EMERGENCE OF TYPE 2 DIABETES IN AN HOSPITAL BASED COHORT OF CHILDREN WITH DIABETES MELLITUS

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SUMMARY - Objectives: Increasing awareness of the heterogeneity of diabetes mellitus (DM) at presentation is changing our approach to this disease. We used the 1999 American Diabetes Association (ADA) criteria to determine the distribution of DM patterns in a large pediatric cohort with the aim of documenting the emergence of type 2 diabetes mellitus.

Material and methods: Charts of diabetic children aged 1 to 16 years and admitted to our center between 1993 and 1998 were reviewed for data needed to achieve classification of the type of diabetes mellitus.

Results: Of the 382 study patients, 327 (85.6%) had autoimmune type 1 DM (clinical insulin-treated type 1 DM with immunologic and/or genetic evidence of autoimmunity) and 6 (1.6%) had idiopathic type 1 DM (clinical insulin-treated type 1 DM without evidence of autoimmunity). Four (1.0%) patients met all the criteria for type 2 DM; all were obese and three had acanthosis nigricans; in one the diagnosis was changed from type 1 to type 2 DM during follow-up. Four patients could be classified as lean patients with type 2 DM. In keeping with recent reports of a rise in the incidence of type 2 DM, 6 of these type 2 cases were diagnosed in the last year of the study.

Conclusion: The ADA classification helps to understand the pathophysiology of pediatric DM, thus providing useful therapeutic guidance. At presentation, most cases of pediatric DM are type 1, but we show here that type 2 DM becomes now a diagnosis to consider although in children. Our study, from a large study center is not an epidemiological one but is consistent with population studies. Systematic or targeted screening for type 2 in children should be discussed.

Key-words: type 1 diabetes mellitus, type 2 diabetes mellitus, children, ADA classification.

RE´ SUME´ - Emergence du diabète de type 2 dans une cohorte de diabétologie pédiatrique hospitalière.

Objectif : L'hétérogénéité de la présentation du diabète sucré de l’enfant est en train de modifier notre approche de la maladie. Nous avons utilisé la classification de 1999 de l’American Diabetes Association (ADA) pour définir les différents types de diabète sucré présents dans une large cohorte d’enfants diabétiques avec le but de documenter l’émergence récente du diabète de type 2 dans cette cohorte pédiatrique.

Matériel et méthodes : Les dossiers d’enfants ayant un diabète, âgés entre 1 et 16 ans et admis dans notre centre entre 1993 et 1998 ont été étudiés pour les données permettant de classer le diabète sucré selon les critères de l’ADA.

Résultats : De 382 patients, 327 (85,6 %) avaient un diabète de type 1 auto-immun (diabète traité par insuline avec des marqueurs immunologiques et/ou génétiques d’auto-immunité) et 6 (1,6 %) avaient un diabète de type 1 idiopathique (diabète traité par insuline sans évidence d’auto-immunité). Quatre patients (1 %) avaient tous les critères de diabète de type 2 ; tous étaient obèses and trois avaient un acanthosis nigricans ; chez l’un deux le diagnostic a été ainsi revu de diabète de type 1 à diabète de type 2. Quatre patients ont pu être classés comme des patients minces ayant un diabète de type 2. En accord avec l’augmentation de fréquence du diabète de type 2, 6 des 8 cas de diabète de type 2 ont vu leur diagnostique posé lors de la dernière année de notre étude.

Conclusion : La classification de l’ADA aide à classer sur une base physiopathologique le diabète sucré chez l’enfant, ce qui permet donc une meilleure prise en charge thérapeutique. Lors du diagnostic de diabète chez l’enfant, la plupart des cas sont des cas de diabète de type 1, mais nous montrons ici que le diagnostic de diabète de type 2 doit être envisagé même chez l’enfant. Notre étude, issue d’un centre à fort recrutement n’est pas une étude épidémiologique, mais est néanmoins en accord avec les études de population. La meilleure stratégie de dépistage du diabète de type 2 chez l’enfant reste à déterminer.

