The Occurrence of Diabetic Ketoacidosis in Type 2 Diabetic Adults

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Running title: The Occurrence of Diabetic Ketoacidosis in Type 2 Diabetic Adults

Abstract

OBJECTIVE. To study the diabetic ketoacidosis (DKA) episodes which occurred in the type 2 diabetic adults.

STUDY DESIGN. We reviewed retrospectively the charts of patients who were admitted to the division of endocrinology and metabolism from Jan. 1991 to Dec. 1997 due to DKA.

RESULTS. Total 121 adult patients with 137 episodes (57 females and 80 males) of DKA, with mean age of 45.90 years. 98 episodes (71.5%) occurred in type 2 diabetes mellitus (DM) with mean age of 48.73, which was significantly older than type 1 diabetic patients. Among ten patients suffered from repeated episodes of DKA,

four patients belonged to type 2 DM. 33 episodes (24.1%) occurred in patients without a history of DM, however, up to 24 episodes were classified as in type 2. Infection was the most important precipitating factor in type 2 diabetic patients, with respiratory tract and urinary tract accounting for the two most common foci. In type 1 diabetic patients, poor drug compliance accounted for the leading one. Twelve patients (one in type 1 DM and eleven in type 2 DM) expired, giving the mortality rate of 8.8%. Only old age contributed to fatality in type 2 diabetic patients. Type 2 diabetic patients had lower value of serum potassium and the occurrence of hyperkalemia was less than that of type 1.

CONCLUSION. Owing to high percentage of adult DKA episodes occurred in type 2 DM, more attention should be pay to these patients.

KEYWORDS: diabetes mellitus, diabetic ketoacidosis

INTRODUCTION

In general diabetic ketoacidosis (DKA) is always described to be closely linked to type 1 diabetes mellitus (DM). The occurrence of DKA has been thought to indicate the underlying significant and irreversible ß-cell damage that classifies these diabetic patients as type 1 DM (insulin–dependent diabetes mellitus). However, many DKA patients do have clinical course and metabolic features of type 2 DM (non-insulin-dependent diabetes mellitus). In Taiwan there have been few

investigations focusing on the type 2 diabetic patients who suffered from DKA episodes. We therefore undertook to examine the clinical characteristics of a cohort of diabetic patients who presented with DKA to a medical center in southern Taiwan. In this retrospective study, we centered on the adult DKA episodes which occurred in the subsequently type 2 diabetic patients, with making a comparison between both types of patients. The precipitating factors, clinical characteristics, and mortality rate were investigated.

Subjects and Methods

The patient population included in this study was adult diabetic victims (age $\geqq$ 18 years) who had been admitted to the division of endocrinology and metabolism of Veterans General Hospital-Kaohsiung (VGH-KS) due to DKA during the past 7-year period from Jan.1991 to Dec.1997. All information was obtained by chart reviews. Charts were collected with a discharged diagnosis of DKA. DKA was defined as hyperglycemia, positive blood ketone test results after twofold dilution, and high anion gap metabolic acidosis.

Clinical and C-peptide criteria were used to classify the diagnosis of diabetes as type 1 or type 2. Individuals who had been managed at some point with diet or an oral antidiabetic drug (OAD) and with no prior history of DKA were classified as type 2 DM. Individuals whose medical records indicating continuous insulin treatment and

prior diagnosis of type 1 DM were classified as type 1. In the patients without history of diabetes, those who had C-peptide value over 2 ng/ml or the insulin treatment could be shifted to diet or OAD were also classified as type 2 DM. Those who had repeated C-peptide measurement below 1 ng/ml and received continuous insulin treatment at follow-up were regarded as type 1 DM. The patients who were not distinguishable were excluded in this study.

The clinical characteristics were compared between both types of diabetes. The information obtained for analysis included the age, gender, precipitating factors, laboratory values and mortality rate. The factors contributed to death in type 2 DM were also investigated.

Statistical analysis

All analysis was performed by using the Statistical Package for the Social Sciences (SPSS for Windows Version 7.0, SPSS Institute, Chicago, IL, USA). Unless otherwise specified, all data was expressed in mean ± standard deviation (SD). The analysis was episodic-based. The statistical method used were Student's *t* test and Chi-square analysis. A p value < 0.05 is regarded as statistically significant. Multiple logistic regression analysis was executed to assess which parameters contributed to mortality.

Results

During the seven-year period, the total of 121 adult patients with 137 episodes achieved the diagnostic criteria of DKA and was included in this analysis. The clinical characteristics are shown in Table 1. There were 98 episodes (71.5%) occurred in the type 2 DM with other 39 episodes (28.5%) in the type 1 DM, for total 57 females and 80 males. The mean age at the time of the episodes was 45.90 ± 16.06 years. The age of type 2 diabetic patients was significantly older than that of type 1 DM (48.73 ± 15.45 *vs*. 38.77 ± 15.50 years, $p = 0.001$).

