An Unusual Case of a Teenager with Diabetes

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ABSTRACT

Double diabetes or Hybrid Diabetes (HD), presenting in childhood and adolescence, includes characteristics of T1D, positive Diabetes Associated Auto-antibodies (DAA), and T2D, obesity and insulin resistance, and also positive family history of T1D and T2D. It is characterized by a rapid beta cell failure. Due to the increasing prevalence of childhood obesity, the possibility of the presentation of unusual types of diabetes belonging to the grey area between T1D and T2D is expected to be increased. In this study, we report an adolescent patient who presented initially with symptomatic hyperglycemia, overweight, insulin resistance, normal C-peptide levels and positive DAA, and 8 months later developed complete insulin dependence and presented with Diabetic Ketoacidosis (DKA). He had clinical and laboratory features of both T1D and T2D and a high risk haplotype for T1D, while his clinical course was similar to that of patients with Double Diabetes (DD). We also review the literature and we present the differential diagnosis of this entity, which entails characteristics of both T1D and T2D. We finally include suggestions for its management, for the beta cell function preservation and achievement of a better glycemic control.

Introduction

In the last decades, the distinction between Type 1 and Type 2 Diabetes (T1D and T2D) has been based on the age at onset of the disease, the occurrence of obesity and insulin resistance, the relative insulin deficiency and the presence of diabetes associated Autoantibodies (DAA), with the latter considered to be characteristic of T1D [1]. Recently, the increasing prevalence of obesity in all age groups has complicated the classification of diabetes and several studies have shown that both types of diabetes may include patients with clinical and laboratory heterogeneity [2]. Among them are patients with Double Diabetes (DD) or Latent Autoimmune Diabetes in Adults (LADA). Double diabetes or Hybrid Diabetes (DD) [3] is an entity presenting in childhood and adolescence, which includes characteristics of T1D (positive DAA) and T2D (obesity and insulin resistance), and also positive family history of T1D and T2D, who progress rapidly to insulin dependence. The incidence of double diabetes is approximately 5% of newly diagnosed children and adolescents and seems to be highest in patients from African or American/
Hispanic origin [4]. In the adult population, another entity with similar to double diabetes characteristics is LADA, which consists of a heterogeneous group of patients sharing clinical, metabolic and genetic features of both T1D and T2D. These patients have a slow onset type of diabetes, having initially the clinical and laboratory features of T2D together with the presence of DAA, but progress to insulin dependence more rapidly than in T2D, after a period of time ranging from months to few years after diagnosis [5]. LADA by definition includes only adult patients, however very few cases of a similar phenotype in childhood have been reported [6,7].

Here, we report a teenage patient who presented initially with features of T2D and positive DAA, who within 8 months developed significant beta cell dysfunction and insulin dependence, a clinical course similar to that of double diabetes patients.