Mots-clés : diabète de type 1, diabète de type 2, enfant, étiologies, classification de l’ADA.
Increasing awareness of the heterogeneity of diabetes mellitus (DM) at presentation is changing our approach to this disease. This is particularly true in children. Classically, there are two main types of diabetes mellitus (DM), insulin-dependent DM (IDDM) and non-insulin-dependent DM (NIDDM). Because this classification does not reflect the pathophysiological and clinical heterogeneity of DM, the American Diabetes Association (ADA) recently developed a new classification scheme [1]. In children, the most common form by far is autoimmune type 1 DM [2], in which pancreatic tissue is destroyed by an autoimmune process, causing insulin deficiency. Other types of diabetes found in children include maturity onset diabetes of the young (MODY), lipodystrophic DM, and DM secondary to diseases of the exocrine pancreas or to endocrine disorders. Type 2 DM is the most common form in adults [3], but its prevalence in children is rising in parallel with the prevalence of childhood obesity [4, 5]. In some populations of children and adolescents, type 2 DM has reached epidemic proportions and is having a severe impact on public health [3, 6]. In practice, however, pediatric diabetologists usually do not make a diagnosis of type 2 DM in a child without risk factors for this disease until they have ruled out other forms of DM.

We studied the frequency of the various ADA-defined categories of DM in a large cohort of children seen over a six-year period at one center, a pediatric teaching hospital, with the goal of 1) identifying and characterizing children with type 2 diabetes mellitus referred to our center in Paris, France, 2) gathering data of use to pediatric endocrinologists in their everyday practice to classify the type of diabetes mellitus encountered in children.

**PATIENTS AND METHODS**

### Inclusion criteria

We conducted a retrospective review of the medical records of all the children who were admitted between the ages of 1 and 16 years to the pediatric endocrinology department of the Robert Debré Teaching Hospital, Paris, France, between January 1993 and December 1998, and who were given a discharge diagnosis of DM (n = 382). Diabetes was defined based on the ADA criteria [1]: (a) symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) and casual plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/L) or (b) fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/L) or (c) 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/L) during an oral glucose tolerance test (OGTT). We excluded patients with transient hyperglycemia by requiring documented hyperglycemia of at least six months’ duration [7]. Of the 382 patients who met our criteria, six were excluded because their medical records were unavailable, six because they had received follow-up at another center and the hyperglycemia persistence more than 6 months could not be ascertained. 29 had known specific forms of DM (see results; [8-11]). This left 341 patients for further classification.

### Parameters

Parameters determined at diagnosis and used for DM classification were a history of DM in first-degree relatives; polyuria, polydipsia, and/or weight loss; age, sex, and body mass index (BMI) expressed the number of standard deviations (SDs) from age- and sex-specific reference values [12]; whether the diagnosis was made fortuitously or upon evaluation of symptoms; and laboratory data (plasma levels of glucose and HbA1c, ketonuria, and urinary pH). Insulin secretion capacity was assessed on the basis of insulin secretion at a distance from the initial hyperglycemic peak during an intravenous glucose tolerance test (IVGTT) and autoimmunity based on presence of β-cell autoantibodies (ICA, GAD-65, and IA2) and on the HLA DQ genotype. The treatment was recorded, as well as the insulin dose after 2 years of diabetes.

### Classification

Type 1 DM was diagnosed on the basis of [1] at least one detectable anti β-cell antibody;[2] an HLA DQB1 genotype associated with a high risk for type 1 DM, i.e., 0201/0302 or 0302/x where “x” is 0302 or
an undefined allele: (the 0602 allele was considered protective, and the other combinations neutral [13, 14]);[3] polyuria, polydipsia, and/or weight loss with ketoacidosis;[4] a need for insulin treatment to ensure survival (except during the honeymoon period).

Typical type 2 DM was diagnosed on the basis of the absence of a need for insulin therapy to ensure survival (not taking into account a transient need for insulin at diagnosis of the disease), presence of obesity, absence of antiβ-cell antibodies, and absence of an HLA DQ genotype associated with a high risk of type 1 DM. A family history of type 2 DM was looked for. When the same criteria were present but in a non obese child, and when a MODY 2 and a MODY 3 mutation were not found, a diagnosis of type 2 DM in a lean subject was given (“lean type 2 DM”).

