Ketoacidosis at diagnosis of type 1 diabetes in French children and adolescents

C. Choleau a,∗, J. Maitre a, b, A. Filipovic Pierucci c, C. Elie c, P. Barat d, A.-M. Bertrand e, M. de Kerdanet f, C. Letallec g, C. Levy-Marchal h, M. Nicolino i, N. Tubiana-Rufi j, M. Cahané a, J.-J. Robert a, b, the AJD Study Group

Abstract

Objectives. – This study aimed to evaluate the frequency of diabetic ketoacidosis (DKA) and its associated factors at the diagnosis of type 1 diabetes (T1D) in French children and adolescents prior to launching a public-health campaign of information to prevent DKA.

Patients and methods. – Over a 1-year period, 1299 youngsters (aged <15 years) were diagnosed with T1D at 146 paediatric centres in all regions of France. Age, gender, duration of symptoms, patient’s pathway to diagnosis, clinical and biological signs, and family history of T1D were collected for each newly diagnosed patient. DKA was defined as pH < 7.30 or bicarbonate < 15 mmol/L, and severe DKA as pH < 7.10 or bicarbonate < 5 mmol/L.

Results. – At the time of diagnosis, 26% of the children were aged 0–5 years, 34% were 5–10 years and 40% were 10–15 years. The overall prevalence of DKA was 43.9% (0–5 years: 54.2%; 5–10 years: 43.4%; and 10–15 years: 37.1%) and 14.8% for severe DKA (0–5 years: 16.6%; 5–10 years: 14.4%; and 10–15 years: 13.9%; < 2 years: 25.3%). Severe DKA was more frequent when the child was hospitalized at the family’s behest (26.6%) than when referred by a general practitioner (7.6%) or paediatrician (5.1%; 30.6%, 53.7% and 9.2%, respectively, by patients’ age group). The frequency of DKA decreased to 20.1% (severe DKA: 4.4%) in families with a history of T1D. Multivariate analysis showed that age, pathway to diagnosis, duration of polyuria/polydipsia (< 1 week) and family history of T1D were associated with the presence of DKA, while pathway to diagnosis and family history of T1D were associated with severe DKA.

Conclusion. – DKA at the time of T1D diagnosis in children and adolescents is frequent and often severe. Patients’ age, pathway to hospitalization and family history of diabetes were the main factors associated with DKA. These data suggest that a public-health campaign to prevent DKA at diagnosis can help reduce the frequency of DKA and also provide baseline data for evaluating the efficacy of such a campaign.

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Keywords: Ketoacidosis; Type 1 diabetes; Diagnosis; Public-health campaign

1. Introduction

The incidence of type 1 diabetes (T1D) is steadily increasing in children and adolescents by 3–4% annually in those 0–15 years of age [1–3], and is growing approximately twice as fast in children aged <5 years [4,5]. The symptoms of diabetes often develop acutely in children and adolescents, especially in
the youngest ones. The clinical condition can deteriorate rapidly, and diabetic ketoacidosis (DKA) is a common complication at the time of diagnosis [6–8]. The prevalence of DKA varies widely in different countries (15–67%) [9–22]; it has also been reported that DKA at diagnosis is less frequent when there is greater awareness, and when the disease is more common and better known [19]. In France, a study from about 20 years ago showed that the prevalence of DKA at diagnosis was > 40% [21].

DKA at diagnosis has a major impact in terms of morbidity and even mortality. In France [21], severe DKA represents a life-threatening risk and may require hospitalization in an intensive care unit (ICU), as described in around 10% of new cases, while five to six young people are expected to die of it every year [22], which is particularly intolerable as it can be avoided. Indeed, a campaign directed at health professionals and families launched in the Italian province of Parma lowered the prevalence of DKA from 78 to 12.5%, and has had long-lasting effects [23,24]. For this reason, the association L’Aide aux jeunes diabétiques (AJD ; help for young diabetics) has decided to launch a national campaign for the prevention of DKA at the time of T1D diagnosis. The campaign’s objective is to inform families and their doctors of the symptoms to look out for and that a quick diagnosis can shorten the time lag between the onset of symptoms and initiation of insulin treatment, thereby reducing the risk of DKA.

To evaluate the impact of the campaign, paediatric centres across France were invited to participate in a survey to prospectively determine the prevalence of DKA at diagnosis. The collection of data started a year before launching the campaign to establish current baseline rates on the frequency of DKA at diagnosis to allow for later evaluation of the impact of the campaign, and to identify any factors that might inform the best design for such a campaign. The present report is of the results on the frequency of DKA and its associated factors observed at centres participating in the French survey during the year prior to the campaign.

