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Ketoacidosis as the First Presentation of Type 1 Diabetes Mellitus in Children and Adolescents during the Period 2010-2014 in Albania

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Abstract: ***Background: Diabetic ketoacidosis (DKA) is the second most common form of presentation of type 1 diabetes mellitus (T1DM) in children and adolescents and the leading cause of morbidity and mortality. The aim of this study is to assess the frequency and characteristics of DKAin children and adolescents of newly diagnosed T1DMin Albania, at the national level during the period 2010-2014. Methods: The clinical and laboratory characteristics of 152 patients <15 years old newly-onset T1DM from 1 January 2010 to 31 December 2014 were studied. T1DM was diagnosed according to WHO 2006 criteria and DKA was diagnosed based on ISPAD 2014 criteria based on values of 1) pH <7.30; 2) plasma bicarbonate concentration <15 mEq/L; 3) ketonuria> 2+. Statistical analysis was performed using SPSS 26. Results: The overall incidence of ketoacidosis was 67.8%. The mean age of children with DKA was 7.75 ± 3.64 years, while that of children without DKA was 9.29 ± 3.39 years (P = 0.012). There were no statistically significant differences by age subgroup and living residence; the percentage of females was higher in T1DMchildren with DKA (54.4%) than among those without DKA (34.7%) (p = 0.025). There is no family history of T1DM statistically significant difference between cases with and without KAD at diagnosis of T1DM. Children presented with KAD had higher mean glycemic values (p < 0.001) and triglycerides (p = 0.001) compared to children without DKA. No statistical differences were observed between in the average values of glycated hemoglobin (HbA1c) children with KAD and without KAD (p=0.195). The most common presentation symptoms of children with DKA were polyuria (100%), polydipsia (100%), and weight loss (98.1%). The frequency of malaise, vomiting, enuresisnocturna, acetone odor, dyspnea, drowsiness and confusion was higher among children with DKA (p < 0.001). Conclusion: This is the first study to report the incidence of DKA as a presentation of newly diagnosed T1DMamong Albanian children. The mean age of children with DKA was lowerand girls were found to have higher rates of ketoacidosis. The incidence is higher compared to the countries of the region. Delayed diagnosis and mismanagement are responsible for this high prevalence, the more severe presentation, especially in young children and girls. Prevention campaigns are needed to raise the awareness of healthcare providers, parents and the general public to improve early diagnosis and treatment of T1D.***

Keywords: *epidemiology, children, diabetes mellitus 1, diabetic ketoacidosis, Albania*

What is already known on this topic?

- DKA is the second most common form of presentation at diagnosis of T1DM in children and adolescents; 6-fold variation (12.8%-80%).
- DKA is a serious life-threatening condition and medical urgency of T1DM and the leading cause of morbidity and mortality of children with T1DM.
- Given the above information, awareness campaigns should involve both families and health care professionals, to be able to detect the signs and symptoms of the disease as well as early.

What this study adds?

- This is the first report examining the incidence rate and the clinical characteristics of cases of DAK in newly diagnosed T1DM children in Albania over a five-year period.
- Regardless of the improvement of the quality of life, the care of the health service, the Albania remains into countries with high incidence of DKA, especially younger age group and girls are more affected. This figure is higher than the levels reported in the international literature.
- Our study provides an additional contribution to the international literature.

1. Introduction

Diabetes mellitus type 1 (T1DM) which is the result of autoimmune destruction of insulin producing beta cells (1) accounts for 5-10% of the total burden of diabetes mellitus and is the most common endocrine disease in children and adolescents. DKA (hyperglycemia and ketoacidosis) is the second most common form presentation of newly diagnosed T1DM in children and adolescents (2). The frequency of DKA as a manifestation of newly diagnosed T1DM is different in different countries (3).

Although the incidence of DKA in many developed countries has been reduced (4-6), various studies around the world report a 6-fold variation of DKA from 12.8% to 80% of children diagnosed with T1D for the first time (7). The highest incidence of DKA is observed in United Arab Emirates (80%) [8], Nigeria (77%) [9], Romania (67%) [3], Taiwan (65%) [7], and Saudi Arabia (44.9%) [10]. The lowest incidence is observed in Sweden (14%) [7], Denmark (14.7%) [9], Canada (18.6%) [5], Finland (19.4%) [4], and USA (30%) [11].