**Case Presentation**

A 13.5 year old boy of North African origin was referred to the Diabetes Outpatient Clinic of a University Department of Pediatrics in a tertiary Children’s Hospital, complaining of polyuria, polydipsia, and Weight loss of 5 kg during the past 2 months. His fasting blood glucose levels, ranged from 115 mg/dl to 126 mg/dl. He was the first child of healthy unrelated parents, born at term with cesarean section due to fetal macrosomia (birth weight: 4200 gr) after a pregnancy complicated by Gestational Diabetes Mellitus (GDM). From the family history, both his maternal and paternal grandmother had been diagnosed with T2D, his maternal uncle suffered from T1D and his mother, father and sister had impaired glucose tolerance under diet control. He was overweight with a BMI of 27 kg/m2 (75th percentile), pubertal Tanner stage III; otherwise clinical examination was unremarkable. His OGTT (oral glucose tolerance test) was at the diabetes range with value at 120’ over 200 mg/dl (glucose levels at 0’: 141 mg/dl, 30’: 194 mg/dl, 60’: 253 mg/dl, 120’: 281 mg/dl), while his insulin levels were normal (Table 1). HbA1c was elevated (7.4%, RR: 4.5-6.2%), while fasting C-peptide levels were normal and tripled after Glucagon stimulation (fasting: 1.1 ng/ml, 1 hour after stimulation by 1 mg Glucagon intravenously: 2.9 ng/ml, reference range (RR): 0.4-4.0 ng/ml). Also his fasting insulin was 12.5 (mIU/L) and after two hours it was raised to 24.4 (mIU/L), HOMA-IR was 3.5 (<2.1) [8] showing significant insulin resistance. DAA were positive and in high levels, for both glutamic acid decarboxylase 65 (anti-GAD) (19.5 U/ml) and insulinoma-associated antigen IA-2 antibodies (anti-IA2) (4.1 U/ml), (RR: <0.9 U/ml and <0.75 U/ml respectively). Because of the strong family history of T2D, presence of overweight and normal fasting and after Glucagon stimulation C-peptide levels he was diagnosed as T2D with double DAA positivity (Table 1). With the diagnosis of T2D he was managed with diet and exercise and, due to poor diabetic control (HbA1c:7.4%), he was commenced on treatment with oral metformin (850 mg/day before lunch). He had initially good glycemic control (HbA1c: 7.2%) with fasting blood glucose ranging between 95-110 mg/dl and post prandially 110-170 mg/dl. Five months later he presented with significant metabolic derangement (elevated pre- and postprandial glucose levels especially at dinner, 170-180 mg/dl and 180-230 mg/dl respectively) and a second dose of metformin was added before dinner. Eight months after the diagnosis of T2D, he presented with metabolic derangement and weight loss of 12 kg within two weeks’ time and was admitted with severe Diabetic Ketoacidosis (DKA). His BMI was significantly reduced (20.5 kg/m2) (25-50th centile) (normal weight) and his HbA1c levels were 9.7%. He was initially managed as per the DKA protocol and after stabilization he was started on SC insulin treatment with long and short acting insulin analogues at bed-time and before the 3 main meals respectively. C-peptide levels at that time were significantly reduced, both fasting and after Glucagon stimulation (0.78 ng/ml and 0.67 ng/ml, respectively) (RR: 1.77-4.68 ng/ml). Both DAA were still positive and in elevated titers, (anti-GAD: 10.6 U/ml and IA2: 3.2 U/ml) (RR: <0.9 U/ml and <0.75 U/ml respectively). Screening for antibodies associated with celiac disease and autoimmune thyroiditis was negative. The patient...
also presented microalbuminuria (53 mg/L) (RR<20 mg/L) with normal blood pressure levels. HLA genotyping revealed the presence of the DRB1*0301-DQA1*05-DQB1*0201 haplotype (DR3-DQ2), which is associated with T1D.

The initial diagnosis of T2D was reconsidered and at present, 6 months after his admission with DKA, the patient is managed as T1D with basal-bolus SC insulin, requiring 0.76 IU/kg/day. He has become overweight again (BMI: 24.4 kg/m2, <75th percentile), and his glycemic control remains poor (HbA1c: 9.1%). Although he was advised to continue metformin in parallel with the multiple injection regimen due to insulin resistance, the patient discontinued metformin one month after insulin treatment initiation. His microalbuminuria is intermittent [3-33 mg/L/24h] and has subsided, while his blood pressure is normal.

### Table 1: Clinical and laboratory characteristics of our patient at initial presentation and 1 year later.

<table>
<thead>
<tr>
<th></th>
<th>1st presentation</th>
<th>1 year later</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>13.5</td>
<td>14.5</td>
</tr>
<tr>
<td><strong>Ketoacidosis</strong></td>
<td>absent</td>
<td>present</td>
</tr>
<tr>
<td><strong>BMI (kg/m2)</strong></td>
<td>27 (75th)</td>
<td>20.8 (25th-50th)</td>
</tr>
<tr>
<td><strong>OGTT (glucose (mg/dl) at 0'/30'/60'/120]</strong></td>
<td>[141/ 194/ 253/ 281]</td>
<td>[12.4/27.4/24.4/26.6]</td>
</tr>
<tr>
<td><strong>Fasting C-peptide (ng/ml)</strong></td>
<td>1.1 (0.4-4.0)</td>
<td>0.78 (1.77-4.68)</td>
</tr>
<tr>
<td><strong>Postprandial C-peptide (ng/ml)</strong></td>
<td>2.9 (0.4-4.0)</td>
<td>0.67 (1.77-4.68)</td>
</tr>
<tr>
<td><strong>Anti-GAD (U/ml)</strong></td>
<td>19.5</td>
<td>10.6 (&lt;0.9)</td>
</tr>
<tr>
<td><strong>Anti-IA2 (U/ml)</strong></td>
<td>4.1</td>
<td>3.2 (&lt;0.75)</td>
</tr>
<tr>
<td><strong>HLA</strong></td>
<td>-</td>
<td>DRB1<em>0301-DQA1</em>05-DQB1*0201</td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td>7.4%</td>
<td>9.7% (4.5-6.2%)</td>
</tr>
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### Discussion

