ORIGINAL ARTICLE

Diabetic ketoacidosis at diagnosis of type 1 diabetes mellitus in Malaysian children and adolescents

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Abstract

Background: Diabetic ketoacidosis (DKA) is a late presentation of newly diagnosed type 1 diabetes mellitus (DM) in children. The aim of this study was to determine the clinical characteristics of type 1 DM at presentation so that appropriate actions can be taken to promote early diagnosis.

Methods: This was a retrospective cohort review from a patient registry database. Data on all patients younger than 20 years old diagnosed with type 1 DM who had been registered with the Malaysian Diabetes in Children and Adolescents Registry (DiCARE) from its inception in 2006 until 2009 were analysed.

Results: The study included 490 children and adolescents, out of which 57.1% were female. The mean (SD) age at diagnosis was 7.5 (3.7) years, which increased from year 2000 to 2009 [6.6 (3.3) years to 9.6 (3.5) years; p = 0.001]. An increasing percentage of DKA at diagnosis was observed from year 2000 (54.5%) to year 2009 (66.7%), which remained high and leveled between 54.5% and 75.0%. DKA was more common in patients with normal weight (p = 0.002) with no significant association with age, gender, ethnicity and status of family history of diabetes mellitus.

Conclusion: An increasing trend of age at diagnosis of patients with type 1 DM was observed. Besides that, proportion of DKA at diagnosis had remained high over the past decade. This study found that normal weight was associated with status of DKA, thus more detailed investigations are required to determine the risk factors for DKA.

Introduction

Type 1 diabetes mellitus (DM) accounts for more than 90% of childhood and adolescent diabetes.[1] Of the estimated 479,600 type 1 diabetic children worldwide, 24% were from the South-East Asian region and 6.4% from the Western Pacific region.[2–3] The annual incidence for childhood type 1 DM (0–14 year age group) ranged from 0.1 per 100,000 in China to 57.[6] per 100,000 in Finland.[3–5] The incidence of type 1 DM appeared to be low in the Western Pacific region with the exception of Australia and New Zealand.[4] In Malaysia, type 1 DM was estimated to account for 69.2% of children and adolescents with diabetes.[6]

Diabetic ketoacidosis (DKA) is a common presentation in children with new-onset type 1 DM, characterised by hyperglycaemia, ketosis and acidosis.[7] In addition, DKA is associated with cerebral oedema, which is the most common cause of diabetes-related death in children.[7] The prevalence of DKA at disease presentation can be reduced if diabetes is recognised early. A British study reported that delay in diagnosis had a significantly increased risk of DKA at disease onset.[8] It was also reported that 38.8% of children with type 1 DM had seen at least one doctor prior to the presentation with DKA.[9] This may suggest that early symptoms of type 1 DM might have been missed or misdiagnosed until the onset of DKA. Hence, adequate awareness and high index of suspicion among primary healthcare providers are crucial to prevent the occurrence of DKA and its associated morbidity and mortality. Besides that, DKA incurs extra medical expenditure. In the United States, the annual cost of treating DKA was estimated to be more than $1 billion when 25% of new-onset type 1 DM presented with DKA.[9]

This study aimed to determine the trend, the clinical presentation of type 1 DM and

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the pattern of DKA at diagnosis among Malaysian children and adolescents. We also aimed to determine the association between demographic profile of patients and status of DKA at disease presentation.

Methods

This was a retrospective cohort review from a patient registry database. Dataset of all patients with type 1 DM who had been reported to the Malaysian Diabetes in Children and Adolescents Registry (DiCARE) from August 2006 to December 2009 were retrieved and analysed. DiCARE was initiated in August 2006 as an ongoing online registry for <20-years-old diabetic patients from hospitals in Malaysia. Site participation and reporting of patients to DiCARE were entirely voluntary.[6]

The registered dataset comprises patients' demography, weight status (underweight, normal weight and overweight), symptomatic (DKA versus non-DKA) or asymptomatic, and treatment options at disease onset. Year-end census was collected annually to monitor treatment changes, diabetes re-classification and complications. The diagnosis of type 1 DM was made by the treating physician based on the clinical characteristics and insulin dependence (i.e. insulin requiring for survival), in keeping with the 1999 revised WHO diagnostic criteria for diabetes mellitus.[10] The measurement of insulin autoantibodies of all patients was not performed due to the limited resources in the local setting. Patients were excluded from this study if they were not dependent on insulin or their diagnosis had been reclassified by the attending physicians to other types of diabetes in the year-end census.

