Adult-Onset Atypical (Type 1) Diabetes

Additional insights and differences with type 1A diabetes in a European Mediterranean population

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OBJECTIVE — In 1997, the American Diabetes Association proposed two subcategories for type 1 diabetes: type 1A or immunomediated diabetes and type 1B or idiopathic diabetes characterized by negative β-cell autoimmunity markers, lack of association with HLA, and fluctuating insulinopenia. The aim of this study was to examine clinical characteristics, β-cell function, HLA typing, and mutations in maturity-onset diabetes of the young (MODY) genes in patients with atypical type 1 diabetes (type 1 diabetes diagnosed at onset, without pancreatic autoantibodies and fluctuating insulinopenia).

RESEARCH DESIGN AND METHODS — Eight patients with atypical type 1 diabetes (all men, 30.7 ± 7.6 years) and 16 newly diagnosed age- and sex-matched patients with type 1A diabetes were studied retrospectively. Islet cell, GAD, tyrosine phosphatase and insulin antibodies, and basal and stimulated plasma C-peptide were measured at onset and after 1 year. HLA-DRB1-DQA1-DQB1 typing and screening for mutations in the HNF-1α and HNF-4α genes were performed from genomic DNA.

RESULTS — Atypical patients displayed significantly higher BMI and better β-cell function at onset and after 12 months. Three patients carried protective or neutral type 1 diabetes haplotypes, five patients displayed heterozygosity for susceptible and protective haplotypes, and seven patients showed $Asp^{\beta 57}$. We found a nondescribed variant Pro436Ser in exon 10 of the HNF-4α gene in one atypical patient without susceptible haplotypes.

CONCLUSIONS — In our population, there are atypical forms of young adult–onset ketosis-prone diabetes initially diagnosed as type 1 diabetes, differing from type 1 diabetes in the absence of β-cell autoimmunity, persistent β-cell function capacity, fluctuating insulin requirements and ketosis-prone episodes, as well as clinical features of type 2 diabetes. Only one subgroup could be strictly classified as having type 1B diabetes. Additional information is still needed to improve our understanding of the mechanisms that finally lead to the disease.

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In 1997, the American Diabetes Association proposed two subcategories for type 1 diabetes: type 1A or immunomediated diabetes and type 1B or idiopathic diabetes (1). Absence of β-cell autoimmunity markers and lack of association with HLA haplotypes predisposing diabetes mainly characterize the latter subcategory. Individuals with this form of diabetes can develop ketosis/ketoacidosis and exhibit various degrees of insulin deficiency between episodes. Only a minority of patients with type 1 diabetes fall into this subcategory and most are of African-American or Asian origin (2–4). Recently, some authors have described this subcategory in other ethnic groups, such as Native Americans and Hispanic Americans (5). The initial manifestation of the diabetes in these cases may be ketoacidosis similar to type 1A diabetes, although the course of the disease is unusual as insulin therapy is initially needed to maintain metabolic control and, after a variable period of time (usually within months), good control can be achieved with either diet or oral agents (5–9). On the other hand, these patients differ from those with type 1A diabetes because their physical characteristics are more typical of patients with type 2 diabetes; they are often obese or overweight at the time of diagnosis and, in most of the cases, there is a family history of type 2 diabetes (5).

Little is known about the pathogenesis of type 1B diabetes. It has been suggested that a mechanism other than the autoimmune destruction of β-cells produces β-cell failure. After insulin therapy is initiated, there is β-cell recovery, which is usually short in duration. Other factors such as glucotoxicity and lipotoxicicity, as well as environmental factors, have also been involved (5,10,11).

Type 1B diabetes is highly common in North America, especially in areas with a patient population including African Americans and Latin Americans (10). Nevertheless, there is scarce information concerning the prevalence of type 1B diabetes in Caucasians (12,13). It is well known that a variable proportion of patients with newly diagnosed type 1 diabetes are negative for β-cell autoimmunity markers, and this proportion may oscillate depending on the population (14,15). These patients cannot be included in the subcategory of type 1B diabetes because they usually show clinical and β-cell function characteristics similar to those with positive pancreatic markers and HLA haplotypes predisposing diabetes (14,16–19).

