Journal of Pediatric Genetics 2 (2012) 131–134
DOI 10.3233/PGE-2012-021
IOS Press



# The phenotype masks the genotype: A possible new expression of diabetes

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Received 14 September 2010
Revised 31 January 2011
Accepted 19 March 2011

**Abstract.** The concept of a new form of diabetes, with signs of both types 1 and 2, has not been often considered, until recently. It is of immense interest to explore the role of the admixture that characterizes the Uruguayan population (higher and different from other Latin America countries) for the presence of such expression of that particular disease. We describe here a child who possibly presents with this expression. He had typical signs of both diabetic conditions: type 1 (young age, positive immunologic and genetic markers, ketoacidosis) and type 2 (obesity [body mass index = 36 kg/m$^2$] and acanthosis nigricans). In spite of complying with the established guidelines, therapeutic and nutritional control, quality of life and good metabolic control, the patient's obesity had been continually increasing. Looking for a genetic explanation, we studied three single nucleotide polymorphisms involved in three different metabolic pathways (peroxisome proliferator-activated receptor gamma 2, insulin receptor substrate-1 and uncoupling protein-2) associated with insulin resistance. Our patient showed three mutations, GG, GA, GG, associated with insulin resistance that explains obesity associated with limited response to the commonly used drugs. According to the clinical presentation and the genetic and immunological background, we considered that this patient presents with a new form of diabetes. We have termed this particular disease "hybrid diabetes" because of the involvement of genes associated with both the classical type of diabetes. However, at least in an admixed population such as in Uruguay, clinical classification would not strictly dictate the choice of treatment.

Keywords: Type 1 diabetes, HLA, GAD antibody

## 1. Introduction

Type 1 diabetes (T1D) is characterized by insulin deficiency and type 2 diabetes (T2D) has been linked to insulin resistance [1]. In the past, most children and adolescents affected by the disease were diagnosed as T1D. However, the American Diabetes Association recognizes in the consensus statement titled "T2D in children and adolescents" the presence of T2D at an early age [2,3].

There have been numerous reports describing an increasing number of T2D cases in youngsters [4–7]. Recently, Lidman and Becker [8] have described the coexistence of both types of diabetes in a non-Caucasian individual. Further, Pozzili and Buzzetti [9] have also described several cases with a new type of diabetes and proposed additional studies on different ethnic groups. At present, very few studies have been reported on ethnically mixed populations [10]. Previous publications have

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demonstrated a high degree of admixture among Uruguayan population compared to the rest of Latin-American countries [11–15]. This situation could be contributing to the emergence of this new form of diabetes. The potential importance of making a specific diagnosis has been emphasized since it would determine the form of treatment, associated complications and outcomes [16,17].

This new expression of the disease was characterized by (a) the presence of clinical features of T2D (hypertension, dyslipidemia and increased body mass index [BMI]), (b) the presence of a reduced number of clinical features typical of T1D (weight lost, polyuria and polydispsia and development of ketoacidosis), (c) the presence of autoantibodies to islet cells, although with a reduced number and titer compared with T1D. All of these patients are always characterized by an obese phenotype. However, recognition of this new entity poses diagnostic problems [9]. We describe here a case that is possibly affected by this special form of the disease.

## 2. Case report

A Uruguayan boy (ethnic background: Caucasian, African and Amerindian), born in 1990, was admitted to a pediatric center at age 7 yr and 6 mo due to a respiratory infection with pustular angina and purulent rhinorrhoea. He complained of a history of increasing polyuria, polydipsia, asthenia, fatigue and fever with a body mass index (BMI) of 36 kg/m$^2$ (height = 1.36 m, weight = 58 kg) and presence of acanthosis nigricans. His blood glucose was 320 mg/dL with ketonemia. He was metabolically stabilized with neutral protamine hagedorn (NPH) insulin at 20/15 units adjusted with crystalline insulin prior to a light meal. In the next months, he showed good metabolic control with fasting glucose of 60 mg/dL–130 mg/dL before lunch and 80–120 mg/dL before dinner. Unfortunately, as he was given up for adoption, no family history was available. Follow-up was done in our outpatient clinic for the next years, at 3 month intervals. To confirm the T1D diagnosis, immunological and genetic studies were performed. Glutamic acid decarboxylase antibodies (50.9 U/L) and islet cell antibodies (8 uJDF [unit Juvenil Diabetes Foundation]) positive antibodies and a human leukocyte antigen genotype DQB1*0201/0302-DR3/DR4 (associated to T1D) were present. In the next few months, he showed good metabolic control. However, 3 mo later, nocturnal hypoglycemia and early-afternoon hypoglycemic episodes were observed. Therefore, the amount of insulin was reduced and an insulin sensitizer drug was introduced (metformin 500) before lunch and dinner. Later, the insulin treatment was suspended and he received only metformin 850 in lunch and dinner for 6 yr. During this period he had good metabolic control with HbA1c between 5.8 and 6.1%, with blood glucose levels monitored 3 or 4 times a week with normal values.

