

Ketoacidosis at diabetes onset is still frequent in children and adolescents: a multicentre analysis of 14,664 patients from 106 institutions

Andreas Neu MD¹, Sabine E. Hofer MD², Beate Karges MD³, Rudolf Oeverink MD⁴, Joachim Rosenbauer MD⁵, Reinhard W. Holl MD⁶
for the DPV initiative and the German BMBF Competency Network for Diabetes Mellitus*

*A full list of participating institutions is available in an online appendix at
<http://care.diabetesjournals.org>

Short running title: DKA at onset in children and adolescents

¹ University Children's Hospital, Tübingen, Germany

² Dept. of Pediatrics, Medical University of Innsbruck, Austria

³ RWTH Aachen University, Dept. of Endocrinology and Pediatrics, Germany

⁴ Endocrine Consulting Practitioner, Oldenburg, Germany

⁵ Deutsches Diabetes Zentrum, Düsseldorf University, Germany

⁶ University of Ulm, Dept. of Epidemiology, Ulm, Germany

Corresponding author:

PD Dr. Andreas Neu

Email: andreas.neu@med.uni-tuebingen.de

Submitted 20 March 2009 and accepted 16 June 2009.

This is an uncopyedited electronic version of an article accepted for publication in *Diabetes Care*. The American Diabetes Association, publisher of *Diabetes Care*, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of *Diabetes Care* in print and online at <http://care.diabetesjournals.org>.

Objective: We aimed at analyzing the frequency, clinical characteristics, and trends associated with the occurrence of ketoacidosis at the onset of type 1 diabetes mellitus on the basis of long-term follow-up data.

Research design and methods: A total of 106 paediatric diabetes centres in Germany and Austria participated in this study. Data of 14,664 patients with type 1 diabetes collected between 1995 and 2007 were suitable for evaluation. Ketoacidosis (DKA) was defined and classified according to the ISPAD consensus guidelines.

Results: DKA was observed in 21.1% of patients. The frequency of DKA, including the severe form, remained unchanged throughout the 13 years' observation period. The frequency of DKA was particularly striking among children < 5 years of age (26.5%).

Conclusions: Ketoacidosis occurring at diabetes onset continues to be a difficult problem. Our data show no significant change in the frequency and magnitude of DKA over the last 13 years.

Given that the incidence of type 1 diabetes is rising, and the awareness for this disease is thus broadening, it is probably reasonable to expect a drop in the occurrence of DKA at the onset of diabetes.

By means of a computerized follow-up programme for diabetic children (DPV) we aimed at analyzing the frequency and clinical characteristics of DKA occurring at the time of diabetes onset in order to ascertain whether a change in the frequency of DKA at onset was discernible over the last 13 years.

RESEARCH DESIGN AND METHODS

Data collection: The collection of data was carried out in 106 paediatric diabetes centres in Germany and Austria by means of the diabetes software for prospective documentation DPV (Diabetes Patienten Verlaufsdokumentation). In this report we present an analysis of the incidence rate pertaining to the 13-year period beginning in January 1995 and ending in December 2007.

Patients: The data of 14,664 type 1 diabetics with an average age of 9.0 years (range 0-17.9 years) were found suitable for analysis. Of these, 53.1% (n=7,787) were male and 46.9% (n=6,877) female. For the analysis, we extracted the data of all patients at diabetes onset who were treated at a paediatric diabetes centre at which pH measurement could be done and critical care was available.

Definition of DKA: In our study, a pH value of < 7.3 was the biochemical criterium we chose for defining ketoacidosis. This was based on the ISPAD consensus guidelines, which we also followed for classifying the severity of ketoacidosis: thus mild DKA was $7.2 \leq \text{pH} < 7.3$; moderate DKA, $7.1 \leq \text{pH} < 7.2$; severe DKA, $\text{pH} < 7.1$ [1].

Statistical analysis: We used the software package SAS 9.1 for the evaluation of data and for the statistical analysis. A p value of < 0.05 was considered to be

significant. The individual values are given as means (\pm SEM) unless otherwise indicated.

The analysis of the frequency of ketoacidosis was done without adjusting for age or gender.

RESULTS

Frequency of DKA: Our findings showed that 21.1% of the 14,664 patients had pH values of < 7.3 at the onset of type 1 diabetes, and that the remaining 78.9% did not have ketoacidosis. 1,430 patients (9.8%) showed mild, 788 (5.4%) moderate and 873 (5.9%) severe ketoacidosis.

In analyzing the frequency of ketoacidosis over a span of 13 years, we did not find a statistically significant time trend ($p > 0.163$); thus, we concluded that the frequency of DKA remained consistent throughout this period (Figure 1). Likewise, we found no evidence for a noticeable shift within the individual groups since the percentage of cases with severe acidosis also remained consistent over time ($p > 0.486$).

