

Delayed diagnosis of diabetic ketoacidosis in children—a cause for concern

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Abstract Diabetic ketoacidosis (DKA) is the major cause for mortality in children with diabetes mellitus (DM). Delayed diagnosis or missed diagnosis is common among children with DKA. This study was undertaken to identify the impact of delayed diagnosis on clinical presentation, complications, and mortality of DKA in children from a tertiary care center at Chennai. Among the 118 episodes of DKA in 100 children less than 12 years of age, delayed diagnosis was more common in new onset diabetes mellitus (DM). Forty-four out of 68 children with new onset DM with DKA (64.7 %) had delayed diagnosis. Thirty-two children with established diabetes presented with 50 episodes of DKA. Among these, eight episodes (16 %) had a delay in diagnosis; 85.7 % of infants, 76.9 % of toddlers, and 58 % of the preschool and school children had delayed diagnosis. Urinary tract infections, respiratory illness, vomiting, febrile illness, acute abdomen, and encephalopathy were the common diagnosis in children where DKA was missed. The causes for delay in diagnosis and management of DKA were lack of parental and physician awareness, improper referral, and delayed transport. Presence of shock, altered sensorium, severe DKA, lower PaCO₂ at admission, and complications like renal failure and cerebral edema were higher in children with delayed diagnosis of DKA. This was found to be statistically significant. Delayed diagnosis was a significant risk factor for mortality in children with DKA ($p=0.00$) in this study population.

Keywords Delayed diagnosis · Missed diagnosis · DKA in children

Introduction

Diabetic ketoacidosis is the major cause for mortality in children with diabetes mellitus (DM). Diabetic ketoacidosis is a preventable illness both in new onset and with established DM. The mortality rate in diabetic ketoacidosis (DKA) varies from 0.15 to 0.31 % in developed countries [1–4] and from 3.4 to 13.4 % in developing countries [5–8]. Factors that contribute to such high mortality in developing countries need to be studied. This study was undertaken to identify the role of delayed diagnosis in clinical presentation, complications, and mortality among children admitted with DKA.

Methodology

This descriptive study was done at the pediatric intensive care unit of Institute of Child Health and Hospital for Children, Chennai, dealing with children predominantly from lower socioeconomic strata. Study was conducted between Jan 2010 and Jan 2013. All consecutive children admitted with DKA during the study period were enrolled irrespective of their previous admission status. In this study, how delayed diagnosis in DKA affects the clinical presentation, complications, and outcome were analyzed. Study parameters included age, gender, new onset or DKA among children with established diabetes mellitus, delay in diagnosis, hemodynamic status at admission, sensorium at admission (alert, verbal, pain responsive, unresponsive (AVPU) scale), hydration status, initial blood glucose, blood pH, PaCO₂, osmolality and urea, complications like renal failure, cerebral edema, and final outcome (death or discharge). A child with DKA whose osmotic symptoms were not recognized by the parents and those who were not diagnosed as DKA at the time of first health care visit was considered as delayed diagnosis. Missed diagnosis was termed if any alternate diagnosis was given by

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the treating physician for this episode of DKA, prior to admission in PICU. Delayed treatment for the purpose of this study was defined when appropriate treatment for DKA was not commenced within 3 h of diagnosing DKA. The study parameters were compared among children with and without delayed diagnosis. DKA management was as per unit treatment protocol, and children were followed up till discharge or death as the final outcome. Statistical analysis was done using the software Epi Info™ 7.1.1.0, and *p* values were considered significant if <0.05 . The study was approved by the institute's ethical committee, and informed written consent was obtained from the caregivers of these children.

Results

During the study period of 3 years, 118 episodes of DKA were treated among 100 children, at the pediatric intensive care unit. Out of 118 episodes, 68 were among new onset and 50 were among children with established diabetes. These 50 episodes were among 32 children with diabetes mellitus. Eight of these 32 children had more than one episode amounting to a total of 26 episodes. Male-to-female ratio of the study population was 1:1.7. Overall, 52 episodes (44 %) of DKA had a delay in diagnosis. Of all the 118 episodes, 44 of the 68 new onset DKA (64.7 %) and eight of the 50 with established diabetes had a delayed diagnosis (16 %). Among the 100 children—44 new onset and eight with established diabetes had delayed diagnosis. None of the children with recurrent episodes had delay in the diagnosis. Delayed diagnosis was more common in new onset DM presenting with DKA and was statistically significant ($p=0.00$, odds ratio (OR) 9.4, 95 % confidence interval (CI) 3.9–24). Age distribution revealed 85.7 % of infants, 76.9 % of toddlers, 53.8 % of preschool children and 58 % of school children with delayed diagnosis (Fig. 1). Clinical features like polyuria, polydipsia, abdominal pain, weight loss and breathlessness were misinterpreted for common illness like urinary tract infection, worm infestation, acute severe asthma, bronchopneumonia, etc. Finger prick estimation of blood glucose was done only in 11 children with new onset diabetes. Other than DKA, the referral diagnosis available in 38 children is shown in Table 1.

