ABSTRACT

BACKGROUND
The aim of the study is to study the clinical profile of diabetic ketoacidosis in children with type 1 diabetes to identify the precipitating factors, to assess the metabolic alterations due to this illness and to correlate these parameters with the outcome.

MATERIALS AND METHODS
This was a prospective observational study and 33 children admitted in PICU during the study period were recruited for the study.

RESULTS
24 children were newly-diagnosed cases and 9 children were already established cases of type 1 diabetes. Mean age group was 10.7 years. Major precipitating causes of DKA in established cases were intercurrent respiratory infections and omission of insulin. Nausea, vomiting, thirst and polyuria were the most common symptoms. Mean duration of symptoms before diagnosing DKA were 20 days in newly-diagnosed cases and 4 days in established cases. ¾ of children had dehydration at the time of admission. Severity was more in younger children. Commonest biochemical abnormality was hypokalaemia. Late diagnosis and delay in the initiation of treatment were the commonest predisposing factors for the development of cerebral oedema.

CONCLUSION
DKA is a life-threatening complication of type 1 diabetes and the red flag signs of bad outcome were young age, late diagnosis, late referral and late initiation of treatment. Hence, a high index of suspicion is necessary to diagnose DKA in first presentation of diabetes as well as in established cases.

KEYWORDS
Type 1 Diabetes, Diabetic Ketoacidosis (DKA), Cerebral Oedema, Insulin Therapy.

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Study Design
Prospective observational study.

Study Period
From June 2013 to June 2016 (three years).

Sample Size
33 children admitted in PICU during the study period were enrolled for the study after getting informed consent from the parents.

Methods of Data Collection
Data were collected by interviewing the parents by examining the children and going through the investigation records. These children were followed up during the hospital stay and during follow up visits in the endocrinology clinic.

Inclusion Criteria
Children admitted as DKA during the study period were enrolled in the study. The following parameters were taken as the diagnostic criteria of DKA. Plasma sugar more than 200 mg/dL, acidosis with pH less than 7.3 and presence of ketone bodies in urine. Patients who were hesitant to give consent were excluded from the study.

Exclusion Criteria
Patients admitted with type 1 diabetes who did not fulfil the criteria for DKA and patients who were hesitant to give the consent were excluded from the study.

Method of the Study
Details regarding the duration of diabetes, complications, insulin therapy, frequency of blood glucose testing (using glucometer), dietary habits and duration of symptoms were obtained. An attempt to detect the precipitating events were made in all children. Detailed physical examination including the vitals, anthropometry and examination of the systems were carried out. Essential laboratory parameters done before initiating the treatment included blood glucose, arterial blood gas, sodium, potassium, calcium, phosphorous, magnesium, complete blood counts, blood urea, serum creatinine and an electrocardiogram. Urine examination was done for routine analysis and for detecting ketone body. HbA1c was done in all children to look for long-term glycaemic status. Patients were followed up during the hospital stay by doing subsequent clinical assessments and by repeating the investigations. After discharge, these children were followed up in the endocrinology clinic.

Definitions
Criteria for the Diagnosis1,2,3,4
- Hyperglycaemia- Blood glucose levels more than 200 mg/dL (11.1 mmol/L).
- Metabolic acidosis- pH less than 7.3 and serum bicarbonate less than 15 mmol/L.
- Ketosis- Blood ketones more than 3 mmol/L or urine ketones more than 2+.

Statistical Analysis
Data were analysed using SPSS software package. The statistical significance of different variables was calculated using chi-square test. P value less than 0.05 was considered as statistically significant.

OBSERVATIONS
Among the study population, 11 children (33.3%) belonged to the age group 5-10 years. One child was younger than 5 years. 21 (63.6%) children were older than 10 years. Girls constituted 45% of all cases. Mean age was 10.7 years. 24 (73%) children were newly detected type 1 diabetes and already on insulin therapy, frequency of blood glucose testing (using glucometer), dietary habits and duration of symptoms were obtained. An attempt to detect the precipitating events were made in all children. Detailed physical examination including the vitals, anthropometry and examination of the systems were carried out. Essential laboratory parameters done before initiating the treatment included blood glucose, arterial blood gas, sodium, potassium, calcium, phosphorous, magnesium, complete blood counts, blood urea, serum creatinine and an electrocardiogram. Urine examination was done for routine analysis and for detecting ketone body. HbA1c was done in all children to look for long-term glycaemic status. Patients were followed up during the hospital stay by doing subsequent clinical assessments and by repeating the investigations. After discharge, these children were followed up in the endocrinology clinic.