2. Patients and methods

Between June and November 2009, all metropolitan paediatric centres in France were invited to participate in the evaluation and follow-up study of the prevalence of DKA at diagnosis of T1D. Out of 230 paediatric centres in 22 metropolitan regions, 146 agreed to participate, representing 63% of all centres (33–83% depending on the region), 19% of which were university hospitals. Hospitals had the use of an ICU in 46% of cases. Healthcare providers at each participating centre volunteered to complete an anonymous information sheet for each new patient hospitalized in paediatrics departments with a diagnosis of T1D, starting from 14 November 2009 (November 14 is World Diabetes Day).

The information survey sheet was developed by the AJD scientific and educational committees to collect the following data: date of birth; date of first insulin injection; gender; zip code of residence; duration of symptoms (polyuria/polydipsia, enuresis); pathway to hospitalization (number of days between first medical consultation and first insulin injection, person referring the patient to hospital, department of initial hospitalization; clinical (weight loss, nausea/vomiting, dehydration, polyphagia, coma) and metabolic (blood glucose, ketonaemia/ketonuria, pH, bicarbonate, Hba1c) symptoms at admission; initial treatment (intravenous insulin); and family history of T1D (siblings, parents, grandparents). These data were transmitted via the Internet or fax and entered into the AJD database. Consistency and quality controls were regularly performed and quarterly email contacts were established with the participating centres to check on the accuracy and completeness of the data, and to offer regular feedback on the progress of the evaluation. The diagnosis of T1D was based on clinical criteria, but could later be corrected on request by the centre or AJD if justified (for example, in cases of excess weight or absence of autoantibodies). DKA was defined as per International Society for Pediatric and Adolescent Diabetes (ISPAD) recommendations: pH < 7.30 or bicarbonate < 15 mmol/L; severe DKA pH < 7.10 or bicarbonate < 5 mmol/L [6]. In cases of missing data, classification was based on the available data.

3. Statistical analyses

Data for patients aged < 15 years were included in the analyses. Categorical data were expressed as numbers and percentages, with continuous quantitative data as means ± standard deviation (SD). Comparisons were performed across three groups (no DKA, moderate DKA and severe DKA) by univariate analysis, using analysis of variance (ANOVA) for quantitative variables and chi-square test for categorical variables. Variables significantly associated with the presence of DKA or severe DKA were then selected for multivariate analysis using two logistic-regression models, one for the presence of DKA independent of its severity, the other for the presence of severe DKA. P values < 0.05 were considered statistically significant. All analyses were performed using R software (R Development Core Team (2010). R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org).

4. Results

During the year of data collection, 146 paediatric centres provided information on 1322 patients aged < 15 years: 46.6% of the centres had five new patients or less, while 28.1% had six to 10, 13.7% had 11–20, 6.8% had 21–30, 2.7% had 31–50 and 2.1% had 51–70 new patients. However, 23 patients were not included in the analyses because of missing pH and bicarbonate data. Thus, the analyses included 1299 patients (48% girls and 52% boys). The number of new cases per month varied from 65 in June to 140 in January. Mean age at diagnosis was 8.2 ± 4.0 years, while 26.4% were aged 0–5 years (6.1% < 2 years), 35.3% were 5–10 years and 38.3% were 10–15 years. T1D was reported in 4.8% of siblings, 6.1% of parents and 5.1% of grandparents, yielding a total of 14.5% of families affected (with several cases of T1D in 20 families).

More than half the patients (53.7%) were referred to hospital by a general practitioner, 9.2% by a paediatrician, 6.5% by another hospital and 30.6% by their families directly.
Polyuria and polydipsia were reported in 97.1% of cases. These symptoms lasted $>2$ weeks in 55.6% of cases, and between 1 week and 1 month in the majority of patients (65.5% in those 0–5 years old, 65.3% in those 5–10 years old and 55.7% in those 10–15 years old). However, symptoms more often lasted <1 week in younger children (0–5 years: 17.1%; 5–10 years: 11.3%; and 10–15 years: 8.5%; $P < 0.001$) and $>1–2$ months in older ones (Fig. 1). Enuresis was present in 44% of all patients: 70.6% in 0 to 5-year-olds (data available for 221/348 children in this age group), 48.3% in 5- to 10-year-olds and 26.9% in 10- to 15-year-olds.