Characteristics of patients: The average age at the time of diabetes onset was as follows: patients without ketoacidosis, 9.2 (± 4.1) years; patients with a mild form of ketoacidosis, 8.7 (± 4.5) years; those with severe ketoacidosis, 8.4 (± 4.5) years. Although the age differences are highly significant ($p < 0.001$), they have no clinical relevance. In the total cohort there were more boys (53.1%) than girls (46.9%); however, the proportion of girls was slightly higher in the sub-groups with ketoacidosis: mild ketoacidosis, 50.9% boys vs. 49.1% girls; severe ketoacidosis, 49.4% boys vs. 50.6% girls.

The highest frequency of ketoacidosis (26.5%) was found in children ≤ 5 years of age ($p < 0.001$ vs. other age groups), followed by the 10-15 year-olds (22.0%).

CONCLUSIONS

We present the results of a representative analysis based on the DPV

documentation system by means of which broad data were collected: this involved the participation of 106 paediatric diabetes centres, 14,664 documented patients and a period of observation that exceeded 10 years.

Our findings revealed a high frequency (21.1%) of ketoacidosis at diabetes onset, which, however, is comparable to the results of previous analyses of the data from the DPV network [2]. The comparative frequency between Europe and North America varies between 15 and 70% [1]. In a multicentre study in the US, which comprises a large collective of patients (n = 3,666), the reported frequency of ketoacidosis at diabetes onset was 29.4%, this being somewhat higher than the frequency in Germany [3]. For the timespan of our study, there was a marked increase in the incidence of diabetes in Germany: whereas in 1995 it was at 14.5 (95% CI 13.1-16.8), in 2006 it had reached 21.1/10,0000 (95% CI 18.9-23.3). This corresponds to a mean increase of 4.4% per year [4, 5]. However, the percentage of patients with ketoacidosis at diabetes onset remained relatively consistent during the period of observation. Similar results were found for an analysis of data collected in Germany between 1987 and 1997 [6], which were also corroborated by the SEARCH study in the USA [3].

Studies in other countries [7] have shown that it is possible to achieve a marked decrease in the frequency of ketoacidosis through focussed educational campaigns. The results of the present study, however, indicate that the rate of occurrence of ketoacidosis has remained consistent over two decades despite the rising incidence of the disease and the broadening awareness. The proportion of severe cases of ketoacidosis is high, at 6% of the total group of patients with type 1 diabetes onset. These findings demonstrate that it is imperative for every case of diabetes onset to be regarded as an emergency.

The present study shows that, even in the 21st century, DKA at diabetes onset occurs with a regularity in a percentage of patients that is not at all insignificant. Reinforced efforts aimed at educating the general public, on the one hand, and at practicing physicians, on the other, are imperative if the situation is to improve.

ACKNOWLEDGEMENTS

We appreciate the funding support extended to the DPV system by the following institutions: Bundesministerium für Bildung und Forschung (BMBF), European Foundation for the Study of Diabetes (EFSD), Bundesärztekammer (BÄK), NovoNordisk Pharma GmbH.

REFERENCES

1. Wolfsdorf J, Craig ME, Daneman D, Dunger D, Edge J, Lee WRW, Rosenbloom A, Sperling MA, Hanas R. ISPAD Clinical Practice Consensus Guidelines 2006–2007: Diabetic ketoacidosis. *Pediatr Diab* 2007; 8: 28-42.
2. Kintzel K, Holl W, Haberland H, Grabert M, Dost A. Die diabetische Ketoazidose (DKA) bei Erkrankungsbeginn im Kindes- und Jugendalter in der Bundesrepublik. *Diab Stoffw* 2003; 12: 8-12.
3. Rewers A, Klingensmith G, Davis C, Petitti DB, Pihoker C, Rodriguez B, Schwartz ID, Imperatore G, Williams D, Dolan LM, Dabelea D. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: The search for diabetes in youth study. *Pediatrics* 2008; 121: e1258-e1266.
4. Eehalt S, Blumenstock G, Willasch AM, Hub R, Ranke MB, Neu A, for the DIARY study Group Baden-Württemberg. Continuous rise in incidence of childhood type 1 diabetes in Germany. *Diabet Med* 2008; 25: 755-757.
5. Neu A, Eehalt S, Feldhahn LM, Kehrer M, Willasch AM, Hub R, Ranke MB für die DIARY Group Baden-Württemberg: Diabeteshäufigkeit bei Kindern und Jugendlichen in Deutschland - 20 Jahre Diabetes-Inzidenzregister Baden-Württemberg. *Diabetologie* 2008; 3: 309-313.
6. Neu A, Willasch A, Eehalt S, Hub R, Ranke MB on behalf of the DIARY group Baden-Wuerttemberg: Ketoacidosis at onset of type 1 diabetes mellitus in children – frequency and clinical presentation. *Pediatric Diabetes* 2003; 4: 77-81.
7. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of prevention program for diabetic ketoacidosis in children. *Diab Care* 1999; 22:7-9.

Figure 1: Frequency of ketoacidosis according to years