Ethics approval was obtained from the Malaysian Research Ethical Committee (MREC), Ministry of Health (MOH) and the respective university hospitals. In the data definition, underweight was defined as body–mass index (BMI) below the 5th percentile while overweight was more than 85th percentile based on the Centers for Disease Control and Prevention (CDC) BMI chart that was provided online.[11] In the data registry, DKA was defined as the presence of hyperglycaemia with blood glucose level of >200 mg/dL (11 mmol/L), metabolic acidosis with venous pH <7.3 and/or plasma bicarbonate level of <15 mmol/L associated with ketonaemia and/or ketonuria.[7]

Statistical Analysis

Mean with standard deviation was presented for the numerical variables as there was no serious violation of assumption for normality. Frequency with percentage was presented for categorical variables. Pearson Chi square and Fisher's exact test were used to determine the association between the different age groups with the profile or clinical variables, the association between the profiles or clinical variables with status of DKA, and the association of year at diagnosis with status of DKA. Analysis of variance (One-way ANOVA) was used to determine the mean difference of age at diagnosis by year of diagnosis. All analyses were carried out using the IBM SPSS version 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Results

A total of 490 children and adolescents with type 1 DM were notified by 34 centres from different states of Malaysia over a 40-month period. The mean (SD) age at diagnosis was 7.5 (3.7) years, ranging from 2 months to 16 years. The proportion between genders was almost equal. At diagnosis, majority were 5 to <15 year-old (69.9%). Positive family history of diabetes (either type 1 or type 2) was present in 45.5% of patients. Approximately one-third (34.8%) of the patients were underweight while 10.1% were either overweight or obese (Table 1).

Majority, 98.0% (438/447) of the patients were symptomatic. There were 64.7% (289/447) patients who presented with DKA at diagnosis. Of the symptomatic patients without DKA, 98.0% (146/149) had polyuria/polydipsia and 70.5% (105/149) had weight loss (Table 1). A significant increase in the mean (SD) age at diagnosis over the years from 6.6 (3.3) years in 2000 to 9.6 (3.5) years in 2009 (p = 0.001) was observed (Table 2).

Table 1. Demographic and clinical profile of children and adolescents with type 1 DM (*N* = 490)

Demographic and clinical profile	*n*	(%)	Mean (SD)
Age at diagnosis (years)			7.5 (3.7)
Age group at diagnosis (n = 482)			
Less than 5 years	114	(23.7)	
5 and less than 10 years	185	(38.4)	
10 and less than 15 years	152	(31.5)	
More than 15 years	31	(6.4)	
Gender			
Male	210	(42.9)	
Female	280	(57.1)	
Ethnicity (n = 488)			
Malay	192	(39.3)	
Chinese	170	(34.8)	
Indian	103	(21.1)	
Others	23	(4.7)	
BMI status (n = 396)			
Underweight	138	(34.8)	
Normal	218	(55.1)	
Overweight	40	(10.1)	
Family history with diabetes mellitus (n = 424)			
Yes	193	(45.5)	
No	231	(54.5)	
Clinical features at diagnosis (n = 447)			
DKA	289	(64.7)	
Symptomatic without DKA	149	(33.3)	
Asymptomatic	9	(2.0)	

Table 2. Mean age at diagnosis and frequency of DKA in children and adolescents with type 1 DM from 2000 to 2009