DKA was present at diagnosis in 570 patients (43.9%) and severe in 192 (14.8%) cases; 73 patients (5.6%) had a coma (seven severe, Glasgow score <7). Overall, 16% of patients were hospitalized in ICUs, and 64.8% were initially treated with intravenous insulin. Two 11-year-olds died within 2 days of ICU admission (pH 6.81 and 6.85, and polyuria/polydipsia lasting for 2 and 4 weeks, respectively). Yet another 11-year-old patient suffered prolonged respiratory distress and acute cerebral oedema, and presented with neurological abnormalities for several months. The percentages of DKA ranged from 42 to 62% depending on the time of year, but not significantly ($P = 0.43$). Also, DKA prevalence did not differ between boys and girls (46% vs. 42%, respectively; $P = 0.16$). However, DKA was significantly more prevalent in younger children: 54.2% in those aged 0–5 years (54.4% in those aged <2 years) vs. 43.4% in those aged 5–10 years and 37.1% in those aged 10–15 years ($P < 0.0001$). The percentages of severe DKA did not differ significantly among the 0- to 5-year-olds (16.6%), 5- to 10-year-olds (14.4%) and 10- to 15-year-olds (13.9%), but was 25.3% in children aged <2 years. DKA was more frequently seen in young patients brought directly to hospital by their families (53.5%) or transferred from another hospital (65.1%) compared with patients referred by a general practitioner (36.7%) or paediatrician (39.3%); this significant difference ($P < 0.0001$) was mainly due to rates of severe DKA, which were 26.6, 36.1, 7.6 and 5.1%, respectively. The percentage of DKA was 20.1% (4.4% severe DKA) in patients with a family history of T1D. The relationships between the presence and severity of DKA and diverse clinical and biological parameters are summarized in Table 1.

Two multivariate analyses were conducted to evaluate the association of various factors with DKA and severe DKA, including the following variables: age; patient’s pathway to hospitalization; duration of polyuria/polydipsia; and family history of T1D. Our results indicated that younger age and a duration of polyuria/polydipsia $>1$ week were significantly associated with DKA, but not with severe DKA (Table 2), whereas the patient’s pathway (hospitalization at family’s behest or transfer from another hospital) and absence of family history of T1D were associated with DKA as well as severe DKA (Table 2).

5. Discussion

The prevention of DKA at T1D diagnosis is a priority for ISPAD and the International Diabetes Federation (IDF). The present prospective study of patients newly diagnosed with T1D – performed thanks to the data collected by two-thirds of France’s paediatric centres and representing about two-thirds of all new cases of T1D in people younger than 15 years [25] – had the main objectives of updating our data on the frequency of DKA at diagnosis to allow later evaluation of the efficacy of a national campaign for the prevention of DKA and identifying the factors that might have an impact on the design and efficacy of such a campaign.

Criteria for the definition of DKA strictly adhered to ISPAD guidelines [6] whereby DKA was diagnosed when either of two parameters (pH and bicarbonate) fell below the recommended limits. This has not always been the case in published studies,
although differences in DKA criteria fail to explain the marked differences in its reported frequencies, ranging from 15 to 67% in the EURODIAB study, which applied identical criteria at all centres [3]. Yet, the frequency of DKA has remained stable and somewhat elevated in France for about 20 years [17,21], despite the steady increase in the incidence of diabetes [1]. The frequency of DKA was higher in those of younger age [9,11,12,17,18,20], although severe DKA was not age-related except in those <2 years old [10,20,26,27]. As reported in other studies [17,19,26,28], a family history of T1D was associated with a considerably lower prevalence of DKA, thus confirming that diagnosis may be quicker when alerting symptoms of the disease are better known [29].

The high frequency of DKA at diagnosis in France justifies a public-health campaign to prevent DKA at diagnosis of T1D, as first launched in the province of Parma in Italy [23,24] and then in other areas [30,31]. Polyuria/polydipsia and enuresis were the main alerting symptoms on which the Italian campaign was based, and our present data confirm that polyuria/polydipsia was prominent and lasted >2 weeks in more than half the cases at all ages [3], and that enuresis was present in more than half the children and in one-quarter of the 10- to 15-year-olds. However, other symptoms (intestinal, respiratory, loss of consciousness) also need to be recognized to avoid misdiagnoses, as they are markers of severity and extreme emergency. Duration of symptoms tended to more often be shorter in younger children, although two 11-year-old children died after a relatively short period of symptoms. Nevertheless, these results reinforce the message that the quicker the diagnosis, the less frequent the DKA.

