Microvascular Diabetes Complications in Wolfram Syndrome (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness [DIDMOAD])

An age- and duration-matched comparison with common type 1 diabetes

ALINE CANO, MD[1]
LAURENT MOLINES, MD[1]
RENÉ VALÉRO, PHD[1]
GILBERT SIMONIN, MD[1]
VÉRONIQUE PAQUIS-FLUCKLINGER, MD, PHD[2]
BERNARD VIALETTES, MD[1]
THE FRENCH GROUP OF WOLFRAM SYNDROME*

OBJECTIVE — Some previous studies suggested that patients suffering from Wolfram syndrome or DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness) might be relatively preserved from diabetic retinopathy and nephropathy. However, these data were not conclusive because either observations were only anecdotic or did not match with control type 1 diabetic populations.

RESEARCH DESIGN AND METHODS — A group of 26 French diabetic patients with DIDMOAD was compared with a population of 52 patients with common type 1 diabetes matched for age at diabetes diagnosis (8.62 ± 1.84 vs. 8.27 ± 1.30 years; P = NS) and diabetes duration (12.88 ± 1.58 vs. 12.87 ± 1.13 years; P = NS) to study the quality of glycemic control and the incidence of microvascular complications.

RESULTS — Glycemic control was significantly better in the DIDMOAD group than in the type 1 diabetic group (A1C: 7.72 ± 0.21 vs. 8.99 ± 0.25%, respectively; P = 0.002), with significant lower daily insulin requirements (0.71 ± 0.07 vs. 0.88 ± 0.04 UI · kg^{-1} · day^{-1}, respectively; P = 0.0325). The prevalence of microvascular complications in the DIDMOAD group was half that observed in the type 1 diabetic group, but the difference was not significant.

CONCLUSIONS — Diabetes in DIDMOAD patients is more easily controlled despite the presence of other handicaps. This better glycemic control could explain the trend to decreased microvascular diabetes complications observed in previous studies.

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Diabetes associated with Wolfram syndrome or DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness), an autosomal recessive disease linked to *WFS1* gene, is considered to have the same clinical features as typical type 1 diabetes (1,2). The main difference with common type 1 diabetes is the absence of specific immune and genetic markers of autoimmune diabetes. However, some previous studies (3–6) have suggested that patients suffering from DIDMOAD might be relatively preserved from diabetic retinopathy and nephropathy. However, these data were not conclusive because observations were either only anecdotic or they were not matched with a control type 1 diabetic population. To address this question, we studied a large population of 26 French patients with DIDMOAD (7), in which molecular analysis of the *WFS1* gene had been performed, and compared them with patients suffering from conventional type 1 diabetes. The two groups were matched for both age at diabetes onset and disease duration. These two groups were compared in terms of quality of glycemic control, daily insulin doses, and prevalence of diabetic retinopathy, nephropathy (microalbuminuria or albuminuria), and high blood pressure.

RESEARCH DESIGN AND METHODS

— The DIDMOAD group included 26 insulin-treated diabetic patients with Wolfram syndrome from 23 families. They were recruited from all over France based on the coexistence of at least two major manifestations (i.e., insulin-dependent diabetes and optic atrophy unexplained by any other disease, before the age of 20 years). Diagnosis was confirmed by molecular identification of at least one mutation in the *WFS1* gene in every individual. Molecular variants observed in this series have been previously described (7). The control group included a population of 52 insulin-treated patients with typical type 1 diabetes (selected based on the American Diabetes Association criteria [8]) attending three diabetes departments in Marseilles. These two groups were matched with regard to both age at diabetes onset and duration of diabetes at a ratio of one DIDMOAD patient for two type 1 diabetic patients. Every patient was asked to perform conventional capillary glucose monitoring with at least one blood sample before each insulin injection. We compared the following criteria between the two groups: quality of glycemic control as-

From the [1]Department of Nutrition, Metabolic Diseases and Endocrinology, University of Méditerranée, "La Timone" Hospital, Marseille, France; and the [2]Department of Medical Genetics, University of Nice, "Archet-2" Hospital, Nice, France.

Address correspondence and reprint requests to Bernard Vialettes, MD, Service de Nutrition, Maladies Métaboliques, Endocrinologie, Centre Hospitalier Universitaire La Timone, 264 rue Saint Pierre, 13005 Marseille, France. E-mail: bernard.vialettes@ap-hm.fr.