Maturity-onset diabetes of the young (MODY) is a type of diabetes resulting from genetic defects of β-cell function characterized by an autosomal-dominant inheritance and early age of onset (1). Re-

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Abbreviations: GADAb, GAD antibody; IAAb, insulin autoantibody; IA2Ab, tyrosine phosphatase antibody; MODY, maturity-onset diabetes of the young; SSO, specific-sequence oligonucleoprobe.

cently, mutations in MODY genes have been described in subjects initially classified as having type 1 diabetes, lacking pancreatic autoantibodies and high-risk HLA haplotypes (20,21) and in African-American children with atypical diabetes (22). The most frequent subtype of MODY in our area is MODY 3, which is due to mutations in the HNF-1α gene (23). MODY 1, with mutations in the HNF-4α gene, is a rare disorder. These latter forms of MODY are associated with a progressive decrease in insulin secretion frequently resulting in the need for treatment with insulin (24,25).

The aim of the study was to examine the clinical characteristics, β-cell function, HLA typing, and presence of mutations in MODY genes in a group of Caucasian patients of Mediterranean origin with adult-onset atypical type 1 diabetes (type 1 diabetes diagnosed at onset, with absence of pancreatic autoantibodies and fluctuating insulinopenia).

RESEARCH DESIGN AND METHODS

— We retrospectively studied eight patients with newly diagnosed atypical type 1 diabetes. All of these patients presented with acute hyperglycemia or ketosis without any identifiable precipitating factor (ketonuria: ketones >150 mg/dl; nitroprusside reaction method) and were initially diagnosed and catalogued as having type 1 diabetes according to the National Diabetes Data Group criteria (26). None of them presented with diabetic ketoacidosis (plasma glucose >250–300 mg/dl, arterial pH <7.25, serum bicarbonate <15 mEq/l, and ketones >150 mg/dl). These patients were initially treated with insulin therapy during a variable period of time (usually <6 months after onset of the disease), but none were on insulin therapy 1 year after diagnosis. Five of these patients achieved good metabolic control with diet, and three were under oral agents (acarbose, metformin, or glymepiride). These patients showed negativity for pancreatic autoantibodies and were able to discontinue insulin completely for at least 2 years after diagnosis without development of ketonuria or symptoms of hyperglycemia. During follow-up, these patients showed recurrence of unprovoked ketosis episodes (including those who only presented symptomatic hyperglycemia at diagnosis) or symptomatic hyperglycemia requiring insulin therapy. A group of 16 newly diagnosed age- and sex-matched type 1A diabetic subjects who had been treated in our Diabetes Unit were included as a control group.

All patients with newly diagnosed type 1 diabetes in our hospital are treated in an intensive manner with three or four daily doses of subcutaneous insulin: rapid-acting insulin before meals and NPH insulin before dinner/bedtime. They follow a diet adjusted to their age and BMI, and insulin doses are adjusted to maintain preprandial glucose between 3.9 and 7.0 mmol/l and postprandial glucose <10 mmol/l based on four to six daily capillary blood determinations. At onset of the disease, all subjects are included in a 5-day education program for individuals with newly diagnosed type 1 diabetes. Patients are seen by the same team every 2 weeks during the first 3 months and monthly thereafter until 12 months of follow-up. Patients are instructed concerning glucose goals and self-monitoring glucose control when necessary.

Glucagon tests and antibody measurements are determined initially and at month 12. HbA_{1c} is determined by high-performance liquid chromatography (HA 8121; Menarini Diagnostici, Firenze, Italy) initially and at 12 months (normal range 3.4–5.5%).