Year of diagnosis	Age at diagnosis			
	n	Mean	SD	95%CI
2000	23	6.6	3.3	5.2 - 8.0
2001	32	6.2	3.4	5.0 - 7.4
2002	21	6.5	4.0	4.7 - 8.3
2003	44	6.9	3.3	5.9 - 7.9
2004	43	8.3	3.4	7.2 - 9.4
2005	44	8.2	4.1	7.0 - 9.4
2006	44	8.1	3.6	7.1 - 9.2
2007	49	9.2	3.1	8.3 - 10.1
2008	55	8.4	3.5	7.5 - 9.3
2009	46	9.6	3.5	8.5 - 10.6

Association between year of diagnosis and mean (SD) of age at diagnosis was significant at P-value <0.001, by one-way ANOVA

Positive family history (p = 0.003) of either type 1 or type 2 DM and overweight at diagnosis (p = 0.036) were associated with age group at diagnosis where both were common in the older age-group. Though DKA at diagnosis seemed to be more common in the younger age group; however, it was not statistically significant (Table 3).

Table 3. Clinical characteristics of children and adolescents with type 1 DM by age group at diagnosis

Profile/Clinical	<5 years		5 and < 10 years		10 and < 15 years		≥ 15		*P* value
	n	%	*n*	%	*n*	%	*n*	%	
BMI status									
Underweight	31	32.6	55	36.4	45	37.5	3	12.5	0.036
Normal	57	60.0	85	56.3	56	46.7	18	75.0	
Overweight	7	7.4	11	7.3	19	15.8	3	12.5	
Family history with DM									
Yes	38	37.6	67	42.1	63	48.8	21	75.0	0.003
No	63	62.4	92	57.9	66	51.2	7	25.0	
Status of DKA									
DKA	78	70.9	101	58.7	89	65.4	16	66.7	0.207
Non-DKA	32	29.1	71	41.3	47	34.6	8	33.3	
Symptoms of non-DKA									
Classical	30	96.8	60	89.6	42	89.4	8	100.0	0.483
Non-classical	1	3.2	7	10.4	5	10.6	0	0.0	

Result was analysed using Pearson chi-square

No significant difference was observed between patients presented with and without DKA, and age at diagnosis, gender, ethnicity and status of family history of diabetes mellitus. DKA was more common in children with lower BMI (p = 0.002; Table 4). No multivariate analysis was conducted as only BMI was found to be significantly associated with DKA at diagnosis. An increasing percentage of DKA at diagnosis was observed from year 2000 (54.5%) to year 2009 (66.7%), which remained high and leveled between 54.5%–75.0%. The association between year of diagnosis and status of DKA was not statistically significant (P = 0.927; Table 5).

Table 4. Demographic and clinical profile of children and adolescents with and without DKA at diagnosis

Profile/Clinical	DKA		Non-DKA[b]		*P* value
	n	(%)	*n*	(%)	
Age at diagnosis (year)[a]	7.2	(3.7)	7.6	(3.7)	0.250
Age group at diagnosis (n = 482)					
<5 years	78	(70.9)	32	(29.1)	0.207
5 and <10 years	101	(58.7)	71	(41.3)	
10 and <15 years	89	(65.4)	47	(34.6)	
<15 years	16	(66.7)	8	(33.3)	
Gender (n = 490)					
Male	130	(66.0)	67	(34.0)	0.525
Female	159	(63.1)	93	(36.9)	

Table 4. Demographic and clinical profile of children and adolescents with and without DKA at diagnosis (Continued)

Profile/Clinical	DKA		Non-DKA[b]		*P* value
	n	(%)	*n*	(%)	
Ethnicity (n = 488)					
Malay	110	(65.1)	59	(34.9)	0.392
Chinese	106	(65.8)	55	(34.2)	
Indian	56	(58.9)	39	(41.1)	
Others	17	(77.3)	5	(22.7)	
BMI status (n = 396)					
Underweight	71	(55.9)	56	(44.1)	0.002
Normal	140	(68.3)	65	(31.7)	
Overweight	14	(40.0)	21	(60.0)	
Family history with DM (n = 424)					
Yes	99	(56.9)	75	(43.1)	0.065
No	142	(65.1)	76	(34.9)	

[a] *Reported in mean (SD)*

[b] *Non-DKA is based on symptomatic without DKA and asymptomatic group Result was analysed using Pearson chi-square*