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One newly-diagnosed adolescent girl was on thyroxine tablets for autoimmune thyroiditis during the past one year. No other children were on any long-term medications.

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Nausea, vomiting, thirst and polyuria were the major symptoms at presentation. Abdominal pain and breathlessness were seen in some children. Six children were brought with altered sensorium mimicking encephalitis. One child was referred as a case of status epilepticus and altered sensorium.

<table>
<thead>
<tr>
<th>Symptoms at Admission</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and vomiting</td>
<td>25</td>
<td>75.8</td>
</tr>
<tr>
<td>Thirst</td>
<td>25</td>
<td>75.8</td>
</tr>
<tr>
<td>Polyuria</td>
<td>22</td>
<td>66.6</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>36.4</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>9</td>
<td>27.3</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>6</td>
<td>18.2</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 5. DKA Symptomatology at Admission

Many cases were diagnosed (15) for the first time in children who were admitted for nonspecific complaints and diabetes was being picked up by blood glucose examination. 8 cases were suspected as having diabetes based on the symptomatology, worked up and referred after suspecting DKA. Hence, altogether, 73% of cases were newly diagnosed and had DKA at the onset. Remaining cases were already established cases and on insulin months or years before hospitalisation.

<table>
<thead>
<tr>
<th>Presentation on Admission</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonspecific complaints. Diagnosis picked up after hospitalisation</td>
<td>15</td>
<td>45.5</td>
</tr>
<tr>
<td>Newly diagnosed based on the symptoms and referred to the tertiary care unit</td>
<td>9</td>
<td>27.3</td>
</tr>
<tr>
<td>Already diagnosed and on insulin therapy</td>
<td>9</td>
<td>27.3</td>
</tr>
</tbody>
</table>

Table 6. Mode of Presentation of DKA

Younger the age group, more the chance of delay in diagnosis and management. Hence, chance of DKA at presentation is more in younger children. DKA in previously diagnosed children were also more in younger age groups.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Total Number of Cases</th>
<th>Newly-Diagnosed Cases Presenting as DKA</th>
<th>DKA in Already Diagnosed Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Frequency</td>
<td>Percentage</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>1</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>5-10 years</td>
<td>11</td>
<td>8</td>
<td>72.7</td>
</tr>
<tr>
<td>&gt;10 years</td>
<td>21</td>
<td>15</td>
<td>45.5</td>
</tr>
</tbody>
</table>

Table 7. Age Group and Presentation of DKA

On examination, 22 children had features of dehydration and 1 had severe dehydration. Neurological status was evaluated by Glasgow Coma Scale. Seven children had GCS between 6 and 10. Four had GCS below 6. Tachypnoea was seen in 26 children (78.8%). Kussmaul respiration was noticed in one child. Abdominal guarding and tenderness were observed in 11 children. None had features of congestive cardiac failure.

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Severity</th>
<th>Frequency</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydration status</td>
<td>No dehydration</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>22</td>
<td>66.7</td>
</tr>
<tr>
<td></td>
<td>Severe dehydration</td>
<td>1</td>
<td>3.3</td>
</tr>
<tr>
<td>Glasgow coma scale</td>
<td>&lt;6</td>
<td>4</td>
<td>12.1</td>
</tr>
<tr>
<td></td>
<td>6-10</td>
<td>7</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>10-15</td>
<td>26</td>
<td>78.8</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>No tachypnoea</td>
<td>7</td>
<td>21.2</td>
</tr>
<tr>
<td></td>
<td>Tachypnoea</td>
<td>26</td>
<td>78.8</td>
</tr>
<tr>
<td>Kussmaul respiration</td>
<td>1</td>
<td>3</td>
<td>3.3</td>
</tr>
<tr>
<td>Abdominal guarding or tenderness</td>
<td></td>
<td>11</td>
<td>33.3</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 8. Clinical Presentation of DKA

Many children had plasma glucose level above 300 mg/dL of which some had severe hyperglycaemia (above 400 mg/dL). Those who were diagnosed for the first time had severe hyperglycaemia (mean blood glucose 328 mg/dL) compared to those children who were already on insulin treatment (mean blood glucose 264 mg/dL). There was a statistically significant difference between the mean blood glucose value among the newly-diagnosed cases and already established cases, with a p-value less than 0.05.
Among the biochemical parameters, 27 (81.2%) children had moderate acidosis (pH between 7.1-7.2) and one had severe acidosis (pH below 7.1). Bicarbonate values were below 10 mEq/L in 6 children (18.1%) and between 10-15 mEq/L in 27 children (81.2%). Altogether, 16% were having mild DKA and 81% were having moderate DKA.