Ten patients had suffered from recurrent episodes of DKA, four patients belonged to type 2 DM and the other six patients were type 1 DM. Besides, alternative episodes of DKA and hyperglycemic hyperosmolar nonketotic state (HHNK) were also occurred in type 2 diabetic patients.

The attached figure illustrates the distribution of the two groups by age on presentation with DKA. Only 10% of the type 2 diabetic patients were < 30 years old, 48% were ≧ 50 years old. Type 2 diabetic subjects predominated when the age was over 30 years.

33 episodes (24.1%) occurred among patients without a history of diabetes. Except 16 episodes that were noted of some precipitating factors, there were 17 episodes no obvious factors could be found. Among the 33 episodes, 24 episodes (72.7%) were

subsequently classified as type 2 DM and the other 9 episodes (27.3%) as type 1 DM. The percentage of DKA-onset diabetes in type 2 DM was 24.5%, there was no significant difference when compared with type 1 DM (23.1%, $p = 0.707$).

The major precipitating factors of total episodes included infection (38.0%), poor drug compliance (28.5%), and newly diagnosed diabetes (12.4%). Some episodes of DKA revealed no obvious precipitating factors (8.8%). Among the factors precipitating DKA in type 2 DM, infection was the most important (48.0%), followed by poor drug compliance (19.4%) and newly diagnosed diabetes (10.2%). However, in the type 1 DM, poor drug compliance accounted for the leading one (48.7%). Only 12.8% of episodes resulted from infection.

The precipitating factors of DKA in type 2 diabetic patients were shown in Table 2. Among the factor of infection, respiratory tract and urinary tract were the most common foci.

Twelve patients expired during the 137 episodes, giving the mortality rate of 8.8%. Only one patient was classified as type 1 DM, the other 11 patients belonged to type 2 (2.6 *vs.* 11.2%, $p = 0.107$). Among the 98 episodes occurred in type 2 diabetic subjects, the analysis by multiple logistic regression showed that only old age contributed to fatality (Table 3).

Total 65 cases had received glucagon test (6 minutes after 1 mg i.v. glucagon) for

C-peptide measurement. Among the 45 cases who were belong to type 2 DM the stimulated C-peptide were 2.82 ± 1.75 pmol/ml and it was 0.41 ± 0.26 pmol/ml among the 20 cases of type 1 DM.

Laboratory values on admission are shown in Table 1. There was no significant difference between both types of diabetes except that the concentration of serum potassium were lower in type 2 diabetic patients (4.48 ± 0.97 *vs.* 5.08 ± 1.03, p = 0.003). 37% of DKA episodes occurring among type 2 DM patients were noted of hyperkalemia, which was less than that of type 1 DM (67%, p = 0.002).

Discussion

DKA is common, which not only occurs in the pediatric period but also is frequently observed in adult diabetic patients. In our study of adult DKA patients, the median age was 45.9 years, with insignificant male predominance for both types of diabetes. However, type 2 diabetic patients were significantly older than that of type 1.

Among the episodes occurred in type 2 DM, there were only ten percent of episodes in the patients below 30 years old. About half of the episodes were in the age over 50 years. Most of the DKA episodes with age over 30 years were noted in the type 2 patients. Therefore, the clinical characteristics of DKA occurred in type 2 diabetic patients should be delineated.

Although more classically associated with type 1 DM, DKA can happen in the patients with clinical courses and metabolic features of type 2 DM[1,2,3,4]. In the investigation of the Westerns, DKA mainly appeared in the type 1 diabetic subjects[1,5]. However, in the areas where type 2 DM comprised a majority of diabetic patients, a bulk of DKA episodes occurred in type 2 diabetic patients[2,6,7]. In our study, the patients attacked with DKA were predominant type 2 DM (98 *vs.* 39, $p = 0.000$). There are some possible explanations for this finding. First of all, type 1 DM is predominantly a disease of whites, it is rare in Chinese[8]. Secondly, most of the type 1 diabetic onset develops in the pediatric period. Conversely, type 2 DM in the pediatric subject is of rare occurrence. The clinical features of DKA occurring among the adult patients may therefore present with different characters.

DKA may be the first manifestation of diabetes, refer to as DKA-onset diabetes[9]. The situation is common in the pediatric patients with the percentage of about 24% to 58%[10,11,12]. However, in adult DKA patients, the percentage is less common, ranging from 7% to 27%[1,6]. In our study of all 137 adult episodes, the percentage of DKA-onset diabetes was 24.1%. It was 24.5% in type 2 DM, there was no significant difference when compared with type 1 (23.1%, $p = 0.707$). However, the attack of DKA episodes in newly diagnosed were type 2 DM predominant with the ratio of 2.7:1.