The wide geographical variation of DKA frequency of newly diagnosed T1DM children and adolescents is related to a number of factors (3, 12). DKA frequency is inversely associated with the incidence of T1D. The incidence of DKA is lower (*protective factors*) in countries with a high incidence of T1D due to increased knowledge of pathology, in families having a first generation relative with T1D, parents with higher education, in countries far and near Ecuador and lower GDP (DKA is more common in developing countries) (7). Conversely, the incidence of DKA is higher (*risk factors*) in countries with low incidence of diabetes, in younger children (<3 years old) [13], in families with low socioeconomic status (7, 14-18), in children from deprived communities (minority ethnic groups, groups without insurance and lack of health care, children of immigrant families), distance from diabetes centers, more aggressive forms of diabetes (19, 20), etc. All of these factors lead to delayed diagnosis, misdiagnosis, and delayed treatment (5, 14, 21).

There is currently a growing global interest in assessing the incidence of DKA (22) because it is the leading cause of hospitalization, increased health care costs (23), partial remission with lower incidence (24, 25), fewer functional beta cells left over from destruction (15, 16) and increased incidence for psychosocial disorders (26), morbidity and mortality in children with type 1 diabetes, and influencing the long-term clinical course of type 1 diabetes (27, 28, 29).

DKA is the serious life-threatening complication and medical urgency of T1D and the leading cause of morbidity and mortality of children with T1D (21). Currently the mortality is around 2-5% (28, 30,), with a case-fatality ranging from 0.15 to 0.31% (30-33), and in the absence of insulin therapy the mortality is 100%. Mortality is higher in patients presenting for the first time (30) and is mainly associated with cerebral edema which occurs 4-12 hours after the start of treatment (21, 30, 34, 35). The risk of cerebral edema is 1.2% in first-diagnosed cases and mortality is approximately 25-30% (36) and ≥35% of survivors remain with permanent neurological impairments (30, 37).

When newly diagnosed type 1 diabetes presents with ketoacidosis, symptoms develop within a few days, with progressive dehydration and ketosis. Whereas when diabetes is under development or appearing, ketoacidosis can be precipitated by stress or other diseases, which hide the main problem. Clinically DKA is characterized by symptoms of *acidosis and dehydration* (abdominal pain, vomiting, nausea, decreased peripheral perfusion, severe intra-and extracellular hydroelectrolitic depletion, dyspnea, hyperventilation, Kussmaul respiration, ketone odor, confusion and coma), *hyperglycemia symptoms* (polyuria, polydipsia, nocturia, secondary enuresis, weight loss, pain and muscle cramps) due to insulin deficiency, and non-specific signs of recurrent respiratory and urinary tract infections, malaise that may precede classic symptoms.

DKA is a potentially preventable acute complication of T1DMand the predominant cause of death in children with diabetes (31). Early recognition through awareness raising of the medical staff and the general public about early symptoms of type 1 diabetes in young children would lead to early treatment and significant reduction of the incidence and severity of DKA in newly diagnosed children with T1D (38).

In Albania there is little information on the frequency of DKA among children newly diagnosed with T1D. In this context, the purpose of this study was to assess the frequency of ketoacidosis as a manifestation of type 1 diabetes newly diagnosed among children in Albania during 2010-2014.

2. Methods

Study type

This study represents a series of patients (cases) newly diagnosed with type 1 diabetes mellitus in the premises of the Endocrinology and Diabetes Service, at the University Hospital Center "Mother Teresa", Tirana (QSUT), during the period 2010-2014.

Study population

In this prospective study, January 1, 2010 to December 31, 2014 included 152 patients who met the criteria: children diagnosed with T1D for the first time < 15 years old in Albania. The number of children and adolescents aged 0-14 years old from 2010-2014 according to INSTAT is 3, 032, 819 children (1451992females and 1580827 males). Patients are classified into 3 age groups (I: 0-4 years, II: 5-9 years, and III: 10-14 years).

Ethics approval and consent of participate: Informed written consensus was obtained from all patients' parents. It is approved by the Albanian National Ethics Committee.

Consent For Publication: Not Applicable.

Data collection

Data for this study were collected prospectively using a standardized clinical record. Information was collected on a range of demographic and laboratory data.