T1D is still the commonest type of diabetes in childhood worldwide, despite the increased incidence of obesity in the young population. Of particular interest is the recent recognition of a new type of diabetes in children and adolescents, characterized by the combination of markers of both T1D and T2D. Our patient was a teenager who initially presented with overweight, insulin resistance, symptomatic hyperglycemia, OGTT in the diabetes range and initially normal C-peptide levels, findings consistent with T2D. In addition, the strong family history of T2D, the history of neonatal macrosomia and maternal GDM, as well as the initial good response to treatment with metformin favored the diagnosis of T2D. The only unusual finding was the presence of double DAA positivity, which however can be present in a small proportion (9.8%) of T2D patients [9]. The unexpected finding in our case is that eight months after clinical presentation of T2D the patient developed substantial weight loss, severe DKA and significant reduction of his pancreatic reserve.

The differential diagnosis includes T1D on remission-relapse, T2D with rapid evolution to insulin-dependence, African Diabetes, “Latent Autoimmune Diabetes in Children” (LADC) and double diabetes. Regarding the first differential diagnosis, in T1D the usual time-period of symptoms onset until the development of DKA is 24.5...
± 22.1 days [10]. There are rare cases with T1D on remission, which are characterized by the presence of normal OGTT and normal C-peptide levels in patients with double DAA positivity, who eventually evolve to insulin dependence and overt diabetes; however, when OGTT is impaired in T1D, it is accompanied by low C-peptide levels [11]. Our patient had impaired OGTT at the diabetes range since the initial symptoms presentation, but C-peptide levels were normal, together with all the characteristics of T2D, and thus the diagnosis of T2D was initially made. However, 8 months later he had inappropriately low C-peptide levels, indicative of a very rapid beta-cell destruction, possibly associated with the double pancreatic antibody positivity. Katz LE et al have shown that a fasting C-peptide level of \(<0.85 \text{ ng/ml at diagnosis can differentiate T1D from T2D with a sensitivity of 83% and a specificity of 89%} [12]. Our patient’s fasting C-peptide levels were at initial presentation 1.1 ng/ml, and tripled after Glucagon stimulation, while 8 months later they were 0.78 ng/ml at the T1D range, with further reduction after Glucagon stimulation. Another entity which may be considered is rapidly evolving T2D. It has been reported that T2D in childhood and adolescence evolves to insulin-dependence more rapidly than T2D in adults [13] with 50% of children requiring insulin by 3 years after diagnosis, while reported rates of metformin failure in adults are 21-50% at 5 years [14]. Predictive factors of future insulin dependence in childhood T2D include insulin treatment after diagnosis, and also non-compliance or intolerance of metformin treatment [13]. In our case, although the patient was initially treated with metformin with progressively increasing doses, insulin dependence presented within 8 months after T2D diagnosis, indicating a rapid decline of his pancreatic reserve, which occurred far more rapidly than the usual natural course of T2D.

As already mentioned, adult patients with features of T2D and positive DAA who do not require insulin treatment for at least 6 months after diabetes diagnosis are classified as LADA patients [15,16]. Regarding LADA subtypes, patients with double DAA positivity or with one DAA in high titres and low C-peptide levels are classified as LADA type 1, while those with one DAA positive in low titres, accompanied by normal C-peptide levels and insulin resistance belong to LADA type 2 [17]. The present classification of LADA includes only adult patients >35 years old [18]. However, there are two previous studies [6,7] reporting the cases of three 8-9 year old children with LADC (latent autoimmune diabetes in children). Our patient had all the aforementioned characteristic features of LADA type 1, as he had two DAA positive and significantly reduced C-peptide levels. However, LADA, type 1 is not characterized by the presence of overweight/obesity and insulin resistance [5], which was a persistent characteristic of our patient.