24 children (72.7%) had normal serum sodium levels. Remaining children had hyponatraemia. Of the children with hyponatraemia, one boy was admitted with convulsions. High serum potassium levels (>4.5 mEq/L) were seen in 2 children between 3.3-4.5 mEq/L in 25 children and severe hypokalaemia with serum potassium level below 3.3 mEq/L in 6 children. Serum phosphorous levels were low (<3.7 mg/dL) in five patients. 2 children had serum calcium levels below 8.8 mg/dL. Serum magnesium values were less than 2 mg/dL in 27 patients, but none had a value below 1.5 mg/dL.

Hba1C levels were above 10.5% in 6 children. Between 8.6-10.5% in 21 children between 6.5-8.5% in 6 children. There was no statistically significant difference in Hba1C levels in both newly-diagnosed and already established cases.

### Table 9. Plasma Glucose Level at the Time of Hospitalisation

<table>
<thead>
<tr>
<th>Plasma Glucose Level at the Time of Hospitalisation</th>
<th>Frequency</th>
<th>Percentage (%)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;400 mg/dL</td>
<td>6</td>
<td>18.2</td>
<td>All cases were newly diagnosed</td>
</tr>
<tr>
<td>300-400 mg/dL</td>
<td>16</td>
<td>48.5</td>
<td>14 cases were newly diagnosed</td>
</tr>
<tr>
<td>200-300 mg/dL</td>
<td>11</td>
<td>33.3</td>
<td>3 cases were newly diagnosed</td>
</tr>
</tbody>
</table>

### Table 10. Electrolyte Abnormalities at Presentation of DKA

<table>
<thead>
<tr>
<th>Electrolyte Abnormalities</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyponatraemia</td>
<td>9</td>
<td>27.3</td>
</tr>
<tr>
<td>Hyperkalaemia</td>
<td>2</td>
<td>6.1</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>6</td>
<td>18.2</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>5</td>
<td>15.2</td>
</tr>
<tr>
<td>Hypocalcaemia</td>
<td>2</td>
<td>6.1</td>
</tr>
</tbody>
</table>

Among the 9 established diabetic cases, one child was on insulin analogues and the rest were on plain insulin and NPH. Split mix regime was practiced in 4 children and basal bolus regime in 5 children. None of the children were on insulin pump.

### Table 11. Insulin Regime Used by Established Diabetic Children

<table>
<thead>
<tr>
<th>Insulin Regime Used</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain insulin + NPH - split mix</td>
<td>4</td>
<td>44.4</td>
</tr>
<tr>
<td>Plain insulin + NPH - basal bolus</td>
<td>4</td>
<td>44.4</td>
</tr>
<tr>
<td>Insulin analogues - basal bolus</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td>Insulin pump</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Home monitoring using glucometer strips were practiced by all, but none was using at least 4 strips per day. One child was monitoring blood glucose thrice a day and 6 children were doing it twice a day. Financial constraints were the commonest reason for reduction in the home blood sugar monitoring testing.

### Table 12. Home Monitoring of Blood Glucose. Number of Blood Sugar Monitoring Per Day (in Established Cases)

<table>
<thead>
<tr>
<th>Frequency of Home Monitoring Per Day</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 or more</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>11.1</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>66.7</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>22.2</td>
</tr>
</tbody>
</table>

Children with clinical features of dehydration (70%) were given normal saline and others were given extra oral fluids. All children were put on intravenous insulin infusion. Children were transferred to intermediary care once general condition is stabilised and after initiating subcutaneous insulin therapy.

Most of the children had good improvement and mean duration of stay in PICU was 4.5 days in newly-diagnosed cases and 2.5 days in children with established diabetes. Mean duration of intravenous fluids was 42 hours in established diabetes and 52 hours in newly-diagnosed cases. Shift to subcutaneous insulin was earlier in established diabetes with mean duration of 36 hours compared to newly-diagnosed children in whom mean duration was 55 hours showing a statistical difference in these 2 groups with p values less than 0.05.

Total duration of hospital stay was also longer in new cases (mean duration-16 days) compared to established cases (mean duration 4 days). This was also statistically significant with p-value less than 0.05.

One child (3%) developed features of cerebral oedema and recovered after mannitol, oxygen and supportive care. No mortality was observed in the study period.

