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Geographical variation of presentation at diagnosis of Type I diabetes in children: the EURODIAB Study

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Abstract

Aims/hypothesis. We aimed to describe the frequency and degree of diabetic ketoacidosis in children across Europe at the time of diagnosis of Type I (insulin-dependent) diabetes mellitus and to determine if factors such as age and geographical region contribute to the risk of diabetic ketoacidosis.
Methods. The study was part of the EURODIAB project. A total of 24 centres, covering a population at risk of more than 15 million children below 15 years of age, recruited 1260 children at the time of clinical diagnosis.
Results. Polyuria, by far the most frequent symptom, was observed in 96 % of the children. In only 25 % of the children was the duration of symptoms less than 2 weeks and this proportion was larger in the under 5 year age-group (37 vs 22 %; $p < 0.001$). Of the 11 centres that recorded diabetic ketoacidosis status, the overall proportion with diabetic ketoacidosis (pH < 7.3) was 40 % (95 %-CI: 36–44 %) in at least 90 % of cases. After stratification by centre, the odds ratio for diabetic ketoacidosis in the under 5 age-group was 1.02 (95 %-CI: 0.69–1.49) relative to the older children. There was significant variation between the 11 centres in the frequency of diabetic ketoacidosis which ranged from 26 to 67 % ($p = 0.002$). An inverse correlation between the frequency of diabetic ketoacidosis and the background incidence rate was found in these centres (Spearman's rank correlation, $r_s = -0.715$; $p = 0.012$).
Conclusion/interpretation. Rising standards of medical information and greater awareness concurrent with an overall increase in incidence could have resulted in changes in the clinical presentation at onset of Type I childhood diabetes in Europe. [Diabetologia (2001) 44 [Suppl 3]: B 75–B 80]

Keywords Type I diabetes, incidence, presentation, ketoacidosis, childhood, pH.

Type I (insulin-dependent) diabetes mellitus in childhood results from the chronic autoimmune destruction of the pancreatic beta cells and leads to a pronounced reduction in capacity for insulin secretion at the time of clinical manifestation [1]. The clinical onset of the disease is acute in most cases. Diabetic ketoacidosis (DKA) is commonly found at onset although the frequency varies threefold over time in different settings. A valid comparison is difficult to make because there is no standardized definition for DKA [2–7]. Clinical presentation has been said to have changed over the 1980s to a less severe picture [8, 9]. However, DKA is an important cause of death and morbidity in children, mostly due to cerebral oedema in the course of resuscitation [9–11].

Incidence of the disease in children varies widely across Europe [12]. Several reports from registries included in the EURODIAB network suggest that incidence rates in children have been rising for the last two decades [13–25]. There is no indication so far that the different levels of risk are associated with different patterns of clinical presentation at onset. It is still not known if the risk of disease in the background population is associated with the severity of it at pre-

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Abbreviations: DKA, Diabetic ketoacidosis.

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Table 1. Characteristics of the EURODIAB study centres

Centre	Geographical area	Population at risk	Incidence rate per 100000 from 1989–1995	Estimate of completeness of ascertainment (%)	Total patients registered in year of study	Number of patients recruited for the study
A1	Austria	1 382 514	9.4	100	158	140
C1	Hungary (18 counties)	1 441 485	9.4	100	142	128
E1	Iceland	64 589	13.9	100	10	10
F1	France (four regions)	1 647 218	8.9	99	149	139
H1	The Netherlands (five regions)	554 474	12.5	96	61	53
I2	Italy (Lazio region)	785 619	8.7	100	72	54
I3	Italy (Sardinia)	284 223	37.8	85	78	76
I4	Italy (Eastern Sicily)	220 551	11.6	98	23	23
J1	Israel	1 502 079	5.86	71	70	
K1	Lithuania	816 636	7.6	100	62	58
K2	Latvia	538 560	7.1	100	28	28
K3	Estonia	314 018	11.1	100	38	39
L1	Luxembourg	71 746	11.9	100	11	9
M1	Germany (Düsseldorf region)	397 738	13.2	93	47	46
P1	Portugal (Madeira island)	57 143	6.7	100	3	3
P3	Portugal (Algarve region)	59 195	15.9	85	8	8
Q1	Bulgaria (western part)	484 047	9.9	100	44	44
R1	Romania (Bucharest region)	432 678	4.8	100	22	21
U1	United Kingdom (Northern Ireland)	391 258	22.2	99	77	77
U3	United Kingdom (Leicestershire)	181 762	17.1	98	31	28
W1	Poland (eight regions)	1 297 378	7.0	100	94	59
W2	Poland (three cities)	786 364	6.6	100	17	17
Y1	Slovenia	373 793	8.5	100	21	21
Z1	Slovak republic	1 238 470	9.2	100	120	109

Incidence rates are calculated per 100 000 children below the age of 15 years and per year
[a] Data is for whole countries unless stated otherwise

sentation. With the exception of some reports identifying a young age at onset, risk factors for DKA are not known [1, 10, 26, 27].