Autoantibody measurements

Islet cell antibodies were determined by an immunofluorescence technique (27). GAD antibodies (GADAbs) were determined by a radiobinding assay and were considered positive at >2 units/ml. The assay for GADAbs achieved 100% sensitivity and 100% specificity in the second GAD proficiency test. Tyrosine phosphatase antibodies (IA2Abs) titers were measured in a radiobinding assay and considered positive at >0.8 units/ml. The interassay and intra-assay coefficient of variation of IA2Abs determination were 7 and 5%, respectively. The upper limits of normal values for GADAbs and IA2Abs were defined by the 99th percentile of antibodies measured in 110 nondiabetic subjects without a family history of type 1 diabetes. Insulin autoantibodies (IAAbs) were measured using a radiobinding method. The upper normal limit of 1% was defined after analysis of 500 samples from healthy control subjects. The interassay coefficient of variation of IAAbs was 12%.

Assessment of pancreatic β-cell function

The glucagon test was performed in the absence of hypoglycemia in the previous 48 h and only when fasting blood glucose values were between 5.0 and 8.0 mmol/l. Plasma C-peptide measurements were performed basally and 2, 4, 6, 8, and 10 min after intravenous administration of 1 mg glucagon. C-peptide level was determined using a commercially available kit (Bick Santeg, Dietzenbach, Germany; limit of detection 0.033 mmol/l, intra-assay coefficient of variation 2.6%, inter-assay coefficient of variation 4.4%). Basal and maximal glucagon-stimulated values of C-peptide were used as β-cell function parameters.

HLA typing

HLA-DRB1 typing was performed from genomic DNA. DNA was extracted from peripheral leukocytes. Genomic typing for class II genes was performed by amplification of exon 2 from the DRB1 gene followed by sequencing using commercial kits. Electrophoresis was run on an ALF express automated sequencer (Amersham Pharmacia Biotech, Uppsala, Sweden). Sequence data were processed automatically and evaluated manually. Typing was performed using the Pharmacia Typing Software (Alfwin 1.10/HLA sequityper 2.00 Software) comparing sequences with the manufacturer's database (updated July 2001). In case of ambiguities to assign the allele specificity, high-resolution specific-sequence oligonucleoprobe (SSO) typing was performed (Dynal, Madrid, Spain). The DQA1 and DQB1 alleles were defined by SSOs. The latest recommendations of the World Health Organization committee for factors of the HLA system were employed using four digits (28). For the assignment of alleles as "antigens," only two digits were used. The presence of susceptibility or resistance/neutral HLA-DQ genotypes and $Asp^{\beta 57}$ as a protective factor (susceptibility means increased diabetes relative risk, resistance means decreased relative risk, and neutral means neither susceptibility nor resistance) was also analyzed according to the literature (29,30).

Screening for mutations in the HNF-1α and HNF-4α genes

DNA was isolated from peripheral leukocytes. We investigated the 12 exons (1A-1B-1C and exons 2–10) of the HNF-4α

Table 1—*Sequences of new combinations of primers for amplification of HNF-4α*

Region	Forward primer (5′-3′)	Reverse primer (5′-3′)	Product size (bp)
Exon 1A	GGCGTGGAGGCAGGGAGAAT	GCCTGTAGGACCAACCTACC	263
Exon 1C	TGGCCGACTACAGTGCTGCAC	CCTTGCCGTCTCTCTGAACC	486
Exon 3	CCTAGTTCTGTCCTAAGAGG	GTTGTAAATGACTGTCGGGG	234