Following risk factors were observed in the child who developed cerebral oedema:

- Presented with seizure.
- Newly diagnosed with late recognition of diabetes.
- Young age (<5 years).
- Low Glasgow coma scale (<6).
• Severe dehydration (>10%).
• Tachypnoea with Kussmaul respiration.
• High blood glucose level at the time of hospitalisation (>400 mg/dL).
• Severe acidosis (pH < 7.1 and HCO3 < 10 mEq/L).
• Hyponatraemia (serum sodium 128 mEq/L).
• Hypokalaemia (serum potassium 3.1 mEq/L).

**DISCUSSION**

Diabetic Ketoacidosis (DKA) is a life-threatening complication of childhood diabetes. Quite often, DKA is the first clinical feature in a previously undiagnosed child. Frequency of DKA at the onset range from 15-70% in Europe and north America. Saira Waqar et al noticed that 55.5% all cases of DKA were newly-diagnosed diabetes. Usher-Smith reported 13-80% with highest rate in UAE (80%) and Romania (65%) and lowest rate in Hungary (23%) and Canada (18.6%). Lokulo-Sodipe observed DKA as the presenting feature in 25% newly-diagnosed cases in UK. In the present study, 75.8% of the cases were newly diagnosed. All these observations clearly disclose that, in resource poor countries, there is an alarming delay in diagnosing childhood diabetes resulting in late diagnosis and in many cases children even die without being diagnosed as diabetes.

Mean age of diagnosis in the present study was 10.7 years. Study by Azza Ali showed that the mean age was 8.3 years and Lokulo-Sodipe et al 10.3 years. DKA at the diagnosis were common in younger children less than 5 years, often because the physicians were not thinking about this possibility in their differential diagnosis. The present study also showed that younger the child, more the chance of DKA as the initial presentation. Lokulo-Sodipe observed that DKA at diagnosis was more in children <2 years. In Canada and Europe, hospitalisation rates for DKA in children were 10 per 1,00,000 children over the past 20 years.

Other autoimmune disorders like autoimmune thyroiditis, Addison disease or celiac disease have been reported to precipitate DKA in children who were not diagnosed as having diabetes previously as observed by Szypowska et al. In the present study, one newly-diagnosed adolescent girl was on treatment for autoimmune thyroiditis.

Severity of DKA is directly proportional to the delayed initiation of treatment. This complication often exists in families who do not have ready access to medical care due to lack of facility or due to financial burden. In the present study, one child had cerebral oedema and he was from a tribal colony in Wayanad. Alvi et al showed that Asian children had an eight fold increased chance of DKA compared to non-Asian children.

Most of the studies showed a slight female preponderance. The present study showed a marginal male preponderance. Lokulo-Sodipe observed a male preponderance (54%).

The risk of DKA in established type 1 diabetes is 1-10% per patient per year according to recent studies. This risk is more in children who omit insulin during illnesses like respiratory tract infections or gastroenteritis. Adolescent girls and children with psychiatric disorders pose a greater risk. In the present study, respiratory infection was the commonest precipitating cause of DKA in children with established diabetes (66.7%) followed by drug default (33.3%). Satti Abdurahiman et al. showed that infections were the commonest precipitating events (81%) followed by poor compliance and insulin omission (17.9%). Moussa et al showed that 27 to 60% of children presented with DKA after omitting insulin. Mean reason for insulin omission was non-availability in a study by Saira Waqar Lone et al.

In Western countries, major cause of drug default was behavioural problems.

Major clinical presentations in the present study were nausea, vomiting, thirst and polyuria. Abdominal pain, often presenting as acute abdomen was a less common problem (36.4%). Breathless and altered sensorium were the other presenting symptoms. This was in accordance with the study by Ganesh R et al, which showed that 80% of the children were presented with vomiting, polyuria and polydipsia. Commonest presenting complaints were respiratory distress (87.1%) and nausea (77.7%) in a study by Saira Waqar Lone et al.