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*A list of the members of the French Group of Wolfram Syndrome can be found in the APPENDIX.

Abbreviations: DIDMOAD, diabetes insipidus, diabetes mellitus, optic atrophy, and deafness.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Demographic, clinical, and biochemical characteristics of the DIDMOAD and type 1 diabetic groups matched for age at diabetes onset and duration of diabetes at a ratio of one DIDMOAD subject for every two type 1 diabetic subjects*

	DIDMOAD subjects	Type 1 diabetic subjects	*P*
n	26	52	
Sex ratio (male/female)	15/11	26/26	NS
Age of diabetes onset (years)	8.62 ± 1.84	8.27 ± 1.30	NS, 0.88
Duration of diabetes (years)	12.88 ± 1.58	12.87 ± 1.13	NS, 0.99
A1C (%)	7.72 ± 0.21	8.99 ± 0.25	0.0020
Daily insulin (UI · kg^{-1} · day^{-1})	0.71 ± 0.07	0.88 ± 0.04	0.0325
One to two injections per day	14 (54)	10 (19)	
Three to five injections per day or continuous subcutaneous insulin infusion	12 (46)	42 (81)	0.018
High blood pressure	3 (12)	4 (8)	NS, 0.84
Diabetic retinopathy	2 (8)	14 (27)	NS, 0.12
Diabetic nephropathy	2 (8)	14 (27)	NS, 0.12

Data are means ± SE or *n* (%). NS, not significant.

sessed by the last A1C level (Diabetes Control and Complications Trial/National Glycohemoglobin Standardization Program–validated method, normal value <6%); the daily insulin requirement (unit · kg^{-1} · day^{-1}); the 24-h urinary albumin excretion or, if not possible, the albumin excretion in a urinary sample; fundus examination; and blood pressure. Microalbuminuria was defined by urinary albumin excretion between 30 and 300 mg/24 h or between 20 and 200 mg/l, observed on at least two samples, and macroproteinuria as the 24-h urinary albumin excretion >300 mg/24 h or 200 mg/l (8). Plasma creatinine was in the normal range in every patient. Diabetic retinopathy was assessed by the funduscopic examination performed by a specialized ophthalmologist and was classified in nonproliferative retinopathy, proliferative retinopathy, and maculopathy according to the French-speaking diabetes association (ALFEDIAM [l'Association de Langue Française pour l'Etude du Diabète et des Maladies Métaboliques]) recommendations (9). High blood pressure was defined by either a value >130/80 mmHg (measured after 10 min rest) or ongoing antihypertensive treatment. Other macrovascular manifestations were not studied because the patients were too young to have the risk of developing such complications. This study was conducted in accordance with the Declaration of Helsinki. Data from type 1 diabetic and DIDMOAD groups are presented as means ± SE and were compared using a *t* test. A χ^2 test was performed for categorical variables, such as presence of high blood pressure, diabetic retinopathy, and diabetic nephropathy.

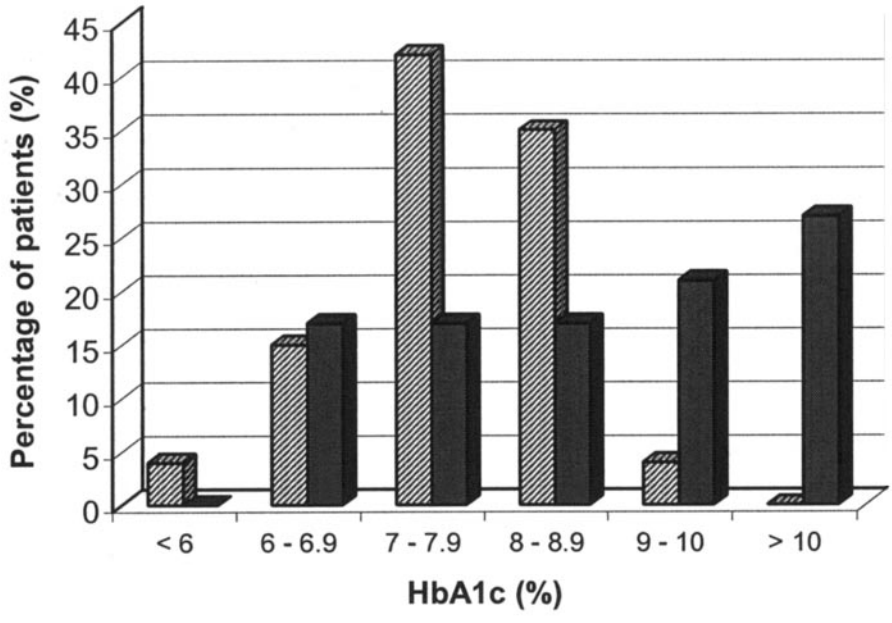

Figure 1—*A1C level distribution in the DIDMOAD (▨) and type 1 diabetic (■) populations.*