gene using PCR. The primers have been previously described, except in the case of exons 1A-1C-3, for which we used a new combination of primers (31,32) (Table 1). The 10 exons of the HNF-1α gene were studied using PCR with previously described primers (33,34). The PCR conditions were denaturation at 94°C for 5 min followed by 35 cycles of denaturation at 96° for 30 s, annealing for 30 s at different temperatures (54° for exons 1A-1C-3-9 of the HNF-4α gene, 58° for exons 1B-2-4-5-6-7-8-10 of the HNF-4α gene, and 62° for all of the exons of the HNF-1α gene), and extension at 72°C for 30 s, with a final extension at 72°C for 5 min. Each reaction contained DMSO (4%) in the case of exons 1A-1C-3 of the HNF-4α gene and exons 1 and 4 of the HNF-1α gene. PCR products of exons 1C, 2, 3, and 8 of the HNF-4α gene and of exons 1, 2, and 4 of the HNF-1α gene were cut into smaller fragments by restriction enzymes before single-strand conformational polymorphism (SSCP) analysis. The restriction enzymes used were *Msp*I for exon 1C, *Rsa*I for exon 2, *Hae*III for exon 3, and *Hin*f I for exon 8 of the HNF-4α gene and *Msp*I for exon 1, *Pst*I for exon 2, and *Hha*I for exon 4 of the HNF-1α gene. These restriction sites were located in intron sequences. The samples with bands with abnormal mobility were studied by automated sequencing.

Statistical analysis

Results are presented as means ± SD. Comparisons between the two groups were performed using Mann-Whitney *U* test for quantitative variables. Comparisons between proportions were performed using χ^2 test. A P value <0.05 was considered statistically significant. All statistical calculations were performed by the Statistical Package for Social Science (SPSS) for personal computers (SPSS, Chicago, IL).

RESULTS

Clinical characteristics, metabolic control, and β-cell function

The clinical, metabolic, and β-cell function characteristics of the two groups of subjects at baseline are shown in Table 2. There were no differences between the two groups in terms of duration of symptoms, insulin requirements, or HbA_{1c} levels. The type of onset was predominantly ketosis in atypical subjects, being ketoacidosis in type 1A diabetic subjects. Subjects with atypical type 1 diabetes displayed a higher BMI; these differences were statistically significant. These patients also showed significantly higher levels of basal and maximal C-peptide. The characteristics of each of the atypical patients at the onset of the disease are shown in Table 3.

The characteristics of both groups of patients 12 months after onset of the disease are shown in Table 4. Patients with atypical type 1 diabetes had significantly higher levels of basal and maximal C-peptide compared with type 1A diabetic subjects.

Table 2—*Baseline characteristics of the study groups*

	Atypical type 1 diabetes	Type 1A diabetes	*P*
n	8	16	
Age (years)	30.7 ± 7.6	28.0 ± 5.5	NS
Sex (men/women)	8/0	16/0	
Family history of type 2 diabetes	7/8	8/16	NS
BMI (kg/m^2)	28.1 ± 4.7	22.9 ± 4.4	0.016
Duration of symptoms (weeks)	12.0 ± 18.0	9.2 ± 11.7	NS
Loss of weight (kg/week)	1.4 ± 1.5	1.4 ± 1.1	NS
HbA_{1c} (%)	11.1 ± 1.5	11.4 ± 2.1	NS
Clinical presentation at onset (hyperglycemia/ketosis/ketoacidosis)	2/6/0	2/5/9	0.02
Insulin dose (units/kg)	0.6 ± 0.1	0.7 ± 0.2	NS
Basal C-peptide (nmol/l)	0.51 ± 0.22	0.22 ± 0.08	0.001
Maximally stimulated C-peptide (nmol/l)	1.12 ± 0.27	0.51 ± 0.22	0.000

Data are means ± SD.

Pancreatic autoantibodies

Considering the frequency of pancreatic autoantibodies among type 1A diabetic subjects at onset, 12 of 16 subjects were positive for islet cell antibodies (75%), 11 of 16 were positive for GADAb (68.7%), 9 of 16 were positive for IA2Ab (56.2%), and 5 of 16 were positive for IAAb (31.2%). As mentioned above, all atypical patients were negative for all pancreatic autoantibodies tested on at least two occasions.