The information campaign will be aimed at both families and health professionals to allow them to react rapidly at the earliest signs of alerting symptoms. Several studies have shown that biological examinations performed at laboratories delay treatment and are factors predictive of DKA at diagnosis [9,10,13,17,18,27]. Yet, a simple search for glucose in urine or measurement of blood glucose using test strips is more than enough to refer a child to the closest hospital emergency department with no further delay. Results for patients’ pathway to hospital [17,21] have shown that children were referred by a paediatrician in <10% of cases and by a general practitioner in just over half the cases. This led to a major impact in the Italian campaign, which was aimed mainly at paediatricians [23,24], and will make a considerable difference on the design of our information campaign as it enormously increases the number of health-professional targets. However, it also raises questions as to the feasibility of dispersing posters, flyers and glucose meters, as in previous campaigns, at a national level and over the long term. In one-third of cases, the family initiated the consultation at hospital and, in those cases, DKA was much more frequent and more severe. The questionnaire used in the present study did not allow confirmation of whether these families had had any previous medical consultations, although such information is important for better identifying campaign targets and

| Table 2: Multivariate analysis of factors associated with the presence and severity of ketoacidosis (DKA). |
| Presence of DKA (moderate/severe) vs. no DKA | OR | Inf 95% CI | Sup 95% CI | P value |
| Age (years) | | | | |
| 0–5 | 1 | | | |
| 5–10 | 0.61 | 0.45 | 0.83 | 0.002 |
| 10–15 | 0.48 | 0.35 | 0.65 | <0.001 |
| Family referral | | | | |
| Paediatric referral | 0.39 | 0.25 | 0.61 | <0.001 |
| General practitioner referral | 0.43 | 0.32 | 0.56 | <0.001 |
| Other hospital referral | 1.20 | 0.72 | 2.01 | 0.49 |
| Polyuria/polydipsia < 1 week | 1 | | | |
| Polyuria/polydipsia ≥ 1 week | 1.93 | 1.34 | 2.78 | <0.001 |
| No T1D family history | 1 | | | |
| T1D family history | 0.23 | 0.16 | 0.34 | <0.001 |

| Presence of severe DKA vs. no or moderate DKA | OR | Inf 95% CI | Sup 95% CI | P value |
| Age (years) | | | | |
| 0–5 | 1 | | | |
| 5–10 | 0.96 | 0.63 | 1.46 | 0.85 |
| 10–15 | 0.98 | 0.64 | 1.49 | 0.91 |
| Family referral | | | | |
| Paediatric referral | 0.12 | 0.05 | 0.29 | <0.001 |
| General practitioner referral | 0.19 | 0.13 | 0.28 | <0.001 |
| Other hospital referral | 1.24 | 0.74 | 2.10 | 0.41 |
| Polyuria/polydipsia < 1 week | 1 | | | |
| Polyuria/polydipsia ≥ 1 week | 1.35 | 0.82 | 2.22 | 0.24 |
| No T1D family history | 1 | | | |
| T1D family history | 0.18 | 0.09 | 0.36 | <0.001 |
consequently adapting its strategy. In addition, the questionnaire did not include any information on the family’s socioeconomic status or other DKA risk factors [9,17–19], as it was designed to be as simple as possible and to identify only those factors that might help in designing the strategy of the campaign.

In conclusion, the data collected over the year prior to launching our information campaign have shown a high frequency of DKA at the time of diagnosis of T1D in children and adolescents in France, as well as certain risk factors, including young age, absence of family history of T1D and duration of symptoms before diagnosis. These findings provide the data needed to evaluate the efficacy of the campaign [30] and also provide some useful insights for conducting the information campaign and defining its preferential targets.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