The EURODIAB network is an epidemiological resource which was established in 1989 with the aim of characterizing more comprehensively the epidemiology and determinants of childhood Type I diabetes across Europe. The first phase aimed to confirm the wide variation in incidence rates across Europe using prospective registration of new cases according to uniform methodology. The highest rates were recorded in Finland, Norway and Denmark, and the lowest in Greece and Romania [28].

This study, part of the EURODIAB project, aimed to describe the severity of the disease at onset throughout Europe based on the frequency and the degree of DKA at the time of diagnosis and to determine if factors such as age and incidence contributed to the risk of DKA.

Methods and materials

Study centres. Altogether 24 EURODIAB centres participated in this study (Table 1) covering a population at risk of over 15 million children under 15 years of age.

Definition of the cases. All children included in the survey were part of the basic incidence surveillance cohort gathered through a prospective and uniform protocol described previously in detail [28]. To maintain the high degree of completeness observed in the previous EURODIAB reports, the study centres aimed to recruit at least 80% of the cases included in the basic incidence surveillance to fulfill the study eligibility criteria. All but 2 of the 24 local study centres met these criteria. Consecutive cases over one full calendar year were examined by each centre, the starting date varying from centre to centre between 1 January 1989 and 1 January 1994.

Validation of ascertainment. The incidence surveillance protocol required that each centre use two independent sources of case identification. Completeness of ascertainment was estimated using the capture-recapture method [29]. The degree of completeness is given for each centre for the study period in Table 1.

Data collection. Data was collected using a standardized questionnaire specifically developed for the study during workshops with representatives of the study centres.

Clinical and biological data was based on characteristics recorded routinely at the time of diagnosis and obtained from the hospital or medical records. The local investigators filled in the questionnaires following the common guidelines supplied to all centres. Questionnaire data was reviewed, entered and analysed at the coordinating centre (INSERM U457, Paris, France).

Characteristics covered the clinical and biological pictures at the time of the first insulin treatment.

The clinical symptoms at entry were determined using a list agreed by the coordinating study group for which the type of symptoms that precipitated the visit to the doctor were assessed with a "yes/no" tick.

The duration of symptoms, the level of consciousness at the first medical examination (classified into three categories of normal, altered consciousness and coma) and the weight loss, expressed as a percentage of body weight, were also assessed.

Table 2. Symptoms before diagnosis among 1260 children with Type I diabetes

	Symptom noted *n* (%)	First symptom *n* (%)
Polyuria	1159 (96)	854 (71)
Weight loss	731 (61)	104 (9)
Fatigue	630 (52)	82 (7)
Abdominal pain	277 (23)	31 (3)
Changes in consciousness	137 (11)	22 (2)
Others	238 (19)	36 (3)
No symptom/unspecified	16 (1)	78 (6)
No information	53	53

Table 3. Characteristics at the time of diagnosis of Type I diabetes in children below 15 years of age

Biological characteristic	*n*	Median (10^{th}–90^{th} centiles)
Plasma glucose	1260	21.8 (13.0–37.7)
pH	1037	7.33 (7.12–7.42)
Osmolarity[a]	1128	430.2 (411.5–451.6)
Ketonuria	1199	970 (81 %)

[a] Osmolarity was assessed as the sum of plasma glucose + 2xNa

The biological characteristics measured at entry were the plasma glucose, ketonuria assessed by urine strips, pH, Na, urea.

As for definitions, osmolarity was calculated as plasma glucose + 2 · Na.

Classification of DKA was based on the pH value, with mild DKA defined as pH < 7.3 and severe DKA as pH < 7.1.

Statistical analyses. All comparisons were stratified by the centre using either the Mantel-Haenszel method for categorical variables or multiple regression incorporating centre effects for quantitative variables.

The association between DKA and the background incidence was assessed using Spearman's rank correlation coefficient.

Data was analysed using the SPSS and SAS statistical software packages. A p value of less than 0.05 was considered to be statistically significant.

Results

Subjects. In total, 1 260 children below 15 years of age at the time of diagnosis were recruited into the study by the 24 centres. Recruitment rates and characteristics of the centres are given in Table 1. Children included in the study represented 91 % of the total number of children included in the incidence surveillance study over the same calendar period.