HLA

There were differences between the two groups in HLA typing: type 1A diabetic patients showed a major proportion of HLA haplotypes predisposing diabetes (30). A total of 85% of type 1A diabetic subjects carried DRB1*03/*04 versus 62% of patients with atypical type 1 diabetes ($P = 0.45$). The most frequent haplotype in both groups was DRB1*0301-DQA1*0501-DQB1*0201 (DQ2) (five of eight patients in the atypical group showed this haplotype versus 8 of 16 patients with type 1A diabetes, $P = 0.80$). None of the type 1A diabetic patients displayed haplotype HLA-DR11, whereas five of eight patients with atypical type 1 diabetes showed it in the haplotype (Table 5 shows HLA haplotypes of patients with atypical type 1 diabetes); this difference was statistically significant ($P < 0.01$). Five of eight patients with atypical type 1 diabetes displayed susceptible type 1 diabetes haplotypes, but in all cases except one, these haplotypes were in combination with a type 1 diabetes–resistant HLA haplotype and/or with the presence of $Asp^{\beta 57}$. Three patients of the atypical group carried resistant or neutral type 1 diabetes haplotypes and $Asp^{\beta 57}$ (30).

Table 3—*Characteristics of patients with atypical type 1 diabetes at onset of the disease*

	Age (years)	BMI (kg/m^2)	HbA_{1c} (%)	Onset	Insulin dose (units/kg)	Basal C-peptide (nmol/l)	Maximal C-peptide (nmol/l)
Patient 1	21	34.4	11.5	H	0.61	0.79	1.45
Patient 2	29	26	11.4	K	0.47	0.49	1.15
Patient 3	30	26.4	11.5	K	0.60	0.49	1.29
Patient 4	42	25.5	9.5	K	0.72	1.02	1.58
Patient 5	20	36	9.1	K	0.40	0.31	0.92
Patient 6	37	27.9	13.5	K	0.71	0.26	0.69
Patient 7	31	26.5	9.7	K	0.57	0.76	1.29
Patient 8	36	22	11.6	H	0.60	0.40	1.22

Data are means ± SD. H, hyperglycemia; K, ketosis.

Mutations in HNF-1α and HNF-4α genes

After analysis of the 10 exons of the HNF-1α gene, we did not find mutations in any group. When we studied the HNF-4α gene, we found a nondescribed variant in codon 436 of exon 10 resulting in a single amino acid substitution (proline by serine) in one of the subjects with atypical type 1 diabetes (Table 3, patient 1). None of the subjects in the type 1A diabetes group showed this variant, and it was absent in DNA of 80 control subjects. Unfortunately, it was impossible to perform a family study of the patient with the variant.

CONCLUSIONS — Our study suggests that atypical forms of adult-onset type 1 diabetes may be detected among subjects of Caucasian origin in a Mediterranean area. Despite an initial clinical presentation compatible with type 1 diabetes, they differ in terms of the absence of autoimmunity, persistent β-cell function capacity, and fluctuating insulin requirements and ketosis-prone episodes. The identification of such a group of subjects is important not only for correct classification but also with regard to treatment options and prognosis. Nevertheless, strictly speaking (absence of type 1 diabetic HLA-predisposing haplotypes), there is only one subgroup of patients with adult-onset atypical type 1 diabetes who fully fit the American Diabetes Association description of type 1B diabetes.