The diagnosis of T1D was determined according to WHO criteria (39); the ISPAD criteria were used to determine DKA (40); hyperglycemia (glycemia> 200 mg/dL or> 11 mmol/L), metabolic acidosis (pH <7.30, and /or plasma bicarbonate level <15 mmol/L or ketones in urine (ketonuria> 2+), accompanied by history of polyuria, polydipsia, nocturia, weight loss, dehydration, tachycardia, tachypnea, deep, prolonged respiration (Kussmaul), acetone odor, nausea, vomiting, abdominal pain, alteration of consciousness (confusion, drowsiness, progressive reduction of consciousness, loss of consciousness, coma). The severity of DKAwas determined by the pH and concentration of plasma bicarbonates and wascategorized into 3 groups: (a) mild: pH <7.30 and/or serial bicarbonate <15 mmol /L; (b) moderate: pH <7.2 and /or bicarbonate <10 mmol /L and (c) severe: pH <7.1 and /or bicarbonate <5 mmol/L (Table 1). According to ISPAD, T1D for the first time with pH> 7.3 and HCO3> 15 mEq/L was classified as T1D without ketoacidosis.

Statistical analysis

Absolute numbers and corresponding percentages were used to describe the categorical data. To describe numerical data, the reporting of the central tendency measures, in this case the mean value, and the dispersion measures, in this case the standard deviation was used. The Chi-square test was used to compare categorical variables; in case the resulting table was in the size of 2x2, then the value of P was reported according to Fisher's exact test, which gives a more accurate calculation of the P-value.

To compare the mean values of the numerical dependent variable according to the categories of the independent variable, the non-parametric Mann-Whitney U test was used for two independent samples in the case where the independent variable had only two categories; otherwise, when the independent variable had>2 categories the non-parametric Kruskal Wallis test was used for k independent samples. Non-parametric tests were used in case the dependent variable was found to be abnormally distributed in the study population. Otherwise, for normally distribute numerical variables, the student's t-test for two independent samples was used.

Binary Logistic Regression test was used to identify the associations between the presence of diabetic ketoacidosis and the independent variables.

Various tables depending on the information were used to present the data. Graphs of different types were used to present and illustrate the study findings.

In all cases, the associations between the variables were considered significant if the value of the statistical significance was ≤0.05 (or ≤5%).

All statistical analyzes were performed through the Statistical Package for Social Sciences, version 26 (IBM SPSS Statistics for Windows, version 26) software program.

3. Results

In this study there were included 152 children with type 1 diabetes mellitus (T1D). Table 1 shows the distribution of subjects in the study by age at the time of diagnosis, gender and place of residence. It can be noticed that the average age of the subjects at the time of diagnosis was 8.3 years ± 3.6 years. Most often, children with T1D belonged to the age group 5-9 years (40.1%), followed by the age group 10-14 years (39.5%) and 0-4 years (20.4%). On the other hand, almost half of the children with T1Dwere male (52%) and the rest were female (48%). Three-quarters of children with T1D lived in urban areas and 25% in rural areas.

Table 1: Basic socio-demographic data of children with T1D in the study

Variable	Absolute number	Frequency (%)
Total	*152*	*100.0*
Age at the time of diagnosis (mean ± standard deviation)	8.3 ± 3.6	
Age group		
0-4 years	31	20.4
5-9 aged	61	40.1
10-14 years	60	39.5
Gender		
Male	79	52.0
Female	73	48.0
Residence		
Urban	114	75.0
Rural	38	25.0

In the diagnosis of T1D for the first time 103 out of 152 children (67.8%) had DKA and 49 (32.2%) did not have DKA (Table 2).

Table 2: Presence of diabetic ketoacidosis in children participating with T1D

Variable	Absolute number	Frequency (%)
Type 1 diabetes type		
T1D with DKA	103	67.8
T1D without DKA	49	32.2

Table 3 presents the comparison of baseline socio-demographic data of participants by DKA status. The mean age at diagnosis of T1D children with DKA was significantly lower than that of T1D children without DKA. Likewise, the percentage of girls was significantly higher among T1D children with DKA than among those without DKA. Differences by place of residence and age group were not statistically significant. However, the tendency was that the 0-4 age group occupies a percentage almost twice as high in T1D children with DKA than in those without DKA.