Procedures and assay methods

Glucose was assayed using enzymatic methods. Glycated hemoglobin was measured using high-performance liquid chromatography (Biorad, France), and the normal range was defined as 5.1 ± 0.6% (mean±2SD). Serum insulin concentrations were measured using an immunoradiometric assay (Bi-Insulin IRMA, Sanofi-Diagnostics Pasteur, Nanterre, France). Oral glucose tolerance tests (OGTT) involved giving glucose orally in a dose of 1.75 g/kg body weight, up to 75 g of glucose, after an overnight fast, as recommended by the World Health Organization [15]; glucose and insulin were assayed in the plasma before and 30 and 120 min after the glucose load. First-phase insulin secretion was assessed by measuring plasma insulin levels 1 and 3 minutes after an intravenous glucose injection, as previously described [16]. Islet-cell antibodies (ICAs) were detected by indirect immunofluorescence on sections of frozen, group O human pancreas [17]; this assay had a detection limit of 4 JDF units, 100% sensitivity, and 88% specificity. GAD-65 antibodies were measured using an immunoradiometric assay (RIA) with 35S-radiolabelled human recombinant GAD65, as previously described [18]; results were expressed as a binding index with reference to two negative and two positive control sera, and sensitivity and specificity were 78% and 98%, respectively. Anti-IA2 antibodies were detected using a RIA with 35S-radiolabelled human full-length recombinant protein [19]; results were expressed as a binding index with reference to two negative and two positive internal control sera. All antibodies measurements were performed at onset of DM or on sera stored at onset of DM. HLA DQB1 was studied by the restriction fragment length polymorphism technique, after polymerase chain reaction (PCR) amplification of exon 2 of the DQB1 locus; this method allows detection of 13 alleles. Screening for MODY 2 and 3 was performed by described techniques at the CEPH (Centre d’Etudes du Polymorphisme Humain) at Saint Louis hospital in Paris, France.

RESULTS (Fig. 1)

Of the 370 study patients, 29 had known specific forms of DM: 12 had MODY [glucokinase gene mutation, \(n = 10\); HNF-1a gene mutation, \(n = 2\) [8], one had mitochondrial DM [9], 10 had DM due to cystic fibrosis [10], two had lipoatrophic DM, and four had drug-induced DM [11].

Of the remaining 341 study patients, 292 had the clinical characteristics of type 1 DM at presentation, were on insulin therapy two years after the diagnosis, and were ICA-positive at diagnosis. These 292 patients were classified as having autoimmune type 1 DM. Another 41 patients had the clinical characteristics of type 1 DM and were on insulin therapy two years after the diagnosis but were ICA-negative at diagnosis. These ICA-negative patients were tested for GAD-65 and IA2 on sera stored at onset of diabetes: only six were found to be negative for both antibodies. Of these six patients negative for all three antibodies tested, three had high-risk HLA alleles (Table I), two others (patients 4 and 5 in Table I) had neutral HLA alleles and one a protective

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Family history</th>
<th>Mode of diagnosis</th>
<th>BMI (DS)</th>
<th>Plasma glucose (mmol/L)</th>
<th>Ketonuria/acidosis</th>
<th>HbA1c (%)</th>
<th>HLA DQB1</th>
<th>Insulin dosage (IU/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11.7</td>
<td>M</td>
<td>No*</td>
<td>symptoms</td>
<td>0.75</td>
<td>19</td>
<td>+/−</td>
<td>12.2</td>
<td>0201/0302</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>M</td>
<td>No</td>
<td>symptoms</td>
<td>0</td>
<td>30.6</td>
<td>+/−</td>
<td>14</td>
<td>0201/0302</td>
</tr>
<tr>
<td>3</td>
<td>3.4</td>
<td>F</td>
<td>No</td>
<td>symptoms</td>
<td>− 1</td>
<td>7.6</td>
<td>+/−</td>
<td>16</td>
<td>0302/0302</td>
</tr>
<tr>
<td>4</td>
<td>12.4</td>
<td>F</td>
<td>No</td>
<td>symptoms</td>
<td>− 0.4</td>
<td>NA</td>
<td>+/−</td>
<td>12.9</td>
<td>0502/0502</td>
</tr>
<tr>
<td>5</td>
<td>11.1</td>
<td>F</td>
<td>No</td>
<td>symptoms</td>
<td>− 0.5</td>
<td>16.7</td>
<td>+/−</td>
<td>11.1</td>
<td>0501/0501</td>
</tr>
<tr>
<td>6</td>
<td>6.4</td>
<td>M</td>
<td>No</td>
<td>symptoms</td>
<td>− 1</td>
<td>29.7</td>
<td>+/−</td>
<td>8.5</td>
<td>0501/0602</td>
</tr>
</tbody>
</table>

F: female; M: male; * Sister with a positive screen for ICA positive but no diabetes. NA: not available. +: Positive; −: Negative. * Dosage two years after the diagnosis of DM.
HLA allele (patient 6); these 6 patients without detectable immunological indicators of autoimmune DM had typical features of IDDM at presentation: according to the ADA classification, they had idiopathic type 1 DM. Thus, of the 370 study patients, 327 (88.4%) were classified as having autoimmune type 1 DM, and 6 idiopathic type 1 DM (Table I).