Table 5. Proportion of Non-DKA/DKA based on year of diagnosis, 2000–2009

Year of diagnosis	Non-DKA (%)	DKA (%)
2000	45.5	54.5
2001	41.9	58.1
2002	40.0	60.0
2003	34.1	65.9
2004	35.1	64.9
2005	25.0	75.0
2006	33.3	66.7
2007	37.5	62.5
2008	36.8	63.2
2009	33.3	66.7

The association between year of diagnosis and status of DKA was not significant (P = 0.927) Result was analysed using Pearson chi-square

Discussion

The proportion of DKA at presentation of type 1 DM among children and adolescents in Malaysia is high (64.7%) as compared to other countries (19.4% in Finland,[12] 25% in Kuwait[13] and Ireland,[14] 37.2% in Austria,[15] and 26.3% in Germany).[16] However, it is similar to the incidence reported in our neighbouring country Thailand (77.0%) more than 10 years ago.[17]

The proportion of DKA at diagnosis of type 1 DM has been persistently high in Malaysia despite advancement in infrastructure and medical supply. This may be due to a persistent lack of awareness about diabetes mellitus in children among the general public, as well as the primary healthcare providers. It had been reported that DKA prevention programme in the province of Parma, Italy, which was primarily aimed at improving the knowledge of diabetes mellitus in children, had resulted in a significant decrease in prevalence of DKA at type 1 DM onset from 78% to 12.5%.[18] Hence, in order to decrease the proportion of DKA at disease presentation in Malaysia, public awareness and education on type 1 DM should be emphasised. This can be done

by campaigning to disseminate information, especially in schools and in primary healthcare centres, highlighting the early symptoms of diabetes mellitus, such as nocturnal enuresis in a previously dry child, polyuria and polydipsia. Messages disseminated to a large population through school, parents associations and primary healthcare centres should be simple and easy to understand. Easy access to healthcare providers who are trained and experienced in diabetes mellitus should be made available. Many patients with type 1 DM could have been diagnosed early and DKA prevented if they were better informed and had presented themselves early to the primary healthcare providers who were trained to recognise classic hyperosmolar symptoms of type 1 DM.

It had been reported that risk factors associated with DKA at diagnosis were young age i.e.<5 years, diagnostic error, ethnic minority, lower BMI, history of preceding infection and delayed treatment.9 Many studies reported a higher risk of DKA at disease onset in children younger than 2 years.[12–14] In our study, though DKA at diagnosis appeared to be more common in children aged >5 years, it was not statistically significant. Also, there was no gender preponderance. Another study reported that most of the children were underweight at diagnosis of type 1 DM,[13] and children with lower BMI had a higher risk of DKA.[12] Our study showed a similar finding where higher proportion of DKA was seen in the normal weight and underweight children with type 1 DM.

We also observed that overweight at diagnosis was significantly more common in the older age group (>10 years old). The observation of overweight in these patients with type 1 DM may be partly explained by the increasing prevalence of obesity worldwide and also the higher susceptibility of peripubertal adolescents to overweight/obesity caused by environmental factors. Although, this observation may cast doubt on the classification of diabetes in these overweight or obese children, the diagnosis of type 1 DM was supported by the year-end census, which reported persistent insulin dependence and no re-classification of diabetes by the treating clinicians. Furthermore, the clinical characteristics of our patients were quite similar to other studies. The mean (SD) age at diagnosis in this study was 7.5 (3.7) years, which is quite similar to other reports (mean of 7.6 to 8.9 years).[8,9]

Although, C-peptide, insulin and pancreatic autoantibodies measurements are useful to classify diabetes, laboratory facilities were not always available in most of the reporting centres. These facilities should be made easily available in all hospitals caring for diabetic patients to accurately diagnose and classify the disease. Correct classification of diabetes enables healthcare providers to treat patients appropriately according to their disease pathophysiology. Patients with type 1 DM require insulin replacement therapy while patients with type 2 DM need treatment to improve insulin resistance and preserve the declining beta-cell function. Accurate epidemiological data are also important to guide planning of healthcare systems and policies to further improve diabetes care in the country.