Table 3: Socio-demographic data of children in the study by type of T1D

Variable	Type of diabetes type 1		Value of P
	T1D with DKA	T1D without DKA	
Group-age			
0-4 years	25 (24.3) *	6 (12.2)	0.082 **
5-9 years	43 (41.7)	18 (36.7)	
10-14 years	35 (34.0)	25 (51.0)	
Age at diagnosis (mean ± standard deviation)	7.75 ± 3.64	9.29 ± 3.39	**0.012**†
Gender			
Female	47 (45.6)	32 (65.3)	**0.025****
Male	56 (54.4)	17 (34.7)	
Residence			
Urban	79 (76.7)	35 (71.4)	0.549 **
Rural	24 (23.3)	14 (28.6)	

* Absolute number and percentage by columns (in parentheses).
** Value of statistical significance according to the square hi test (Fisher's Exact Test for 2x2 tables).
† Value of statistical significance according to the student t test for two independent samples.

Table 4 presents other data related to the clinical picture of T1D children included in the study. The most common symptom was malaise (reported in 86.8% of cases), followed by vomiting (18.5%), enuresisnocturna (17.8%) and abdominal pain (9.9%), while headache and diarrhea were reported by 4.6% and 2.6% of children with T1D, respectively. The prevalence of signs and symptoms was significantly higher among T1D children with DKA than among those with T1D without DKA for all such conditions displayed in Table 4 (P <0.05).

Table 4: Other clinical presentations of the disease by type of diabetes T1D

Variable	Total	Type of diabetes type 1		Value of P †
		T1D with DKA	T1D without DKA	
Enuresisnocturna				
No	125 (82.2) *	77 (74.8)	48 (98.0)	**<0.001**
Yes	27 (17.8)	26 (25.2)	1 (2.0)	
Malaise				
No	20 (13.2)	7 (6.8)	13 (26.5)	**0.002**
Yes	132 (86.8)	96 (93.2)	36 (73.5)	
Vomiting				
No	123 (81.5)	77 (75.5)	46 (93.9)	**0.007**
Yes	28 (18.5)	25 (24.5)	3 (6.1)	
Acetone smell				
No	93 (61.2)	47 (45.6)	46 (93.9)	**<0.001**
Yes	59 (38.8)	56 (54.4)	3 (6.1)	
Kussmaul respiratory distress				
Jo	106 (70.2)	57 (55.9)	49 (100.0)	**<0.001**
Po	45 (29.8)	45 (44.1)	0 (0.0)	
Moaning				
No	117 (77.0)	68 (66.0)	49 (100.0)	**<0.001**
Po	35 (23.0)	35 (34.0)	0 (0.0)	
Dyspnea				
No	107 (70.4)	58 (56.3)	49 (100.0)	**<0.001**
Yes	45 (29.6)	45 (43.7)	0 (0.0)	
Drowsiness				
No	115 (75.7)	67 (65.0)	48 (98.0)	**<0.001**
Yes	37 (24.3)	36 (35.0)	1 (2.0)	
Confusion				
Jo	130 (85.5)	81 (78.6)	49 (100.0)	**<0.001**
Po	22 (14.5)	22 (21.4)	0 (0.0)	

* Absolute number and percentage by columns (in parentheses). Any discrepancy with this number is due to lack of information.
† Value of statistical significance according to Fisher's Exact Test.

Table 5 presents a comparison of data regarding venous pH and/or serum bicarbonates between T1D children with and without DKA. The prevalence of severe, moderate, and mild DKA was significantly higher among T1D children with DKA compared to children without DKA, both in terms of pH level and bicarbonate level.

Table 5: Severity of DKA based on the level of venous pH *and* HCO3 (mmol/L) by type of T1D

Variable	Total	Type of diabetes type 1		Value of P
		T1D with DKA	T1D without DKA	
Severity of DKA based on venous pH				
Severe (<7.1)	17 (32.1) *	17 (38.6)	0 (0.0)	
E moderate (7.1-7.2)	7 (13.2)	7 (15.9)	0 (0.0)	<0.001**
Light (7.21-7.3)	13 (24.5)	13 (29.5)	0 (0.0)	
Normal (7.31-7.5)	7 (30.2)	7 (15.9)	9 (100.0)	
Severity of DKA based on serial HCO3				
Severe (<5)	15 (28.8)	15 (34.9)	0 (0.0)	
Moderate (5-10)	15 (28.8)	15 (34.9)	0 (0.0)	<0.001**
Mild (10.1-15)	18 (34.6)	12 (27.9)	0 (0.0)	
Normal (22-26)	4 (7.7)	1 (2.3)	3 (100.0)	

* Absolute number and percentage by columns (in parentheses).
** Value of statistical significance according to the hi square test.