The eight patients without criteria for type 1 DM formed a heterogeneous group. Four had typical features of type 2 DM (Table II). One was of Caribbean descent and three were Caucasian. All four children were obese (BMI > age- and sex-specific reference value + 2 SDs). Three had acanthosis nigricans, and all were undergoing puberty. Polyuria, polydipsia, or polyphagia were present at diagnosis in three patients, and ketonuria with acidosis in two. All four patients were negative for anti-β-cell antibodies, and none had HLA alleles associated with a high risk of autoimmune type 1 DM. In two children, tests for MODY 2 and 3 were performed and found to be negative. One patient (patient 4 in Table II), a boy, was on low-dose insulin (0.16 U/kg/d) two years after the diagnosis; he had typical features of IDDM at presentation, but the diagnosis was subsequently changed to NIDDM based on the presence of obesity and on the low insulin requirements. Another patient was on oral hypoglycemic therapy. Two patients were treated by dietary therapy alone.

The remaining four patients had all the diagnostic criteria for type 2 DM, except that they were not obese. We characterized them as “lean type 2 DM” (Table II, patients 5, 6, 7, 8). Their ages ranged from 8.5 to 14.9 years. The diagnosis of DM was fortuitous in all four patients. Two patients had a first-degree relative with DM. None of these patients were obese (BMI > age- and sex-specific reference value + 2 SDs). As shown in Table II, the first-phase insulin response during the IVGTT was variable. None of these patients had detectable anti-β-cell antibodies, HLA alleles associated with a high risk of autoimmune type 1 DM, or known mutations in the MODY 2 or 3 genes. At some point during the course of their disease, three of these four patients required oral hypoglycemic therapy to maintain normal plasma glucose levels; the remaining patient did not require drug therapy. Altogether in these 8 patients with type 2 diabetes, 7 were diagnosed during pubertal years. Six out of 8 were diagnosed in the last year of the study (i.e. 10% of the patient referred to our center this year).

**DISCUSSION**

We classified our patients using the 1999 ADA criteria classification scheme. This scheme focuses on etiology, whereas earlier schemes were based on treatment requirements. Eighty-seven (333/382) per cent of our patients met clinical and immunogenetic ADA criteria for type 1 DM. In most of our patients, the diagnosis of autoimmune type 1 DM was readily made based on the presence of typical symptoms of DM and anti-β-cell antibodies. Only 6 patients with clinical evidence of type 1 DM had no detectable anti-β-cell antibodies at diagnosis. As reported by others, we found that clinical characteristics and metabolic compensation were similar in the patients with and without anti-β-cell antibodies [20]. These patients had no immunologic evidence of autoimmune type 1 DM, and consequently met the ADA definition of idiopathic type 1 DM.

Only four of our 370 patients (1%) showed typical features of type 2 DM. Four others showed features of type 2 DM except that they were not obese. Nevertheless, concern has been voiced recently about the increasing prevalence of diagnosed type 2 DM in children. In keeping with this, 6 out 8 cases of type 2 DM

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**Table II. Characteristics of the eight patients with type 2 diabetes mellitus.**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sex</th>
<th>Family history</th>
<th>Mode of diagnosis</th>
<th>BMI (DS)</th>
<th>Tanner</th>
<th>Acanthosis nigricans</th>
<th>Plasma glucose (mmol/L)</th>
<th>Ketonuria</th>
<th>Hb1Ac (%)</th>
<th>Insulin secretion*</th>
<th>Treatment (time**)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>13.0 F</td>
<td>yes</td>
<td>fortuitous</td>
<td>8.0</td>
<td>4</td>
<td>yes</td>
<td>8.9</td>
<td>no</td>
<td>7.5</td>
<td>normal</td>
<td>Diet</td>
</tr>
<tr>
<td>2</td>
<td>13.6 F</td>
<td>yes</td>
<td>symptoms</td>
<td>5.9</td>
<td>5</td>
<td>yes</td>
<td>17.3</td>
<td>no</td>
<td>11.6</td>
<td>low</td>
<td>OHAs (0d)</td>
</tr>
<tr>
<td>3</td>
<td>12.5 F</td>
<td>yes</td>
<td>symptoms</td>
<td>8</td>
<td>3</td>
<td>yes</td>
<td>15</td>
<td>yes</td>
<td>NA</td>
<td>normal</td>
<td>Insulin (0d)</td>
</tr>
<tr>
<td>4</td>
<td>13.3 M</td>
<td>yes</td>
<td>symptoms</td>
<td>5</td>
<td>3</td>
<td>no</td>
<td>19.3</td>
<td>yes</td>
<td>11.6</td>
<td>ND</td>
<td>Diet only: 1.5 y</td>
</tr>
<tr>
<td>5</td>
<td>12.0 M</td>
<td>yes</td>
<td>fortuitous</td>
<td>1.0</td>
<td>2</td>
<td>no</td>
<td>8.3</td>
<td>no</td>
<td>7.1</td>
<td>normal</td>
<td>0.16U/k/d</td>
</tr>
<tr>
<td>6</td>
<td>12.8 M</td>
<td>yes</td>
<td>symptoms – 0.7</td>
<td>1</td>
<td>no</td>
<td>7.2</td>
<td>no</td>
<td>6.7</td>
<td>low</td>
<td>OHAs (36 m)</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>14.9 M</td>
<td>no</td>
<td>fortuitous</td>
<td>0.3</td>
<td>3</td>
<td>no</td>
<td>14.8</td>
<td>no</td>
<td>8.1</td>
<td>low</td>
<td>OHAs (12 m)</td>
</tr>
<tr>
<td>8</td>
<td>8.5 M</td>
<td>no</td>
<td>fortuitous</td>
<td>0</td>
<td>1</td>
<td>no</td>
<td>10</td>
<td>no</td>
<td>6.5</td>
<td>normal</td>
<td>OHAs</td>
</tr>
</tbody>
</table>