Presentation at diagnosis. Clinical symptoms at the time of diagnosis are given in Table 2. Polyuria was by far the most frequent symptom observed in 96 % of the children at the time of clinical diagnosis. Abdominal pain was seen in 23 % of the children.

Table 4. Description of the patients diagnosed with severe DKA (pH < 7.1; n = 100)

Clinical characteristic[a]	
Age (year) means ± SD	8.25 ± 4.17
Duration of symptoms < 2 weeks	25 %
Delay before diagnosis ≤ 1 day	76 %
Delay before treatment < 1 day	95 %
Weight loss (% body weight) means ± SD	–5.02 ± 5.44
Altered consciousness or coma	60 %
Coma	16 %
Plasma glucose (mmol/l) means ± SD	29.78 ± 11.40
Ketonuria	89 %
Osmolarity (mmol/l) means ± SD	437 ± 30
Hospitalization	89 %
IV treatment	87 %

[a] means ± SD are indicated unless otherwise stated

The most frequent cluster of symptoms at diagnosis was polyuria, fatigue and weight loss. The most common first symptoms to be noticed by the family were polyuria (71 %), weight loss (9 %) and fatigue (7 %).

In only 25 % of the children was the duration of symptoms shorter than 2 weeks and this proportion was larger in the younger children (37 % in 0 to 4 year-old age group vs 22 % in older age groups; Mantel Haenszel $\chi^2 = 21.4$, $df = 1$; $p < 0.001$). In 76 % of the children the delay between the first visit and diagnosis was less than 2 days, with no statistical difference evident between age groups (Mantel Haenszel $\chi^2 = 0.00$, $df = 1$; $p = 0.96$). A simultaneous febrile illness was noted in 20 % of the cases and was more frequently observed in the young (25 % in 0 to 4 year-old age group vs 18 % in older age groups; Mantel Haenszel $\chi^2 = 7.30$, $df = 1$; $p = 0.007$).

Altogether, 23 children (2 %) were in coma and a further 14 % presented with altered consciousness at the time of diagnosis. As many as 89 % of the children were admitted to hospital for initial treatment and this treatment was initiated on the day of diagnosis in 91 % of the cases.

Diabetic ketoacidosis. Biological characteristics measured at diagnosis are indicated in Table 3.

Overall 82 % of the patients had pH data recorded and the proportion of DKA (pH < 7.3) among these patients was 42 % (95 %-CI: 39–46 %). When DKA was further subdivided into mild DKA (7.1 < pH < 7.3) and severe DKA (pH < 7.1), the proportions were 33 and 9 %, respectively. In at least 90 % of the patients a slightly lower figure of 40 % (95 %-CI: 36–44 %) was obtained when the frequency of DKA (pH < 7.3) was calculated in the 11 centres that recorded DKA status.

The data of patients with severe DKA is given in Table 4. Comparisons of the characteristics of patients with DKA (pH < 7.3) and those without are shown in Table 5.

Table 5. Comparisons of the presentation at diagnosis between children with or without DKA (pH < 7.3)

Clinical characteristics[a]	No DKA (n = 595)	DKA (n = 440)	p value[b]
Age (year) means ± SD	8.67 ± 3.78	8.34 ± 4.00	0.18
Duration of symptoms < 2week (%)	24.2	24.8	0.80
Delay before diagnosis ≤ 1 day (%)	76.9	76.7	0.63
Delay before treatment < 1 day (%)	89.4	93.6	0.047
Weight loss (% body weight) means ± SD	3.32 ± 3.53	4.84 ± 3.87	< 0.001
Altered consciousness or coma (%)	7.6	31.4	< 0.001
Coma (%)	0.7	4.7	< 0.001
Plasma glucose (mmol/l) means ± SD	23.2 ± 10.8	26.4 ± 10.5	< 0.001
Ketonuria (%)	78.3	88.8	< 0.001
Osmolarity (mmol/l) means ± SD	431 ± 16	432 ± 24	0.16
Hospitalization (%)	92.0	89.5	0.41
IV treatment (%)	46.6	77.1	< 0.001

[a] means ± SD are indicated unless stated otherwise
[b] All comparisons are stratified by centre