4. Discussion

The prevalence of diabetic ketoacidosis (DKA) in diabetic children in our study was quite high, at 67.8%. This figure is higher than the levels reported in the international literature. For example, a study among children with T1D aged 1 month to 16 years reported that the prevalence of DKA at the time of diagnosis was 39.8% (41). Another study reported that about one-third of children newly diagnosed with T1D present with DKA at the time of diagnosis, and DKAwas associated with a relatively high mortality rate of 0.3%-0.5% despite aggressive treatment (42). Another study among children with T1D aged 0-12 years in Saudi Arabia reported a prevalence of DKA of 31.4% in children with T1D aged 0-5 years and a prevalence of 15.3% in children with T1D over 5 years (Al-Fifi, 2010). Another study among 650 medical records of children with T1D reported a DKA prevalence of 58.4% of DKA in children newly diagnosed; also, 18.8%, 35.6%, and 45.6% of children was diagnose severe, moderate, and mild DKA [43]. Another study in Poland among children aged 0-14 years followed over a 26-year period from 1987 to 2012, reported a 22.4% DKA prevalence among children diagnosed with T1D (44). A study among 4038 children with T1D in Australia reported that the prevalence of DKA at the time of diagnosis was 37.2%; 26% of these children had mild DKA and 12% had severe DKA (45).

In England during the period 1987-1996 the prevalence of ketoacidosis among children with T1D was estimated at 27%, being about eight times higher among Asian children under the age of 5 compared to non-Asian children of the same age; this large difference was due to the underestimation of the situation in healthcare settings where type 2 diabetes is more prevalent and the delay in referral of cases to the hospital, accompanied by inadequate management of the condition due to misdiagnosis; another explanation included the possibility that Asian children have a faster decompensation compared to non-Asian children (46).

A study in France among children 0-14 years with T1D reported a DKA prevalence of 43.9%; the prevalence of severe DKA was 14.8% and the prevalence of moderate DKA was 29.1% (47), whereas a study in Belgium in children with T1D aged 0-17 years reported a prevalence of DKA of 42% (48).

However, a prospective study among children under the age of 16 diagnosed with T1D during 2009-2018 at a children's hospital in China reported that the prevalence of DKA at the time of hospitalization was 50.1%, of which 36% had mild DKA, 30% moderate DKA and 33.9% severe DKA (49). Another study identified a high prevalence of ketoacidosis among children with T1D diagnosed during the period 1992-2004, at the level of 55.3% at the time of diagnosis (50).

Regarding the severity of DKA, in our study about 29%-32% of diabetic children with DKA had severe DKA, 13%-29% had moderate DKA and 25%-35% had mild DKA (Table 5), finding those that are consistent with the literature reports (43, 47).

Based on our findings, it turns out that the prevalence of DKA in children with T1D in our country remains very high, and higher than reports in the international literature, which range from about 15% to a maximum of 67% (51). This means that children with T1D show up too late at the health care service in Albania, they show up in a worse condition as a result of this delay, which for the most part is related to parental negligence or their ignorance about this disease. This finding is critical and should serve as an alarm for the health care system and public health structures in Albania, in order to take appropriate measures to properly address this issue.

In terms of the clinical picture of children with DKA, the study in China reported that children with DKA were significantly more likely to report vomiting, abdominal pain, and fatigue, compared with children with T1D but without DKA (49). Also, a study among children aged 0-14 years diagnosed with T1D in France, reported that the prevalence of vomiting was only 9.3% in T1D children without DKA, but 33.2% in T1D children with moderate DKA and very high (78.1%) in T1D children with severe DKA (47). These data are similar to our study, where the prevalence of these conditions is increasingly higher among T1D children with DKA compared to T1D children without DKA, and in terms of the prevalence of vomiting and malaise, the differences were statistically significant (vomiting: 24.5% in T1D children with DKA vs.6.1% in T1D children without DKA, P = 0.007; malaise: 93.2% in T1D children with DKA vs.73.5% in T1D children without DKA, P = 0.002).