Among the study group, 99 % (67) of children with new onset DM had osmotic symptoms and 32 of these 67 (47.7 %) were not considered abnormal by the parents and physicians. Though secondary nocturnal enuresis was present in 31 of the 44 children, this was not the presenting complaint in any child. Similarly, itching and white discharge over the genitalia were not given importance by the parents and physicians. Children with DKA were evaluated but not recognized or recognized but not referred or inappropriately referred leading to delayed diagnosis. Twenty-two children with new onset DM had

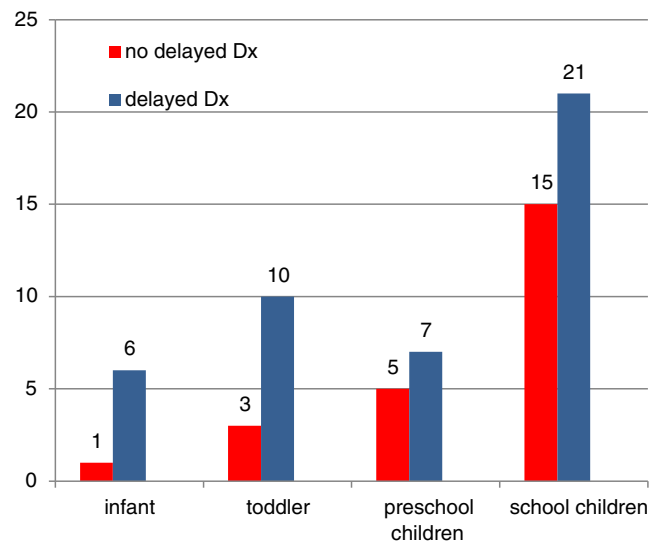


Fig. 1 Showing the delayed diagnosis of new onset DKA in different age groups

documented hyperglycemia or glycosuria prior to referral. Seven of these were not recognized by the physician as abnormal and was not informed to the caregivers; 9 were recognized, but not referred immediately for management. Parents of six children who were referred did not believe in the diagnosis of diabetes (denial) and had revisited the physician only after worsening of DKA symptoms. Seven children whose abnormal lab results were not recognized were brought to medical care only after symptoms of ketoacidosis, which worsened in 24–72 h. Despite a diagnosis of DKA, delay in referral to an appropriate tertiary care center (delay more than 3 h ranging from 3 to 72 h) leading to delayed treatment was encountered in 12 children.

The number of medical visits for this episode of illness among the new onset DM prior to diagnosis as DKA ranged from one to five in numbers. The number of previous medical visits prior to the admission is as follows: 1 medical visit in 15 children, 2 visits in 14 children, 3 visits in 6 children, 4 visits in 6 children, and 5 visits in 3 children. Only three children in this study group had utilized the emergency free ambulance available for transport to reach the hospital.

The reasons for delayed diagnosis were lack of parental awareness about diabetic symptoms, lack of awareness among physicians (misinterpretation of diabetic symptoms, exclusive treatment of intercurrent illness, lack of finger prick estimation of blood glucose, non-recognition of lab abnormalities, and lack of immediate referral) and delay in transport to an appropriate center for treatment (improper referral, due to parental causes, native treatment, social reasons, and economic constraints).

Children with established diagnosis of DM had delayed diagnosis due to misinterpretation of symptoms of vomiting, abdominal pain, and breathlessness, and eight children had

Table 1 The referral diagnosis other than DKA

Diagnosis	N	Diagnosis	N
Bronchopneumonia, bronchial asthma, bronchiolitis	6	Acute febrile illness/viral fever/viral gastritis	5
Urinary tract infection	5	Acute abdomen/constipation	4
Sepsis, septic shock	4	Acute CNS infection, encephalopathy	3
Acute glomerulonephritis, renal failure	3	Myalgia/generalized weakness	2
Hemoptysis/hematemesis	1	Vomiting for evaluation	1
Inborn error of metabolism	1	Others	3

delayed diagnosis. Ten children with established diabetes were brought to the hospital by parents without any physician reference.