According to previous studies, infection, poor drug compliance and newly diagnosed diabetes without obvious factors were the three most common precipitating factors for those DKA episodes to occur[2,13,14,15]. Our study exhibited the same results. In type 2 patients, the infection was the most important which accounted for 48.0%, followed by poor drug compliance (19.4%). On the other hand, the leading factor in type 1 patients was poor drug compliance (48.7%), and infection accounted for only 12.8%. We therefore presume that type 2 diabetic patients may become transient insulin deficiency during severe physical stress (such as infection) and recover when the insults subsided. This differs for the patients of type 1 DM, who easily suffer from DKA when omission of medication. However, DKA-onset diabetes could be observed in the type 2 diabetic patients and the occurrence of DKA was also noted in poor compliance type 2 patients without other precipitating factors. We therefore assume that marked hyperglycemia may induce severe insulinopenia and prone to DKA even in type 2 diabetic patients. Nevertheless, there was still no obvious precipitating factor occurring to episodes of DKA. We suppose that the lack of thorough history taking and physical examination may partly accounted.

In this study, the physical stress that precipitated DKA in type 2 diabetic patients included infection, poor drug compliance, newly diagnosed DM without obvious precipitating factors, pancreatitis, herbs administration, gouty arthritis, acute

myocardial infarction and cerebral vascular accident. The common infectious foci were respiratory and urinary tract. However, there were episodes that no obvious infectious foci could be identified.

Among the ten patients who suffered from recurrent episodes of DKA, six patients belonged to type 1 DM and the other four patients were type 2 DM. Nearly all recurrent episodes in type 1 diabetic subjects were due to omission of insulin. In type 2 diabetic subjects, however, most recurrent episodes occurred in patients of poor diabetic control combined with significant stress. Hence, the education and diabetic control are important for the prevention of repeated DKA attack in both types of DM.

Some investigators had postulated that the hyperglycemic crises were states of severe decompensated hyperglycemia, which differed only in the magnitude of dehydration and the severity of acidosis[16,17]. Tracing back to the history of some type 2 diabetic subjects in our study, alternate episodes of HHNK and DKA were also documented. This evidence seemed to be concordant with the assumptions. Nevertheless, further investigation to delineate the status of acute de-compensation of hyperglycemia is needed.

In Taiwan the mortality rate of DKA ranged from 3.8 to 12.2% in different studies[14]. The fatality of adult onset DKA was 8.8% in our hospital. The mortality rate was 11.2% in type 2 DM, comparing to that of 2.6% in type 1 DM (p = 0.107). It

presented that the mortality rate in type 2 DM was higher, though statistically insignificant. Among the 98 episodes of DKA occurred in type 2 diabetic patients, analysis by multiple logistic regression showed that only old age contributed to fatality. The episodes precipitated by infection did not have higher fatality. Moreover, the severity of acidosis was not the factor contributed to fatality.

Concerning the laboratory values on admission, there were no significant differences between both types of diabetes except the concentration of serum potassium was lower in type 2 DM. DKA induced hyperkalemia had been described by some investigators. Van et al implied that hyperglycemia due to insulinopenia was one of the factor[18]. In our study, hyperkalemia occurred in 45% of episodes. Besides, hyperkalemia was noted in 67% of type 1 diabetic subjects, comparing to that of 37% in type 2 DM (p = 0.002). The risk of hyperkalemia in type 2 DM is relatively lower.

The classification of diabetes in our retrospective study was by clinical and C-peptide criteria, therefore, the possibility of latent or slowly progressive autoimmune diabetes may not be excluded. In 1997, the American diabetic association had suggested the etiologic classification of diabetes[19]. The autoimmune markers include islet cell autoantibodies (ICAs), autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase (GAD_{65}) and autoantibodies to the tyrosine phosphatases IA-2, and IA-2 beta, and the HLA association should be

measured for the classification of diabetes. The etiologic classification of diabetes may resolve some controversy according to previous classification by clinical and C-peptide criteria.

In conclusion, our study exposed that majority of the adult DKA episodes in our hospital occurred in type 2 diabetic DM patients. They tended to be older than type 1 diabetic patients were, and the mortality rate was also slightly higher. Although most of the episodes were precipitated by infection, there were some episodes without obvious factors. These findings merely represent the evidence of one medical center in southern Taiwan; nevertheless in Taiwan, an area with high prevalence of type 2 DM, the importance of the occurrence of DKA in adult type 2 diabetic patients will not be overemphasized. Therefore, the diabetic control and education to the adult type 2 diabetic patients is much important. The screening for diabetes in the adults should not be neglected.