Due to the African origin of our patient, the differential diagnosis of African Diabetes is also possible. This is an atypical presentation of diabetes, affecting both adolescent and adult populations [19], which is characterized by an acute onset with severe hyperglycemia and ketosis (ketosis prone diabetes) and a clinical course of T2D. Subsequently, after initiation of insulin therapy, prolonged remission is often possible with cessation of insulin therapy and maintenance of appropriate metabolic control. The molecular mechanisms underlining the insulin secretory dysfunction are still to be understood and may involve glucolipotoxicity processes. The HLA alleles associated with susceptibility to T1D were reported of high frequency in some populations with this form of diabetes, in the absence of makers of pancreatic beta cell autoimmunity [19]. From the above characteristics, our patient was of African origin, initially presented with the clinical and laboratory findings of T2D and had the HLA alleles associated with T1D. However, he had double pancreatic antibody positivity, which is not characteristic of African Diabetes. Furthermore, he rapidly progressed to insulin dependence, which is not a feature of African Diabetes, usually leading to remission. Another possible diagnosis for our patient could be Double or Hybrid Diabetes (DD) [3], which is a type of diabetes overlapping diabetes phenotype of T1D and T2D. These patients are youths with features of both T1D
(multiple DAA positivity) and T2D (obesity and insulin resistance), accompanied by the presence of family history of both T1D and T2D. These patients, who were initially diagnosed as having T2D, are characterized by rapid beta cell loss and are at increased risk of the development of complications [20]. HLA haplotypes associated with DD are DR3-DQ2, DR4-DQ8, DQ6 and other [21]. All the above characteristics were present in our patient as well as the high risk genotype.

Several current studies have investigated the genetic predisposition of different types of diabetes [22-24]. It is well known that the Human Leukocyte Antigen (HLA) class II genes harbor susceptible or protective alleles for the development of T1D. In particular, among the high risk for T1D haplotypes are DRB1*0301-DQA1*0501-DQB1*0201, DRB1*0401-DQA1*0301-DQB1*0302, and DRB1*0401-DQA1*0301-DQB8*0302 (ORs 11.37, 8.39, and 3.63 respectively) [22]. The DRB1*0301-DQA1*05-DQB1*0201 haplotype, which is found in our patient, is a high risk haplotype mainly associated with T1D. However, studies in patients with double diabetes and LADA have shown that both entities share the same high risk HLA haplotypes with T1D [21,22]. Specifically, a previous study showed that 81% of patients with double diabetes had a high or medium risk genotype, including the DRB1*0301-DQA1*05-DQB1*0201 haplotype that was present in our patient [21]. It is evident though that the presence of high risk genotypes in combination with DAA positivity predicts a more aggressive clinical course and this could explain our patient’s rapid evolution to insulin dependence.

It has been reported that in patients with double diabetes, high titres of anti-GAD are positively associated to increased BMI [25]. Previous studies suggest that there is a link between obesity and the development of autoimmunity. The possible mechanism involved could be that inflammatory hormonal signals associated with insulin resistance (mediated by leptin and adiponectin) might contribute to the development of autoimmunity in genetically susceptible individuals [3].

Regarding therapeutic strategy, taking into account data from adult studies in patients with LADA, that share similar features with young patients with double diabetes, there are three main reasons why appropriate classification is necessary. Firstly, patients with double diabetes or LADA, after identification, should be placed on insulin therapy earlier, which will improve their metabolic control, as shown in adult population studies [26,27]. Furthermore, many of these patients are reported to have poor glycemic control under insulin therapy [28], as did our patient, probably due to a certain degree of insulin resistance. Thus, according to recent evidence, the management of these patients should include metformin, glycosidase inhibitors, as well as Glucagon-Like Peptide 1 (GLP-1) receptor agonists, together with fitness intervention program, in order to increase insulin sensitivity. In addition, the early use of insulin has been proposed to prevent the decline of beta cell function [20,29]. Regarding complications, recent studies have shown that patients with double diabetes have an increased prevalence of micro- and macrovascular complications, as did our patient, even if they maintain good glycemic control [26,30]; therefore, early identification is crucial.

**Conclusion**

The present case is reporting on a teenager with double DAA positivity, who initially presented with clinical and laboratory features of T2D and 8 months later presented rapid decline of his pancreatic reserve. With the increasing prevalence of childhood overweight/obesity, the present study underlines the possibility of the presentation of this unusual type of double diabetes with clinical and laboratory characteristics of both T1D and T2D, belonging to the grey area between T1D and T2D. This would assist clinicians to identify and manage appropriately this distinct group of pediatric patients with diabetes, in order to preserve their beta cell function, achieve a better glycemic control, and avoid the early development of microvascular complications.

**References**