Clinical and biochemical parameters at presentation were compared among children with and without delayed diagnosis (Table 2). Presence of shock, altered sensorium (pain responsive or unresponsive as per AVPU scale), lower pH, lower PaCO₂ on admission, complications like cerebral edema, and renal failure were higher in children with delayed diagnosis. This was statistically significant. Other parameters like dehydration, blood glucose, osmolality, and urea levels did not show any significant difference between the two groups. Eighty-five percent of children who died of DKA had delayed diagnosis in this study group. Delayed diagnosis was significantly associated with mortality among children with DKA ($p=0.002$), OR=8.58, (95 % CI 1.9–40.72).

Discussion

Cerebral edema is the most common cause for mortality in children with DKA. Overall mortality in DKA is much higher in developing countries like India and Pakistan compared to developed countries. Literature evidence reveals sepsis, renal failure, and shock as other major contributory factors for mortality in DKA [5, 9, 10]. Delayed diagnosis as a significant contributory factor for complications like cerebral edema, shock, and renal failure has not been reported in literature. Delayed diagnosis or missed diagnosis of DKA is not

uncommon based on the existing literature from developing countries [11–13]. However its association with presentation, severity of DKA, complications, and outcome has not been studied. This is of much relevance in countries like India where mortality in DKA is still high. Cerebral edema, shock, sepsis, and renal failure were the cause for increased mortality in children with DKA. This study has revealed delay in the diagnosis as the root cause for increased mortality in children with DKA.

Based on this study, delayed diagnosis is more common in children with new onset DKA. Despite clinical symptoms of DKA, nearly 65 % of children with new onset DM had their diagnosis delayed. It is not uncommon to have delay in diagnosis of DKA among children with established DM. This study group comprised of children predominantly from lower socioeconomic strata. Literature revealed that children from lower socioeconomic families were more frequently misdiagnosed before admission ($p<0.01$) [14]. Parents of children with new onset diabetes, who had noted the osmotic symptom, did not consider this abnormal due to lack of awareness. Delay in part of the physician was also common in the study group. The presentation of polyuria and polydipsia and recent onset nocturnal enuresis were misinterpreted as urinary tract infection and as normal phenomenon in children. Unfortunately, this is immediately linked to hyperglycemia/glycosuria only in a minority of cases. The same has been documented in literature [15]. Secondary nocturnal enuresis, one of the early symptoms of diabetes, was overlooked by the parents as well as physicians. This has been reported in

Table 2 Study parameters versus delayed diagnosis in DKA

Parameter	Delayed diagnosis (n=52)	No delay in diagnosis (n=66)	p value	OR	95 % CI
New onset	44	24	0.00	9.4	3.9–24
Shock	12	3	0.003	6.2	1.7–28.9
Altered sensorium	36	32	0.026	2.39	1.11–5.11
pH (median)	7.03	7.14	0.006	NA	NA
PaCO ₂ (median)	12	17	0.039	NA	NA
Cerebral edema	28	8	0.000	4.47	1.79–11.89
Renal failure	10	1	0.001	15.1	2.4–343
Death	11	2	0.002	8.4	1.9–58.56

literature too, close to 90 % of parents when questioned directly [16]. Those who had weight loss, lethargy, and increased tiredness were considered to have generalized weakness and were treated with multivitamin preparations and calcium. Abdominal pain in DKA was treated as worm infestation. Among the girls, genital itching and white discharge were treated as poor hygiene and fungal infection without any evaluation. Breathlessness was misinterpreted as bronchopneumonia, acute severe asthma, foreign body aspiration, and sepsis in these children. Surgical consultation with evaluation by ultrasonogram for acute abdomen was seen in children with DKA. Vomiting was misinterpreted as gastritis related to flu like viral illness, and similar literature does exist [17]. Studies show that the initial diagnosis was wrongly categorized as respiratory system infection (46.3 %), perineal candidiasis (16.6 %), gastroenteritis (16.6 %), urinary tract infection (11.1 %), stomatitis (11.1 %), and appendicitis (3.7 %) [18]. In this study UTI, respiratory illness, febrile illness, encephalopathy, and genital candidiasis were considered as diagnosis among children, where DKA was missed. (Table 1).