At the age of 14-years (March 2004) the patient presented again with hyperglycemic glucose levels and uncontrolled gain of weight (68 kg) and a height of 160 cm (BMI = 26.56 kg/m$^2$). Insulin treatment was re-introduced again. His metabolic control improved, but in spite of treatment and diet, he continued to be overweight.

Looking for an explanation for his persistent obesity and insulin resistance, after informed, written consent, several single nucleotide polymorphisms (SNPs) from different metabolic pathways were studied: (a) Pro$^{12}$→Ala (rs1801282) substitution in the peroxisome proliferator-activated receptor gamma 2 (*PPARγ2*) gene (b) Arg$^{972}$IRS-1 (rs1801278) in insulin receptor substrate-1 (*IRS-1*) and (c) –866G/A variant (rs659366) in the promoter region of uncoupling protein 2 (*UCP2*). The results demonstrated a homozygous mutation genotype for Pro$^{12}$→Ala (Pro/Pro) and –866G/A variant (GG), and heterozygous state (Gly/Arg) for the Arg$^{972}$IRS-1 variant. At present, he is 20-years old with a height of 168 cm, weighing 66 kg (BMI = 23.38 kg/m$^2$), and an HbA1c of 7%. He did not show microalbuminuria and the fundi of both eyes were normal. He practices physical exercises (swimming) three times a week. The therapeutic treatment in this moment is NPH insulin and rapid-action insulin analogue.

## 3. Discussion

Different population studies conducted in Uruguay have shown that the contribution of different ethnicities in the recent past has led to the existence of an admixed population. It is of interest to point out that the acquired results are not always comparable to the data obtained from research conducted exclusively in Caucasian populations [11–15]. The particular genetic mix would facilitate the presence of a different expression of the classic presentation of diabetes [18]. An accurate diagnosis is important for the implementation of an appropriate treatment, improvement in the

screening for associated abnormalities and future outcomes. This fact is also relevant for researchers and epidemiologists interested in the impact, etiology and pathogenesis of diabetes [8].

At the onset of the disease in our patient, (13 yrs ago), the clinical features did not permit differentiation between both diabetes types. Typical signs of T1D and T2D were present. He was treated with insulin in the acute phase. After 3 mo, he had good metabolic control but hypoglycemic episodes and physician evaluation determined insulin suspension. Unfortunately, no measurements of C-peptide levels were available at that time, but his low insulin requirements after diagnosis and following the suspension of insulin treatment suggest a relatively low HbA1c value. Molecular and serological studied demonstrated the presence of islet cell autoimmunity. If a T1D typical diagnosis was correct, it is hard to believe that the expected "honeymoon" period would extend for 6 yrs. In spite of a controlled diet and physical exercises, uncontrolled obesity was increasingly established during this period. Accordingly, we decided to investigate some SNPs involved in insulin resistance: (a) PPAR$\gamma$2. This gene is a nuclear receptor that regulates adipocyte differentiation. Variations in the PPAR$\gamma$ gene may affect the function of the protein PPAR$\gamma$ and, therefore, body adiposity [19,20]. A study based on other samples of our population found that a direct relationship between the intakes of trans fatty acids and T2D exists [21], (b) IRS-1: The Arg972 variant is more prevalent in subjects with T2D who have insulin resistance, whether associated or not with dyslipidemia. This polymorphism can lead to defects in the protein involved in insulin signaling, causing insulin resistance and damage to peripheral insulin secretion. [22–24] (c) UCP2: This gene is an integral protein of the inner mitochondrial membrane, uncoupling oxidative metabolism of glucose in the production of ATP [24]. The –866G/A polymorphism has been associated with obesity, insulin secretion, and T2D [25–29].

The patient presented three genotypic variants, which would explain the presence of insulin resistance and obesity. Furthermore, it is possible that observed genotype would explain the difficult metabolic control because these mutations would limit a proper response to commonly used drugs. A population study now in progress will give us information in this matter.

The present case report would confirm the existence of the new expression of the disease, although it is not clear whether different classifications should always affect treatment choices. The addition of insulin sensitizers to the therapeutic regimen should be considered under appropriate clinical circumstances and lifestyle changes should be attempted in patients with features of T2D. Whether insulin should always be part of the regimen in T2D remains controversial [22,23,30,31].

According to the clinical presentation and the genetic and immunological background, we consider that this patient represents a new form of diabetes. At least for this patient, to use the term "hybrid diabetes" postulated by other authors [8,9] to refer to this particular expression of the disease would be adequate. The evidence at the molecular level with the presence of mutations in genes that associate with both the classical types of diabetes would support this term. However, in an admixed population such as ours, clinical classification would not strictly determine the treatment choice.

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