* Intravenous glucose tolerance test at or near diagnosis.

** Time from the diagnosis of diabetes to treatment initiation.

ND: Not determined. OHAs: oral hypoglycemic agents.
in our study were diagnosed during the last year of the study. Our study, from a one large study center is not an epidemiological one but is consistent with population studies which have demonstrated the same phenomenon [5]. Our finding are also similar to the ones of a study concerning one large center in the USA, but with a delay of 6 years in the increasing appearance of type 2 DM children in pediatric cohorts [21]. The increasing prevalence of diagnosed type 2 DM in children may be due in part to heightened awareness among physicians that type 2 DM can occur in childhood and in part to an increase in the incidence of type 2 DM in children. We excluded children with impaired glucose tolerance, a condition usually associated with obesity, which is becoming increasingly prevalent in children. Only one of the four patients with type 2 DM had alleles associated with a high risk of this disease. Puberty was ongoing in seven out of these 8 patients, in keeping with earlier reports [5]. Puberty plays an important role in the development of type 2 DM because it is associated with resistance to insulin [22]. Three of the four typical type 2 patients had acanthosis nigricans at presentation; this proportion is higher than in studies of adult type 2 DM but similar to that found in other pediatric studies [4]. It is important to note that one of the patients with type 2 DM was first classified as having IDDM. Making the diagnosis of type 2 DM improved the management and follow-up in this patient. It is of importance to note that ketonuria and ketoacidosis at onset does not rule out the diagnosis of type 2 DM as already very well established and documented [5]. In the two “lean type 2 patients” with a low insulin secretion, we cannot rule MODY related to an as yet unknown mutation (MODY 2 and 3 were excluded). The absence of obesity militates against, but does not exclude, type 2 DM [5].

To our knowledge this is the first work to stress that type 2 DM should be considered in France in the etiological diagnosis of DM in children very recently reported in the UK [23]. Systematic screening for the detection of type 2 DM in children should be discussed, especially in obese children. The best way to perform it will have to be addressed in protocols.

In conclusion, although type 1 DM is still by far the most common form of DM in children, type 2 DM also occurs, and there is some evidence that the prevalence of diagnosed type 2 DM is increasing in children. The most helpful criteria for diagnosing type 2 DM in our pediatric population were obesity and acanthosis nigricans. When obesity was lacking exclusion of MODY using genetic screening were important. Of diagnosed type 2 DM children may be due in part to heightened awareness among physicians that type 2 DM can occur in childhood and in part to an increase in the incidence of type 2 DM in children. We excluded children with impaired glucose tolerance, a condition usually associated with obesity, which is becoming increasingly prevalent in children. Only one of the four patients with type 2 DM had alleles associated with a high risk of this disease. Puberty was ongoing in seven out of these 8 patients, in keeping with earlier reports [5]. Puberty plays an important role in the development of type 2 DM because it is associated with resistance to insulin [22]. Three of the four typical type 2 patients had acanthosis nigricans at presentation; this proportion is higher than in studies of adult type 2 DM but similar to that found in other pediatric studies [4]. It is important to note that one of the patients with type 2 DM was first classified as having IDDM. Making the diagnosis of type 2 DM improved the management and follow-up in this patient. It is of importance to note that ketonuria and ketoacidosis at onset does not rule out the diagnosis of type 2 DM as already very well established and documented [5]. In the two “lean type 2 patients” with a low insulin secretion, we cannot rule MODY related to an as yet unknown mutation (MODY 2 and 3 were excluded). The absence of obesity militates against, but does not exclude, type 2 DM [5].

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