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Table 1. Characteristics of adult diabetic acidosis, classified by type of diabetes

Characteristic	Type of diabetes		
	Type 1 (n=39)	Type 2 (n=98)	*p* value
Age (yr)	38.77±15.50	48.73±15.45	0.001
No. of male	26 (66.7%)	54 (55.1%)	0.394
History of diabetes	30 (76.9%)	74 (75.5%)	0.707
Precipitated by:			
Infection	5 (12.8%)	47 (48.0%)	0.000
Poor drug compliance	19 (48.7%)	19 (19.4%)	0.001
Newly diagnosed	7 (17.9%)	10 (10.2%)	0.216
Unknown cause	8 (20.5%)	8 (8.2%)	0.071
Mortality	1 (2.6%)	11 (11.2%)	0.107
Laboratory values:			
Sugar (mg/dL)	543.72±161.40	547.56±189.84	0.905
PH	7.16±0.15	7.12±0.34	0.341
BUN (mg/dL)	27.54±11.81	29.40±16.66	0.464
Creatinine (mg/dL)	3.21±0.83	3.56±1.23	0.054

Osmolarity (mEq/kg)	310.51±14.92	310.95±16.83	0.558
Sodium (mEq/L)	130.77±6.80	130.85±7.50	0.953
Potassium (mEq/L)	5.08±1.03	4.48±0.97	0.003

Table 2. Precipitating factors of adult diabetic ketoacidosis in type 2 DM

Precipitating factor	No. cases (%)
Infection	47 (48.0)
Respiratory tract	17 (17.4)
Urinary tract	16 (16.3)
Unknown focus	7 (7.2)
Cellulitis	5 (5.1)
Joint	1 (1.0)
Parotid gland	1 (1.0)
Poor compliance of medication	19 (19.4)
Newly diagnosed without obvious precipitating factors	10 (10.2)
Pancreatitis	7 (7.2)
Herbs administration	2 (2.0)
Gouty arthritis	2 (2.0)
Pregnancy	1 (1.0)

Acute myocardial infarction	1 (1.0)
Cerebral vascular accident	1 (1.0)
Unknown cause	8 (8.2)

Table 3. Factors contributed to death in diabetic ketoacidotic episodes occurrence in type 2 diabetic patients

Factor	coefficient (ß)	SE of (ß)	X^2	df	*p* value
Age	0.309	0.156	3.930	1	0.048

Other factors included: sex, precipitating factors (infection, poor drug compliance, newly diagnosed diabetes). laboratory values of serum sugar, osmolarity, pH, sodium, potassium, BUN, creatinine.

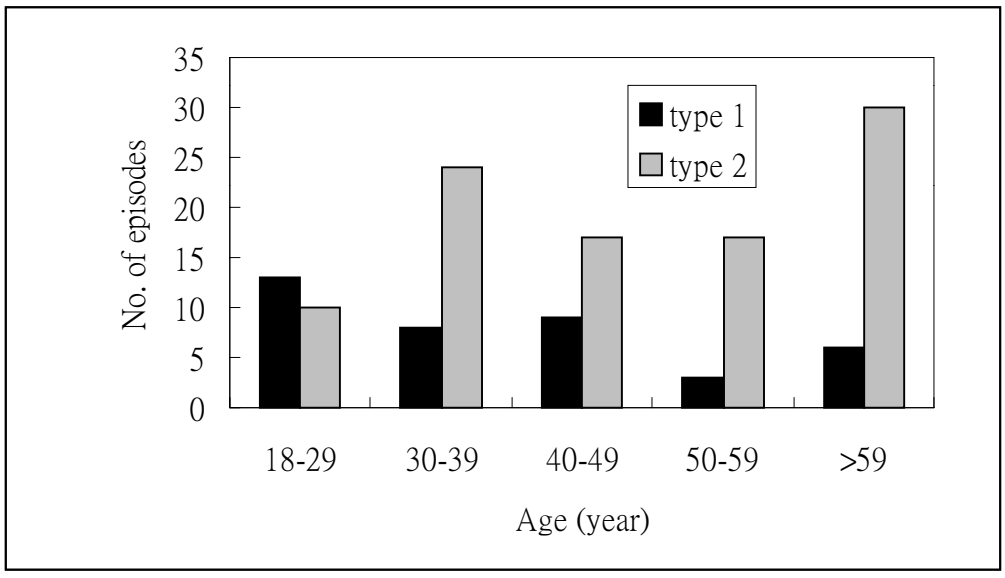

Figure. Numbers of episodes with type 1 and type 2 DM in each age group on admission with DKA.