RESULTS — Demographical, clinical, and biochemical characteristics of the DIDMOAD and type 1 diabetic groups are represented in Table 1. The two populations were well matched in terms of age, sex ratio, age at onset of diabetes (8.62 ± 1.84 vs. 8.27 ± 1.3 years, respectively; *P* = NS), and duration of diabetes (12.88 ± 1.58 vs. 12.87 ± 1.13 years, respectively; *P* = NS). The DIDMOAD group was characterized by a significantly lower A1C values (7.72 ± 0.21 vs. 8.99 ± 0.25%, respectively; *P* = 0.002). This difference in plasma glucose control could mainly be explained by a bimodal distribution of A1C values in the type 1 diabetic group. In this group, patients with very high A1C levels (>9%), mostly adolescents, represented 47.2% of the effected (Fig. 1). This situation was almost absent in the DIDMOAD population (4.3%). The DIDMOAD group also exhibited a significantly lower daily insulin dose than the control group (0.71 ± 0.07 vs. 0.88 ± 0.04 units · kg^{-1} · day^{-1}, respectively; *P* = 0.0325). Basal-bolus insulin regimen was significantly less frequent in the DIDMOAD group (*P* = 0.018), as half of the patients were still under one or two daily injections. Continuous insulin infusion system was used in two patients with DIDMOAD and four subjects in type 1 diabetic group.

In terms of microvascular complications, diabetic retinopathy was found in

Table 2—*Demographic, clinical, and biochemical characteristics of the DIDMOAD and type 1 diabetic subgroups matched for age at diabetes onset, duration of diabetes, and A1C level*

	DIDMOAD subjects	Type 1 diabetes	*P*
n	20	20	
Sex ratio (male/female)	12/8	13/7	NS
Age of diabetes onset (year)	6.55 ± 1.28	6.25 ± 1.48	NS, 0.88
Duration of diabetes (year)	13.95 ± 1.87	14.80 ± 2.07	NS, 0.76
A1C (%)	7.67 ± 0.24	7.72 ± 0.25	NS, 0.89
Daily insulin (UI · kg^{-1} · day^{-1})	0.72 ± 0.07	0.77 ± 0.07	NS, 0.59
One to two injections per day	10 (50)	4 (20)	
Three to five injections per day or continuous insulin infusion system	10 (50)	16 (80)	0.0467
High blood pressure	3 (15)	2 (10)	NS, 0.94
Diabetic retinopathy	2 (10)	5 (25)	NS, 0.49
Diabetic nephropathy	1 (5)	3 (15)	NS, 0.60

Data are means ± SE or *n* (%). NS, not significant.

only 2 of the 26 DIDMOAD patients. In every case, retinopathy was classified as nonproliferative. In the type 1 diabetic group, 17% had nonproliferative retinopathy and 9% had proliferative retinopathy.

The prevalence of nephropathy in the DIDMOAD group was 8%, and only microalbuminuria was observed. In the type 1 diabetic group, microalbuminuria was present in 8% of the patients and macroalbuminuria in 19%. We observed a trend to a lower prevalence of microvascular complications in the DIDMOAD group in comparison with the type 1 diabetic group (patients with at least one microvascular manifestation: 4 [16%] vs. 18 [36%], respectively), but the difference did not reach statistical significance ($P = 0.12$). The prevalence of hypertension was similar in the two groups.

To overcome the possible bias linked to a significantly poorer glycemic control in the type 1 diabetic group, a new set of matches were adjusted for the same characteristics, but the A1C level was matched as well. After further adjustment, no difference was observed in diabetic retinopathy and/or nephropathy frequency (Table 2).

The two DIDMOAD patients with retinopathy exhibited at least 20 years of diabetes duration and were found to be either compound heterozygous or homozygous for a frameshift mutation in the *WFS1* gene. The two patients with microalbuminuria were compound heterozygous for frameshift/misssense mutations or frameshift/deletion. There was no correlation between the genotype and the occurrence of microangiopathy in the DIDMOAD French group (data not shown).

