

Microvascular diabetic complications in Wolfram Syndrome (DIDMOAD): an age- and duration-matched comparison with common Type 1 diabetes.

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Short running title: Microvascular diabetic complications in DIDMOAD

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Abstract

Objective: Some previous studies suggested that patients suffering from Wolfram syndrome (DIDMOAD) might be relatively preserved from diabetic retinopathy and nephropathy. However these data were not conclusive because either observations were only anecdotic or not matched with control T1DM populations.

Research Design and Methods: A group of 26 French diabetic patients with DIDMOAD was compared to a population of 52 patients with common type 1 diabetes matched for age at diabetes diagnosis (8.62 ± 1.84 yrs vs. 8.27 ± 1.30 yrs; $p=NS$) and diabetes duration (12.88 ± 1.58 yrs vs. 12.87 ± 1.13 yrs; $p=NS$) to study the quality of glycemic control and the incidence of microvascular complications.

Results: The glycemic control was significantly better in the DIDMOAD group than in the T1DM group (HbA1c: 7.72 ± 0.21 % vs. 8.99 ± 0.25 % respectively; $p=0.002$) with significant lower daily insulin requirements (0.71 ± 0.07 ui/kg/day vs. 0.88 ± 0.04 ui/kg/day respectively; $p=0.0325$). The prevalence of microvascular complications in the DIDMOAD group was half that observed in the T1DM 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 micro vascular diabetic complications observed in previous studies.

Abbreviations:

DIDMOAD: Diabetes insipidus, diabetes mellitus, optic atrophy, deafness

T1DM: Type 1 diabetes mellitus

NS: not significant

Introduction

Diabetes mellitus associated with Wolfram syndrome or DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, and Deafness), an autosomal recessive disease linked to *WFS1* gene, is considered as having the same clinical features as typical type 1 diabetes mellitus (T1DM) (1,2). The main difference with the common T1DM is the absence of specific immune and genetic markers of autoimmune diabetes. However some previous studies suggested that patients suffering from DIDMOAD might be relatively preserved from diabetic retinopathy and nephropathy (3,4,5,6). However these data were not conclusive because observations were either only anecdotic or they were not matched with a control TDM1 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 it 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 glycaemic 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 diabetic patients with Wolfram syndrome from 23 families and treated with insulin. They were recruited from all over France based on the coexistence of at least two major manifestations i.e. insulin-dependent diabetes mellitus 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 T1DM (selected on the American Diabetes Association criteria (8)) attending three diabetes departments in Marseilles. These two groups were matched both with regards to age at diabetes onset and duration of diabetes in a ratio of one DIDMOAD patient for two T1DM 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 assessed by the last HbA1c level (DCCT/NGSP validated method, normal value below 6 %), the daily insulin requirement (unit/kg/day), the 24h 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/24h or between 20 and 200 mg/l, observed on at least two samples and macroproteinuria as the 24h urinary albumin excretion > 300 mg/24h or 200 mg/l (8). Plasma creatinine was in the normal range in every patient. Diabetic retinopathy was assessed by the fundoscopic examination performed by a specialized ophthalmologist and was classified in non proliferative retinopathy, proliferative retinopathy and maculopathy according to French speaking diabetes association (ALFEDIAM) recommendations (9). High blood pressure was defined by either a value higher than 130/80mmHg (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 T1DM and DIDMOAD groups are presented as means \pm SEM 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.

Results

Demographical, clinical and biochemical characteristics of the DIDMOAD and T1DM groups are represented in table 1. The 2 populations were well matched in terms of age, sex ratio, age at onset of diabetes (8.62 ± 1.84 yrs vs 8.27 ± 1.3 yrs respectively; NS) and duration of diabetes (12.88 ± 1.58 yrs vs 12.87 ± 1.13 yrs respectively; NS). The DIDMOAD group was characterized by a significantly lower HbA1C 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 HbA1c values in T1DM group. In this group, patients with very high HbA1c levels ($> 9\%$), mostly adolescents, represented 47.2% of the effective (figure1). 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 one (0.71 ± 0.07 u/kg/day vs. 0.88 ± 0.04 u/kg/day respectively; $p=0.0325$). Basal-bolus insulin regimen was significantly less frequent in DIDMOAD group ($p=0.018$) as half of the patients were still under 1 or 2 daily injections. Continuous insulin infusion system (CSII) was used in 2 patients with DIDMOAD and 4 subjects in T1DM group.

In term of microvascular complications, diabetic retinopathy was found in only 2 of the 26 DIDMOAD patients. In every case, the retinopathy was classified as non proliferative. In the T1DM group, 17% had a non proliferative retinopathy and 9% had a proliferative retinopathy.

The prevalence of nephropathy in the DIDMOAD group was 8% and only

microalbuminuria was observed. In the T1DM 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 to T1DM (patients with at least 1 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 T1DM group, a new set of matching was adjusted for the same characteristics, but the HbA1c level was matched as well. After this 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).

Discussion

DIDMOAD and T1DM diabetes share some clinical characteristics as ketosis prone juvenile diabetes and absence of obesity. However, they differ by the mechanisms leading to specific loss of pancreatic beta cells. DIDMOAD is due to impaired homeostasis of beta cells (increased apoptosis and/or failure of regenerative processes). In contrast, in T1DM the beta 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 T1DM with lower daily insulin doses. The recruitment of patients and controls 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 T1DM patients were followed in the same type of institution, i.e. diabetes departments of French University hospitals. Amazingly, despite a better HbA1c value, DIDMOAD group paradoxically exhibited less sophisticated insulin regimen as less than 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). On the other hand, data of Ishiara *et al.* based on an animal model showed that in addition to the documented loss of beta cell mass, impaired stimulus-secretion coupling in beta cells could participate to defective insulin secretion (15). Consistent with the existence of some reserve in endogenous insulin secretion, the rarity of diabetic ketoacidosis was noticed previously (1,5,14). Both the lower daily insulin requirement and the higher prevalence of non intensive insulin regimen observed in our DIDMOAD group in comparison with T1DM suggests a persistence of some residual pancreatic beta cells which could explain the better glycemic control.