Patients with adult-onset atypical type 1 diabetes represent a very small minority among all new diagnoses of type 1 diabetes in our area (<10%), in contrast to data obtained in North America, mainly in adult obese individuals of African-American ancestry (5). Although there are some reports from other ethnic groups, data concerning a European population is very scarce (12,13). Although all of the subjects included in our study were initially classified by clinicians as having type 1A diabetes and were treated as such, they displayed some characteristics not usually associated with the most typical form of the disease. Mean age at diagnosis was higher than usually described in type 1A diabetes, as was BMI when compared with age- and sex-matched control subjects, being >90% above normal weight at diagnosis. As in other studies reporting a significant male predominance (5), all patients with adult-onset atypical type 1 diabetes included in our study were men. This is in contrast with a 2:1 man-to-woman ratio usually observed in type 1A diabetic subjects aged 15–35 years in our population (19). After correction of initial metabolic disturbances, patients with adult-onset atypical type 1 diabetes showed a higher basal C-peptide and β-cell response to glucagon when compared with type 1 diabetic control subjects, and this difference increased after 12 months of follow-up. Therefore, the initial impairment of β-cell function unable to maintain glucose and ketone production within normal levels is a reversible phenomenon in adult-onset atypical type 1 diabetes, although it may relapse later on after diagnosis.

In our study, we also included the examination of type 1A diabetic HLA risk alleles (30), because according to the Expert Committee on the Diagnosis and Classification of Diabetes of the American Diabetes Association, idiopathic type 1B diabetes should be non–HLA associated. In this context, and from a rigorous point of view, only three of eight patients with adult-onset atypical type 1 diabetes included in the study could be ascribed in the type 1B diabetes subcategory because none carried HLA antigens associated with type 1A diabetes. These patients carried protective or neutral type 1A diabetes HLA haplotypes, and the presence of $Asp^{\beta 57}$ residue was identified in HLA-DQ analysis in all of them. A striking feature was that the DRB1*11 haplotype was also present in all of the subjects in this subgroup, although this haplotype is not very common among type 1A diabetic subjects or in a normal control population in our country (3 and 7%, respectively) (35). In terms of HLA, all but one of the remaining five subjects with adult-onset atypical type 1 diabetes carried type 1A diabetic risk HLA haplotypes in combination with

Table 4—*Characteristics of the study groups after 12 months of follow-up*

	Atypical type 1 diabetes	Type 1A diabetes	*P*
Number of subjects	8	16	
BMI (kg/m^2)	27.5 ± 3.5	22.9 ± 4.4	0.047
HbA_{1c} (%)	5.1 ± 0.6	5.7 ± 0.8	0.052
Insulina dose (units/kg)	0	0.4 ± 0.2	0.000
Basal C-peptide (nmol/l)	0.89 ± 0.35	0.21 ± 0.10	0.000
Maximum stimulated C-peptide (nmol/l)	1.59 ± 0.43	0.41 ± 0.19	0.000

Data are means ± SD.

Table 5—*HLA haplotypes in patients with atypical type 1 diabetes*

	DRB1-DQA1-DQB1	DQB57	Susceptibility	Resistance
Patient 1	0101-0101-0501/1104-0505-0301	D/V	—	DQA1*0505-DQB1*0301 + Asp$^{\beta57}$
Patient 2	1302-0102-0604/1101-0501-0301	D/V	—	DQA1*0501-DQB1*0301 + Asp$^{\beta57}$
Patient 3	1104-0505-0202/1201-0503-0302	D/A	—	Asp$^{\beta57}$
Patient 4	0403-0301-0302/1102-0501-0301	D/A	DQA1*0301-DQB1*0302	DQA1*0501-DQB1*0301 + Asp$^{\beta57}$
Patient 5	0301-0501-0201/0401-0303-0301	D/A	DQA1*0501-DQB1*0201	Asp$^{\beta57}$
Patient 6	0301-0501-0201/0101-0501-0101	D/V	DQA1*0501-DQB1*0201	Asp$^{\beta57}$
Patient 7	0301-0501-0201/1104-0501-0301	D/A	DQA1*0501-DQB1*0201	DQA1*0501-DQB1*0301 + Asp$^{\beta57}$
Patient 8	0301-0501-0201/1601-0102-0502	A/S	DQA1*0501-DQB1*0201	—

A, alanine; D, aspartic; S, serine; V, valine.