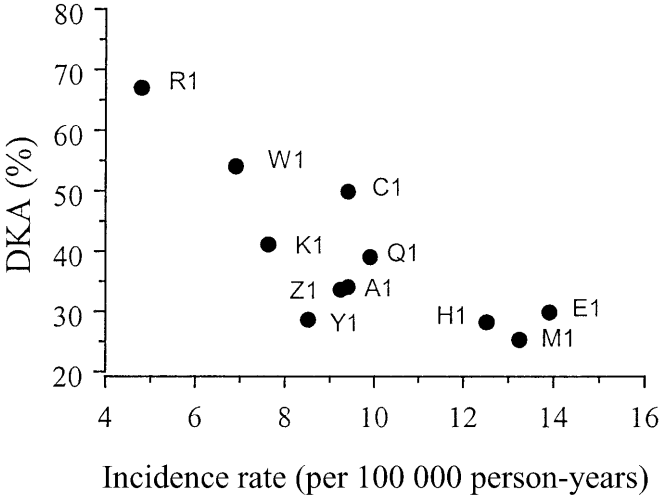

Fig. 1. Correlation between the proportion of DKA at diagnosis and the background incidence rates for 11 centres where DKA data collection was 90% complete. For key see Table 1

The proportion of patients with DKA ranged from 11 to 67% across centres. The proportion of patients with DKA varied between the 11 centres which had the most complete data, from 26 to 67% (p = 0.002). There was a inverse correlation between the proportion of DKA and the background Type I incidence rate for these centres (r_s = –0.715; p = 0.012) (Fig. 1).

There was no evidence of differences in DKA frequency according to gender (data not shown). After stratification across 11 centres, the Mantel Haenszel estimate of the odds on DKA for the under-5 age-group relative to the rest was 1.02 (95% CI = 0.69–1.49).

Discussion

The EURODIAB network has confirmed large variations in the incidence rates of Type I diabetes in children across Europe [28]. The same network has also established age-group differences in incidence rate by geographical region [4]. This study shows that no differences in the proportion of children presenting with ketoacidosis could be observed between age groups but that differences existed between geographical regions with higher rates of diabetic ketoacidosis found in regions with lower incidence rates. The proportion of children with DKA at diagnosis was 40% of the whole study population. When the calculation was restricted to the centres where completeness of data was 90% or more, this proportion rose to 42%. The large variation in the rate of DKA at diagnosis is in keeping with results previously published in different countries [2, 3, 5–7, 30]. Although this study was based on a uniform and prospective protocol and on a population base larger than in any previous survey, we found only a slightly lower range of variation for DKA across the centres compared with previously published literature. Given that the rate of DKA did not change much for complete or incomplete data, it is not likely that the completeness of data explains the large variability in the proportion of DKA across centres.

Death was not registered in this study. It is plausible that the children who die at onset of the disease have ketoacidosis, in which case the proportion of patients with DKA has been underestimated in our study. It is also probable that deaths are more common in poorer countries. Therefore the magnitude of variation in the proportion of children with DKA could actually be larger than the one we have reported but it is not likely that the small number of deaths missing from our series could introduce much bias in our conclusions.

Collection of data was based on a prospective protocol and information routinely recorded during the initial care of the diabetic children. Children were therefore observed at different times of the day. This could partly explain why 7.6% of the children with no biological DKA were reported to have had chan-

ges in consciousness. It is also well known that clinical condition can fluctuate very rapidly in children.

An inverse relation was found between incidence rates and proportions of children with DKA. This analysis was restricted to the centres where completeness of data was 90 % or more. This 90 % figure was chosen arbitrarly as a compromise to minimize a possible bias while retaining a larger number of centres in the analysis. Primary care organization and the care of diabetic children does vary across countries. The frequency of DKA might be lower in countries with a more prosperous lifestyle and with a more organized and efficient health care system. The most recent data produced by our network suggest that indicators of wealth are strongly associated with incidence rates across Europe [31, 32]. The inverse relation between incidence rates and proportions of children with ketoacidosis is consistent with a high level of medical awareness which increases the chances of early diagnosis and consequently reduces the risk of ketoacidosis. Our observation supports the hypothesis that the proportion of DKA is partly, and inversely, related to health-care standards.

The clinical presentation at diagnosis of Type I is more sudden and severe in children under 5 years of age [2, 5–7, 27, 33]. In contrast with previous studies from single centres, our data does not show a sharp increase in the risk of DKA in the young. This probably cannot be explained by a drastic change in the overall picture of presentation at onset because the average proportion of DKA is 42 % in our study. A minimal delay was observed in the initiation of treatment, and the interval between the first visit and initial treatment was not affected by age. These observations suggest that the medical awareness of childhood Type I diabetes has increased in Europe leading to more rapid and efficient initial care.

Our data shows the geographical variation in the risk of DKA at the onset of Type I diabetes in children. Our results also point towards increased medical awareness in Europe so that the risk of DKA in the most sensitive patients, such as very young children, is reduced even though DKA at diagnosis remains common. Standards of medical information and greater awareness, which have been rising parallel with incidence, could have induced changes in the clinical presentation at onset of Type I childhood diabetes in Europe.

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