Protective factors associated with reduced risk of DKA at diagnosis reported in other studies include positive family history of first degree relative with type 1 DM, higher parental education level and higher background incidence of type 1 DM in the community.[9] Although nearly half (45.5%) of Malaysian children and adolescents with type 1 DM had positive family history of diabetes mellitus (type 1 and/or type 2) in their first-degree relatives, we still experience a high proportion of DKA at presentation. The protective effect of positive family history was not shown in our study as many of the patients might had positive family history of type 2 DM with slower onset of disease.

From the 2010 Population and Housing Census of Malaysia, the Malaysian population of 28.3 million consist of Malay 67.4%, Chinese 24.6%, Indian 7.3% and others 0.7%.19 Malay, Chinese and Indian made up 39.3%, 34.8% and 21.1% of the type 1 DM patients, respectively. Our study found a higher proportion of Malaysian Chinese and Indian with type 1 DM, compared to Malay. Variable gene polymorphism in the major histocompatibility complex (MHC) or other genetic susceptibility regions in this ethnic group may have predisposed the individuals to the development of type 1 DM when triggered by various environmental agents.[20]

Up to 2.0% (9/447) of patients in this study was reported to be asymptomatic at diagnosis. These patients were likely to be those with positive family history of diabetes who had greater awareness of the disease, resulting in

early diagnosis before manifestation of overt classical symptoms, or those with the disease detected incidentally during an outpatient clinic visit for other medical conditions.

From year 2000 to 2009, there was a significant increase in the mean (SD) age at diagnosis in Malaysian children with type 1 DM. In other studies, age at diagnosis had also been reported to increase with time, which may indicate a change in non-genetic risk factors affecting specifically young children.[21,22] Although, most of the autoimmune diseases are more common in females, most of the studies including ours did not show any gender preponderance.

These results are useful to increase awareness among healthcare providers, especially to the general practice with regards to the magnitude of the disease. Besides that, it is also aimed to create awareness among parents, especially to prevent late diagnosis of children with type 1 DM. Last but not least is to share the information, which will be useful for the researchers who are interested to do research on children with DM.

Limitations

This is a register based cohort study. The data was provided by the clinicians managing the patients. At the time of our study, not all hospitals in Malaysia were able to participate in DiCARE. The results of our study need to be interpreted with caution in view of the missing data that is inevitable with registry based data. However, the sample is nearly to 500 and considered as large especially for data children with type 1 diabetes mellitus. Previous study has found that a sample size of approaching 500 or more are to be of adequate in estimating the parameter in the intended population.[23]

Another limitation of our study is that the clinical data on access to primary care prior to the indexed hospital visit where patients were diagnosed and notified were not captured. Improvement in case report forms, training of personnel in filling the forms, extension to nationwide coverage of DiCARE, involvement of the relevant government agencies are currently in progress. We hope that the improved cumulative data in the near future would give us a clearer picture of the clinical presentation of type 1 DM in Malaysia.

This study underscores the persistently high percentage of DKA in Malaysian children and adolescents at diagnosis of type 1 DM over the past decade. DKA was more common in patients with normal weight or underweight. There was also an increase in age at diagnosis over the last 10 years. The gap that was identified includes the lack of early detection at primary care level, since almost all of the patients with type 1 DM were symptomatic at presentation. Effective training of primary care providers on symptoms and signs and prompt treatment could have prevented many patients from developing DKA. Besides that, awareness must be created amongst the younger population, parents and teachers.

Biochemical testing for classification of diabetes should be made easily available in developing countries to provide accurate diagnosis and hence appropriate patient management. Though the present data from DiCARE may not accurately represent all Malaysian children, further improvement in patient coverage, training of personnel in data collection, upgrading the reporting system and involvement of the government agencies will definitely help in our initial steps to prevent DKA at diagnosis in these children and adolescents.

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Conflict of interest

The author(s) declared no conflict of interest during the conduct of the study, nor its findings.

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