developed cerebral edema (11 year old male with T1DM for one year)
2) 1 (1%) patient developed acute renal failure and was referred to a tertiary medical center for dialysis (9 year old male, a known case of T1DM for 4 years, presented with sever dehydration and acidosis)
3) 5 (5%) patients developed hyponatremia during treatment
4) 4(4%) patients developed hypoglycemia during treatment
5) 4(4%) patient developed hypokalemia during treatment.

4. Discussion

DKA is a life threatening condition that requires early recognition and specific management to avoid serious morbidity and mortality.

Management of an episode of DKA is not complete until its cause has been identified and an attempt made to treat it.
0.5-0.9% (1), (9). Other complications included hyponatremia (5%), hypoglycemia (4%), hypokalemia (4%) and one patient developed acute renal failure which is a rare complication of DKA and was referred for dialysis.

5. Conclusion

- DKA remains a significant complication of T1DM both at diagnosis and in established cases.
- It is the most common cause of morbidity and mortality in T1DM.
- The only way to prevent DKA is by identifying the risk factors and dealing with them.
- Risk factors for new onset diabetes include age, low socioeconomic level, general population awareness and primary healthcare alertness.
- Risk factors for established cases include peri pubertal and adolescent females, poor metabolic control, personal behavioral problems and family conflict, low socioeconomic level, and inter current infection.
- Careful replacement of insulin, fluid and electrolytes and close monitoring of the patient to reduce the complications.
- Cerebral edema is the main cause of death therefore early recognition of it’s signs and symptoms and early intervention will help to reduce it.

6. Recommendation

**Regarding new onset T1DM**

1) Programs to increase the general population awareness about childhood diabetes. An example is that of the Italian School and Physician Awareness Program directed to 6 – 14 year age group that reduced the rate of DKA from 78% to nearly 0% over 6 years.(5)

2) Increase awareness of primary medical personnel for early detection.

**Regarding established cases of T1DM**

1) Educational programs for both patients and parents regarding
   - Diet control
   - Metabolic control (regular home checking of blood sugar, ketone in urine and regular visits to outpatient diabetic clinics).
   - Signs and symptoms of DKA for early recognition

2) Adult supervision regarding the dose and administration of insulin

3) Psychiatric therapy especially for adolescent females with recurrent episodes of DKA

4) Proper management of inter current infection

**Regarding outcome and complications**

1) Patients should be treated by experienced medical staff and those with severe dehydration, severe acidosis and distributed level of consciousness should be treated in pediatric intensive care units.

2) Close monitoring of the patient using specific flow charts regarding the amount of fluid given, insulin does and electrolyte replacement to minimize complications.(10)

3) Close monitoring of the patient for early sings of cerebral edema (headache, irritability, unexplained fall in heart rate and increase in blood pressure) to insure early intervention. (10)

References

[8] William English, North Bristol NHS Trust, Bristol, UK Peter Ford, Royal Devon and Exeter Hospital, Exeter, UK Diabetic Ketoacidosis, Anaesthesia Tutorial of the week 128, 6th April 2009
[10] BSPED Interim Guideline for management of Children and young people under the age of 18 years with diabetes Ketoacidosis, April 2020.