<table>
<thead>
<tr>
<th>Presenting Complaints</th>
<th>Present Study Number 33 Frequency Percentage</th>
<th>Saira Waqar Lone Number 117 Frequency Percentage</th>
<th>Satti Abdurahiman Number 80 Frequency Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachypnoea</td>
<td>9</td>
<td>102</td>
<td>87.7</td>
</tr>
<tr>
<td>Vomiting</td>
<td>25</td>
<td>75.8</td>
<td>91</td>
</tr>
<tr>
<td>Polyuria</td>
<td>22</td>
<td>66.6</td>
<td>84</td>
</tr>
<tr>
<td>Polydipsia</td>
<td>25</td>
<td>75.8</td>
<td>69</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12</td>
<td>36.4</td>
<td>79</td>
</tr>
<tr>
<td>Altered sensorium</td>
<td>6</td>
<td>18.2</td>
<td>59</td>
</tr>
</tbody>
</table>

**Table 13. Presenting Complaints of DKA. Comparison of Various Studies**

Mean duration of symptoms before diagnosis varied greatly in newly-diagnosed cases (20 days) from already established diabetes (4 days) in the present study. Most of the newly-diagnosed cases were being treated for abdominal pain or urinary tract infection before the final diagnosis. Wolfsdorf J et al. opined that DKA is often missed than found out if the child didn’t have any features of diabetes before, especially if he is very young.

Dehydration is a prominent clinical sign in DKA. 5-10% dehydration was seen in 25-75% of cases in various studies. Severe dehydration was rare. Ildiko et al. reported that 18 out of 37 children in their study group (48.7%) had
In the present study, 66.7% of cases had moderate dehydration and one had severe dehydration. In the present study, 66.7% of cases had moderate dehydration and one had severe dehydration, but Satti Abdurahiman26 reported a high incidence of dehydration with all children having dehydration (100%) and 33 (43.4%) having severe dehydration. Koves IH et al12 observed that degree of dehydration is more in younger children. Other major clinical features in the present study were altered sensorium, tachypnoea and abdominal tenderness. Satti Abdurahiman et al26 observed that tachypnoea (60%), acidic breathing (60%), drowsiness (25%) and hepatomegaly (15%) as other prominent clinical features. Mahoney CP12 et al observed that altered sensorium is the most dangerous sign of DKA and blunting of consciousness with seizure is a sign of impending cerebral oedema. This observation was true in the present study also.

In the present study, 16% had mild, 81% of children had moderate and 3% had severe DKA. Studies in west including a Danish study by Fredheim12 showed a marginal increase in mild DKA (46%) compared to moderate DKA (44%). Studies from middle east showed increased incidence of moderate DKA similar to the present study.33,34,35,36

Duration of stay in PICU was longer in newly-diagnosed cases (4.5 days) compared to established cases (2.5 days) in the present study. Total duration of hospital stay was also more in newly-diagnosed cases. Many studies confirmed this finding.37,38 This is due to more time spent in educating the parents about the illness.39

In many resource poor setting, conventional plain insulin and NPH were in use. Insulin analogues were the treatment of choice in developed countries.40 In many countries, insulin pumps were being used.41 Conventional plain insulin and NPH were the mainstay (88.9%) in the present study. Many resource rich countries were doing daily 4-6 blood glucose measurements per day using glucometer.12 Because of the exorbitant cost, most of the children in the present study were doing the test once or twice a day, which was the situation in many Indian studies.43

Reported mortality from DKA remains fairly constant as per the studies in developed countries and it varies from 0.15% in USA, 0.18% in Canada and 0.31% in UK.44,45,46 In places with less developed medical facilities, the risk of death from DKA is greater.47 It is a depressing fact that many children die before receiving any specific treatment.48

Cerebral oedema is the major cause of mortality causing 60-80% of all deaths due to DKA.49 In the present study, there was no death. One child who developed cerebral oedema was referred late. A study by Gruber et al50 revealed that children presenting late had more severe acid base abnormalities and more risk of mortality. Nicole Glaser et al51 noticed that clinically apparent cerebral oedema occurred in 0.9% of hospitalisation for DKA.

**SUMMARY AND CONCLUSION**

Diabetic ketoacidosis is a life-threatening complication of childhood diabetes. This condition is often the first clinical presentation in a previously undiagnosed case. It can occur in already diagnosed cases also, usually following intercurrent infections or due to omission of insulin. Commonest symptomatology at presentation are nausea, vomiting, polyuria and polydipsia. Later the diagnosis of DKA, more will be the morbidity and mortality. Cerebral oedema is the commonest cause of mortality and poor prognostic factors are low Glasgow coma scale, seizures, severe dehydration, severe acidosis, very high blood glucose levels, severe hyponatraemia and hypokalaemia.

**Limitation of This Study**

Sample size was small. Since, this is a hospital-based study, it is not a true reflection on the incidence of DKA in the country. Serum ketone measurements were not done in this study due to lack of facility.

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**Contribution**

MV has contributed in researching and assimilating the required material. He was involved in writing the manuscript, citation search, literature review and bibliography. KM has helped in collecting the cases and noting down the relevant information. MV will act as a guarantor.