CONCLUSIONS — DIDMOAD and type 1 diabetes share some clinical characteristics, such as ketosis-prone juvenile diabetes and absence of obesity. However, they differ by the mechanisms leading to specific loss of pancreatic β-cells. DIDMOAD is due to impaired homeostasis of β-cells (increased apoptosis and/or failure of regenerative processes). In contrast, in type 1 diabetes the β-cell loss is secondary to an organ-specific autoimmune reaction. This study comparing the clinical features of both forms of diabetes using highly matched populations shows that glycemic control is easier to obtain in DIDMOAD than in type 1 diabetes, with lower daily insulin doses. The recruitment of patients and control subjects have been performed in a national consortium and in a single town, respectively. But one can suppose that this discrepancy did not lead to differences in diabetes care quality, as both DIDMOAD and type 1 diabetic patients were followed in the same type of institution (i.e., diabetes departments of French University hospitals). Amazingly, despite a better A1C value, the DIDMOAD group paradoxically exhibited a less sophisticated insulin regimen, as <50% of the patients were submitted to a basal-bolus schema. A more likely hypothesis might be a difference in insulin reserve in both diseases, even if data concerning C-peptide secretion in DIDMOAD have been controversial, ranging from severe insulin deficiency (10,11) to small but significant insulin secretory reserve (12,13). The data of Ishiara et al. (14), based on an animal model, showed that in addition to the documented loss of β-cell mass, associated impaired stimulus secretion in β-cells could contribute to defective insulin secretion. Consistent with the existence of some reserve in endogenous insulin secretion, the rarity of diabetic ketoacidosis was previously noticed (1,5,15). Both the lower daily insulin requirement and the higher prevalence of a nonintensive insulin regimen observed in our DIDMOAD group in comparison with the type 1 diabetic group suggests a persistence of some residual pancreatic β-cells, which could explain the better glycemic control.

However, behavioral differences could also account for the discrepancy in term of glucose control. Our population was close to adolescence. In common type 1 diabetes, puberty is considered a difficult period with poor management of diabetes by the patients themselves. The very high proportion of patients in our control group with A1C values >9%, suggesting behavioral shortcomings, is an illustration of such difficulties. In contrast, in DIDMOAD, the accumulation of handicaps linked to both diabetes and sensory defects and the severity of the prognosis reduce the autonomy of the patients, which likely smooths the puberty crisis and renders the familial environment more present, making every condition prone to a better glycemic control.

In the literature (5,10,16,17), results concerning the incidence of diabetic microvascular complications in the DIDMOAD syndrome have been controversial. The possibility of a lower incidence of specific diabetic microvascular complications in DIDMOAD has been suggested by some anecdotal case reports showing a discrepancy between the severity of optic atrophy and the mildness of diabetic ret-

inopathy (3,4,6). The large series reported by Kinsley et al. (5) showed that the prevalence of retinopathy in patients with long diabetes duration (>15 years) was low and, if present, was less severe and progressed more slowly than expected. Among 26 long-standing diabetic patients, 17 did not exhibit any sign of retinopathy. In the same retrospective analysis, necropsy was performed and kidneys were examined in 11 cases. No glomerulopathy was observed despite a long duration of the diabetes at the time of the death in every patient (mean duration of diabetes 23 years [range 13–35]). Unfortunately, there was no matched control group with type 1 diabetes in this study. Their data have only been compared with microvascular complications in the series of type 1 diabetes previously published in the literature. Our strictly matched series does not support a major protection from such complications in the DIDMOAD syndrome. In fact, even if we observed a trend to lower incidence of retinopathy and/or nephropathy in our DIDMOAD group compared with type 1 diabetic control group, this tendency disappeared after matching the two groups for A1C levels. This suggests that the protection observed in the largest series is likely explained by better glycemic control. We are aware that the last A1C parameter is not totally representative of the A1C mean of the previous 12 years. However, standardization of A1C determination in France has only operative for the past 3–4 years. This approach based on the last value alleviates any bias due to methodological problems or change in medical practice.

In conclusion, this study shows that there are some subtle differences in the clinical presentation of diabetes between DIDMOAD syndrome and common type 1 diabetes. Diabetes in DIDMOAD is controlled more easily despite the presence of other handicaps. This better glycemic control could explain the trend for a decrease of incidence of microvascular diabetes complications observed in some studies.

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