AJD Study Group: list of co-authors

M. Abdelhadi, Provins; C. Ajzenmman, Le Chesnay; R. Amira, Saint-Denis; E. Badet, Chambéry; E. Baechler-Sadoul, Nice; I. Barakat, Gonesse; S. Baron, Nantes; J. Beltrand, Paris; M. Bengrina, Remiremont; C. Bensignor, Dijon; P. Blanc, Poissy; C. Boniface, Saintes; L. Bornesbich, Grasse; M.N. Bortoluzzi, Nice; N. Bouhours-Noet, Angers; S. Boulard, Libourne; H. Bousadia, Montmorency; K. Braun, Amiens; D. Briffaut, Lorient; I. Brintet, Agen; M. Chambon, Villefranche-sur-Saône; A. Chergui, Vierzon; J. Chevré, Dax; I. Cloix, Moulins; A.M. Colin-Gorski, Argenteuil; G. Cottancin, Sallanches; B. Coupe, Vesoul; M.L. Cuvelier, Calais; F. Dulla-Vale, Montpellier; G. Daltroff, Belfort; E. de Meneix, Fréjus; N. Demay, Arpajon; F. Deniau, Dieppe; D. Depret, La Tronche; H. Derquenne, Douai; V. Desgranges, Montluçon; C. Deshayes, Lons-le-Saunier; K. Dieckmann, Blois; S. Ducrocq, Longjumeau; D. Dufillot, Tarbes; C. Dumont, Vienne; J.P. Duquesne, Auch; C. Durand, Saint-Julien-en-Genevois; M.F. Durand, Alès; D. Druon, Soissons; N. Faure, Tours; G. Favaretto, Avranche; P. Ferré, Montreuil; V. Ferrer, Albertville; F. Flamant, Lens; S. Fournier, Boulogne-sur-Mer; V. Gajdos, Clamart; B. Gallois, Metz; N. Garrec, Lagney-sur-Marne; F. Gastaud, Monaco; B. Geneste, Bourg-en-Bresse; E. Georget, Villeneuve-Saint-Georges; I. Gilles, Evreux; K. Goin, Creil; P. Goumy, Vichy; A. Gourdin, Valenciennes; A. Grando, Montbrison; M. Greco, Briey; P. Gronnier, Lille; F. Guemazi-Kheffi, Mulhouse; B. Guerin, Pau; C. Guillen, Mantes-la-Jolie; O. Guilly, Saint-Omer; M.A. Guiteny, Rennes; G. Hoffmann, Saint-Dizier; N. Huin, Romans-sur-Isère; A. Hureau, Sedan; N. Idres, Saint-Brieuc; M. Jalloul, Chaumont; S. Jellimann, Vandozouër-Lès-Nancy; A. Jossens, Saint-Malo; F. Joubert, Avignon; D. Kauffmann, Caen; C. Kerouedan, Lisyue; J. Khoury, Hyères; S. Kozisek, Flers; F. Kurtz, Saint-Avold; F. Labay, Le Mans; F. Lagarde, Montargis; H. Lahrach, Fécamp; N. Laisney, Saint-Lô; D. Laplane, Marseille; B. Laurent-Atthalin, Mâcon; M. Layadi, Guéret; D. Lecomte, Châteauroux; S. Lemerle, Créteil; A. Lienhardt-Roussie, Limoges; G.A. Loueille, Dunkerque; S. Louf, Rang-du-Fliers; N. Lucidarme, Bondy; V. Maire, Annecy; D. Mangin, Colmar; M. Mansilla, Strasbourg; C. Martel, Morlaix; L. Martineau, Angoulême; L. Mathivon, Meaux; A. May, Evry; D. Memiche, Laon; B. Mignot, Besançon; C. Mignot, Boulogne-Billancourt; M.J. Milleret-Proyat, Sens; S. Mochn, Chalon-sur-Saône; S. Monteil, Annemasse; M. Moreigine, Antibes; C. Morin, Toulouse; E. Moullé, Salon-de-Provence; S. Muller, Rambouillet; A.S. Musial-Salmon, Reims; S. Nadif, Béthune; R. Nicolescu, Cambrai; B. Nold, Haguenau; C. Orzechowski, Bry-sur-Marne; L. Pantalone, Pontoise; G. Parlier, Saint-Nazaire; H. Pecheur, Saverne; S. Perdereau, Orléans; F. Popelard, Epinal; E. Questiaux, Aulnay-sous-Bois; C. Raverdy, Paris; B. Razafimanhefa, Toulon; R. Ricard, Mont-de-Marsan; O. Richard, Saint-Etienne; C. Rougeoggle, Melun; S. Rouget, Le Kremlin-Bicêtre; J.P. Saade, Beauvais; N. Sarraf, Cherbourg; G. Simonin, Marseille; H. Staumont, Quimper; C. Stuckens, Lille; C. Tahiri, Dourdan; A. Tamboura, Maubeuge; R. Teissier, Brest; D. Théveneau, Aix-en-Provence; D. Terral, Clermont-Ferrand; F. Tixier, Lyon-Bron; F. Tronc, Carcassonne; A. Valade, Bayonne; V. Vautier, Bordeaux; C. Vervel, Compiègne; C. Wemeau, Seclin; M.C. Wielczech, Rouen; B. Zimmermann, Troyes.

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Appendix A. Supplementary data

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