However, behavioural differences could also account for the discrepancy in term of glucose control. Our population was close to adolescence. In common T1DM, puberty is considered as a difficult period with a poor management of diabetes by the patients themselves. The very high proportion of patients in our control group with HbA1c

values higher than 9%, suggesting behavioural 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, likely smooth the puberty crisis and render the familial environment more present, every condition prone to a better glycemic control.

In the literature, results concerning the incidence of diabetic microvascular complications in DIDMOAD syndrome have been controversial (5,10,16,17). 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 retinopathy (3,4,6). The large series reported by Kinsley *et al.* (5) showed that the prevalence of retinopathy in patients with long diabetes duration (more than 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, in 11 cases, necropsy was performed and kidneys were examined. 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 years). Unfortunately, there was no matched control group with T1DM in this study. The data could only be compared with series of T1DM published previously in the literature. Our strictly matched series does not support a major protection from such complications in DIDMOAD syndrome. In fact, even if we observed a trend to lower incidence of retinopathy and/or nephropathy in our DIDMOAD group compared to T1DM control group, this tendency disappeared after matching the two groups for HbA1c levels.

This suggests that the protection observed in the largest series is likely explained by a better glycemic control. We are aware that the last HbA1c parameter is not totally representative of the HbA1c mean of previous 12 years. However, standardization of HbA1c determination in France is operative only since 3-4 years. This approach based on the last value alleviate any bias due to methodological problems or change in medical practice.

In conclusion, this study shows that there are some subtle differences in clinical presentation of diabetes between DIDMOAD syndrome and common T1DM. 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 diabetic complications observed in some studies.

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Appendix: The French Group of Wolfram Syndrome: JP. Azoulay, H. Bihan, JF Blicke, D. Bonneau, P. Bougnères, JP Brassart, A. Cano, D. Chabas, B. Chabrol, L. Chaillous, P. Chanson, R. Coutant, B. Delobel, H. Dollfus, L. Dufaître, C. Francannet, K. Huber, H. Journal, M. de Kerdanet, A. Kitzis, P. Lecomte, A. Linglart, S. Matthis, V. Mesnage, B. Mignot, K. N’Guyen, S. Odent, V. Paquis-Flucklinger, D. Raccach, T. Rouault, JL Sadoul, P. Sarda, S. Siagudy, G. Simonin, R. Valéro and B. Vialettes.

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Table 1: Demographic, clinical and biochemical characteristics of the DIDMOAD and T1DM groups matched on age at diabetes onset and duration of diabetes in a ratio of 1 DIDMOAD/2 T1DM. (NS=Not significant, CSII: continuous insulin infusion system)

	DIDMOAD	T1DM	
N	26	52	
Sex ratio (M/F)	15 /11	26 /26	NS
Age of diabetes onset (yrs)	8.62 ± 1,84	8.27 ± 1,30	NS p = 0.88
Duration of diabetes (yrs)	12.88 ± 1,58	12.87 ± 1,13	NS p = 0.99
HbA1c (%)	7.72 ± 0,21	8.99 ± 0,25	<i>p</i> = 0.0020
Daily insulin (ui/kg/day)	0.71 ± 0,07	0.88 ± 0,04	<i>p</i> = 0.0325
1 - 2 injections/day- n (%)	14 (54)	10 (19)	
3 - 5 injections/day or CSII- n (%)	12 (46)	42 (81)	<i>p</i> = 0.018
High Blood Pressure - n (%)	3 (12)	4 (8)	NS p = 0.84
Diabetic Retinopathy - n (%)	2 (8)	14 (27)	NS p = 0.12
Diabetic Nephropathy - n (%)	2 (8)	14 (27)	NS p = 0.12

Table 2: Demographic, clinical and biochemical characteristics of DIDMOAD and T1DM subgroups matched on age at diabetes onset, duration of diabetes and HbA1c levels. (NS=Not significant, CSII: continuous insulin infusion system)

	DIDMOAD	T1DM	
N	20	20	
Sex ratio (M/F)	12 /8	13 /7	NS
Age of diabetes onset (yr)	6.55 ± 1,28	6.25 ± 1,48	NS p = 0.88
Duration of diabetes (yr)	13.95 ± 1,87	14.80 ± 2,07	NS p = 0.76
HbA1c (%)	7.67 ± 0,24	7.72 ± 0,25	NS p = 0.89
Daily insulin (UI/kg/day)	0.72 ± 0,07	0.77 ± 0,07	NS p = 0.59
1 - 2 injections/day- n (%)	10 (50)	4 (20)	
3 - 5 injections/day or CSII- n (%)	10 (50)	16 (80)	<i>p = 0.0467</i>
High Blood Pressure -n (%)	3 (15)	2 (10)	NS p = 0.94
Diabetic Retinopathy -n (%)	2 (10)	5 (25)	NS p = 0.49
Diabetic Nephropathy - n (%)	1 (5)	3 (15)	NS p = 0.60

Figure 1: HbA1c level distribution in the DIDMOAD (▨) and T1DM (■) populations