Regarding the distribution of DKA by age of diabetic children, in the study in Saudi Arabia 35.5% of children with T1D with DKA were 0-4 years old, 31.4% in the age group 5-9 years old and the rest of 33.1% were 10-14 years (50). Another study reported the prevalence of DKA by the age of T1D children: 81.4% among children under 2 years, 53.3% in children 2-4 years, 42.7% in children 5.9 years and 49.3% in children 10-15 years (49). A study in Belgium reported that 24.3% of T1D children with DKA were 0-3 years old, 12.2% were 4-5 years old, 31.1% were 6-10 years old and 32.4% were> 10 years old (48). Similar results were evident in our study: 24.3%, 41.7% and 34%, respectively. In general, the prevalence of DKA in persons with T1D decreases with age (52). In our study we did not find statistically significant age differences between T1D children with and without DKA (P = 0.082), whereas the study in Belgium suggested that the proportion of children 0-5 years is significantly higher in children with DKA than in those without DKA (48).

In our study we found that the prevalence of DKA was higher among girls (76.7%) than among boys (59.5%) and this difference was statistically significant (P = 0.025). The higher prevalence of DKA among girls with T1D than among boys with T1D is also reported in the international literature. For example, a large U. S. retrospective cohort study involving data from more than 263 million American patients from 50 U. S. states since 1995 identified all cases of T1D of all ages for the period 1 January 2007 to 31 December 2019, enabling, inter alia, the calculation of the incidence of DKA in these patients; according to this study, the incidence of DKA during this period resulted in 48.6

cases per 1000 person-years in men and 62.9 cases per 1000 person-years in women (53). In the study among 311 children with T1D, the prevalence of DKA was significantly higher among girls than among boys (50), a finding that is consistent with the findings of our study where the prevalence of DKA also resulted significantly higher in girls than in boys. A systematic review of the literature, recently published (in 2017), also reported that the prevalence of DKA is higher among women than among men, and more specifically in women the prevalence of DKA was 55 cases per 1000 person-years whereas in men it was 40 cases per 1000 person-years (52), similar to the findings of our study. Another study also reported that the risk of diabetic ketoacidosis (DKA) is about 1.5 times higher among adolescent girls than among boys; a hypothesis links this finding to issues of body image of these girls pushing them to bypass insulin injections as a way to promote weight loss (54).

However, there are also studies that have not found any gender difference in DKA in children with T1D (48, 55).

In our study we did not find statistically significant age differences between T1D children with and without DKA regarding the average mean values of HbA1c, TSH, FT4, ac. anti TPO, ac. anti-Thyroglobulin, ac anti tissue transglutaminase IgA and IgG at diagnosis and during monitoring at different time points.

Given the above information, then awareness campaigns should involve both families and health care professionals, so that both parties are able to detect the signs and symptoms of the disease early as well as act quickly with their early onset. Awareness campaigns of course need to be carefully evaluated as to what might be detrimental to their success. Here we can refer to studies that suggest that for the management of DKA are also important various socio-economic and factors related to clinical management of diseases, as we identified earlier during the scientific work; and exactly these factors could be targeted by different interventions to enable the reduction of poor glycemic control of these patients, based on the relevant scientific evidence.

5. Study Limitation

This is a prospective study including 152 patients diagnosed with T1D from January 1, 2010 to December 31, 2014. A longer period of this study would have a large number of patients and the results would be more representative.

6. Conclusion

This is the first study to report the incidence of DKA as a presentation of newly diagnosed T1DM among Albanian children. The mean age of children with DKA was lower and girls were found to have higher rates of ketoacidosis. The incidence is higher compared to the countries of the region. Delayed diagnosis and mismanagement are responsible for this high prevalence, the more severe presentation, especially in young children and girls. Prevention campaigns are needed to raise the awareness of healthcare providers, parents and the general public to improve early diagnosis and treatment of T1D.

Conflict of interest: All authors declare that they no conflict of interest.

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