protective haplotypes and/or Asp$^{\beta57}$. In fact, the presence of a higher proportion of HLA-predisposing alleles in subjects with atypical forms of diabetes in comparison to nondiabetic control subjects has already been described (7,36). Considering this, and despite similar clinical and metabolic characteristics when compared with the former subgroup of subjects, these patients cannot strictly be included in the type 1B diabetes definition. Nonetheless, we cannot explain the exact role the combination of susceptible/protective Asp$^{\beta57}$ HLA alleles plays in the pathogenesis of diabetes in this subgroup of subjects. However, HLA-DQB1 codon 57 is a determinant site for peptide binding and for antigen-specific T-cell stimulation and HLA-DQ molecules helping B-cells to produce antibodies (29,37).

The pathophysiologic mechanisms determining atypical forms of type 1 diabetes remain unsolved and may differ, depending on the ethnic background. We herein study the possible role of MODY genes to explain adult-onset atypical type 1 diabetes. In this sense, there have been some descriptions of mutations in genes responsible for MODY in subjects with atypical/idiopathic type 1 diabetes (20–22). We examined regions encoding for HNF-1α (MODY3) and HNF-4α (MODY1) genes in our group of patients with adult-onset atypical type 1 diabetes. We found a new variant (Pro436Val) in exon 10 of HNF-4α in one patient with adult-onset atypical type 1 diabetes without type 1A diabetic HLA-predisposing alleles. There was no history of diabetes in his family, and it was not possible to have access to any family member to analyze the presence or absence of the variant and to study their oral glucose tolerance. Functional tests also would have helped us to determine the role of the mutation in vitro by a transcriptional activity assay. Unfortunately, we could not perform the experiment, and thus, the contribution of this HNF-4α variant to the pathogenesis of diabetes remains only speculative and warrants further investigation.

No evidence of autoimmune destruction of insulin-producing cells has been reported or considered as a possible cause of adult-onset atypical type 1 diabetes, at least as it is described for type 1A diabetes. In fact, data could suggest that a fluctuating β-cell dysfunction in concert with changes in insulin resistance could result in a different clinical picture in this group of subjects. Despite the fact that an insulin secretion defect caused insulinopenia, hyperglycemia, and ketosis, in our subjects, the clinical picture clearly contrasts with the idiopathic diabetes forms described in a Japanese population characterized by abrupt and fulminant onset and high serum pancreatic enzyme concentration (38).

In agreement with Sobngwi and Gautier (39), in our opinion, adult-onset atypical type 1 diabetes could be more closely related to type 2 diabetes than type 1 diabetes. Age at onset, around the thirties, was higher than that observed in type 1A diabetes and could be comparable to that of young type 2 diabetic subjects, mainly in some ethnic groups with the increasing problem of obesity in the western world. Likewise, overweight/obesity was very common at onset, and the BMI remained significantly higher after 12 months of follow-up when compared with type 1A diabetic control subjects. Therefore, this group of patients with atypical type 1 diabetes probably has a young adult–onset ketosis-prone atypical form of type 2 diabetes that affects a predisposed population with a transitory nonprecipitating impairment of insulin secretion, leading to hyperglycemia and ketosis. It may be related to glucose desensitization and an outstanding sensitivity to glucotoxicity or lipotoxicity. However, all of these possibilities remain to be fully elucidated.

In summary, our data suggest that atypical forms of young adult–onset ketosis-prone diabetes initially diagnosed as type 1 diabetes may be detected among subjects of Caucasian origin in a Mediterranean area. Despite having an initial clinical presentation compatible with type 1 diabetes, these patients differ in terms of no evidence of β-cell autoimmunity, persistent β-cell function capacity, fluctuating insulin requirements, and ketosis-prone episodes, as well as clinical features of type 2 diabetes. Among this group of subjects, only one subgroup could be strictly classified as type 1B diabetes. With respect to the pathophysiology of this form of diabetes, additional information is still needed to improve our understanding of the mechanisms that finally lead to the disease.

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