Finger prick blood glucose estimation is a mandatory bedside evaluation in all sick children. This simple investigation is very rewarding in children with polyuria and polydipsia to make an early diagnosis of diabetes [19]. Finger prick estimation of blood glucose, a simple test in a clinician's office, is rarely performed. In this study group, except for 11 children, majority of children did not have finger prick estimation of blood glucose, at the time of first physician consult. Not performing the glucose estimation in children with polyuria, polydipsia, or enuresis may be a primary reason for delayed recognition of diabetes/DKA. Despite documentation of hyperglycemia, improper referral, and lack of immediate referral for inpatient treatment resulted in delay and severe DKA. The laboratory documentation of glycosuria and hyperglycemia was not correlated to diabetes in seven children in the study group. There was no immediate high risk alert to the physician or the parents in the event of documented hyperglycemia or glycosuria from the laboratory.

Delayed transport on the part of the parents due to denial, economic constraints, and ignorance about the availability of the emergency transport system for the health care were encountered in the study. Subsequent to diagnosis of DKA, multiple hospital visits for a sick child due to lack of structured diabetic care team was also seen and the same is reported in literature [20, 21]. Bolus dose of IV insulin, large volume fluid boluses, bicarbonate therapy, and hypotonic fluids were some of the unwarranted prehospital therapy in children referred as DKA. This is attributed to lack of awareness among the physicians about the standard treatment protocols for DKA in children.

Data analysis revealed delayed diagnosis to be significantly associated with presence of shock, altered sensorium, severe

DKA, and lower PaCO₂ at presentation. A simple finger prick estimation of blood glucose in a sick child with polyuria or any child with diagnostic difficulty would have prevented the above mentioned poor prognostic factors at presentation. Delayed diagnosis was significantly associated with cerebral edema, renal failure, and mortality in this study.

DKA is a preventable illness in new onset diabetes as well as in established diabetes [22, 23]. Delay in diagnosis of DKA may contribute significantly to the increased mortality in developing countries. In this scenario, it may be understood that immediate interventions to avoid delay in the diagnosis of DKA may be rewarding. Increasing awareness among the parents and health care givers or primary care physicians will help to reduce the occurrence of DKA as it has been proven in the past elsewhere [22, 23]. Simple interventions like increased awareness through display of posters about the signs and symptoms of diabetes in schools, public places, and physician office will be useful. This awareness will help to reduce mortality in DKA. Since delayed diagnosis is significantly associated with shock, renal failure, and cerebral edema, an earlier diagnosis will help decrease the mortality associated with these factors in DKA. Overall mortality in DKA in this study was 11 %. Delay in diagnosis may be root cause for increased mortality in DKA in developing countries.

Conclusions

Delayed diagnosis of DKA is common in 65 % of new onset DKA and 16 % of children with established DM. Nearly 85 % of infants with DKA have their diagnosis delayed.

Delayed diagnosis was due to delayed health care seeking behavior and lack of awareness by parents, and also non-recognition of DKA symptoms by the treating physician.

Finger prick glucose estimation was not done as a routine test even in sick children

Delay in treatment is also due to improper referral and delay in transport to an appropriate center.

Delayed diagnosis of DKA is significantly associated with shock, altered sensorium, severe DKA, and hypocapnea at presentation.

Delayed diagnosis is significantly associated with complications like cerebral edema and renal failure in DKA.

Delayed diagnosis is significantly associated with increased mortality in DKA

Recommendations

- Awareness programs about diabetes in children are warranted urgently for parents, teachers, and physicians
- Simple posters can be displayed in schools, public places, and physician offices to recognize symptoms of diabetes in children.

- Finger prick glucose estimation should be done as a routine evaluation in any sick child in physician office.
- High risk alert to the physicians or the parents has to be given by the lab personnel in case of hyperglycemia or glucosuria in children.
- Caregivers need to be sensitized about the utility of emergency health care transport services
- A 24-h help line facility should be made available to the physicians for appropriate management of DKA in children.
- Immediate referral of children with hyperglycemia for appropriate management is essential

What is already known? Delayed diagnosis is common in children with DKA

What this study adds? Delayed diagnosis in DKA is significantly associated with shock, altered sensorium, severe DKA, and hypocapnea at presentation.

Delayed diagnosis is significantly associated with cerebral edema, renal failure, and mortality in children with DKA.

Lack of awareness among the parents and the physicians and inadequate referral are the reasons for delayed diagnosis of DKA, and this needs urgent interventional programs.

Delayed diagnosis is the root cause for increased mortality in children with DKA.

Conflicts of interest None

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