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Microvascular Complications of Type 1 Diabetes Mellitus Screening in Children, Adolescents and Young Adults: Report from a Small Center in a Limited Resource Setting, Brazzaville - Congo

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Abstract

Objectives: The aim of this study was to assess the prevalence of microvascular complications of type 1 diabetes mellitus, to define the relationship between the disease duration and the onset of these complications among Congolese children, adolescents and young adults with type 1 diabetes mellitus.

Material and method: A clinical hospital based prospective and cross-sectional study was conducted between January and August 2015 (8 months). The research groups included sixty-two children and adolescents (aged 8 to 19 years), and young adults (aged 20 to 24-years-old) with type 1 diabetes, with disease duration more than 5 years or disease onset during puberty, followed-up at a diabetes center named "l'Institut du diabète Maison Bleue of Brazzaville - CONGO", who signed an informed consent to participate in the study. Complication screening included: Full ophthalmologic examination, microalbuminuria screening by the measurement of the albumin to creatinine (A/C) ratio, and diabetic neuropathy assessment using the Michigan Neuropathy Screening Instrument (MNSI). The HbA1c test was performed twice for all patients.

Results: 64.5% (n = 40) of patients were female, aged between 8.25 and 25 years (16.84 ± 3.88 years). The mean disease duration was 5.12 ± 3.16 years. Retinopathy prevalence was 6.4% (n = 4), the four patients with diabetic retinopathy had disease duration more than 5 years. Microalbuminuria (A/C ratio between 30 mg/g and 299 mg/g) was detected in 21% (n = 13) and 14.5% (n = 9) were at risk of developing microalbuminuria (A/C ratio between 20 mg/g and 29 mg/g). There was a statistically significant association between the HbA1c level and the presence of microalbuminuria for the 2 tests done ($p < 0.05$ for both). The prevalence of diabetic neuropathy (MNSI score ≥ 2.5) was 1.6% (n = 1). Glycemic control: 12.9% for the first HbA1c and 14.5% for the second HbA1C of patients met the optimal control target as set by the ISPAD (HbA1C < 7.5% or < 58 mmol/mol). All the patients were on either premixed insulin alone or premixed plus regular insulin.

Conclusions: The high prevalence of microalbuminuria and the poor glycemic control found in this study among children, adolescents and young adults with type 1 diabetes followed-up at Brazzaville suggest that diabetes care with all its components need to be improved.

Keywords

Type 1 diabetes mellitus, Microvascular complications, Brazzaville - Congo

Introduction

Microvascular complications of type 1 diabetes mellitus (T1DM) include nephropathy, retinopathy and neuropathy.

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Clinically evident diabetes-related vascular complications are rare in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of the disease and often progress during puberty [1]. These vascular changes include basement membrane thickening and mesangial expansion, and are predictive of subsequent albuminuria [2], which may further progress to overt proteinuria (macroalbuminuria) and, without any treatment, to end-stage renal disease (ESRD) [3]. Non-proliferative retinopathy is characterized by microaneurysms, retinal hemorrhages both pre- and intraretinal, cotton wool spots related to ischemia and microinfarction, hard exudates due to protein and lipid leakage, intraretinal microvascular abnormalities (IRMAs), and venular dilatation and tortuosity. Mild and moderate stages of non-proliferative retinopathy are not vision-threatening and do not invariably progress to more severe stages of retinopathy [4]. More severe lesions are seen in severe non-proliferative retinopathy (vascular obstruction, increase in number of retinal hemorrhages and microaneurysms, IRMAs, marked venous abnormalities, and ischemia and infarctions of the retinal nerve fibers causing cotton wool spots) and in proliferative diabetic retinopathy (neovascularisation in the retina and/or vitreous posterior surface, ruptured vessels or bleeding into the vitreoretinal space which is vision threatening) [1].

Vascular complications of T1DM are triggered by chronic hyperglycemia - the main cause - accompanied by non-specific risk factors, either associated with diabetes or independent of it, as well as by a very likely genetic predisposition, which has not been sufficiently elucidated yet [5]; Longer duration of diabetes, older age and puberty are part of them [1]. T1DM in children and adolescents has a much more severe evolution and faster development [6]. The quality of life of patients with T1DM diagnosed during childhood depends on the proper diagnosis, treatment and prevention of complications. Therefore, childhood and adolescence is a period during which intensive education and treatment may prevent or delay the onset and progression of complications in later adult life [7]. There has been a declining incidence of complications reported in many areas with specialized clinics [8,9]. This has occurred over a period of time during which there have been major changes in diabetes management, identification of putative risk factors, and the advent of regular screening for complications. There is no evidence that this is a world-wide occurrence: In areas where health care is not optimal, a greater risk of complications will remain. Information on chronic complications of diabetes in sub-Saharan Africa is scarce; however, its incidence has gone hand in hand with the growing disease prevalence, demonstrating the importance of assessing complications. The few studies on chronic complications of diabetes in Africa have shown a high prevalence of both acute and chronic complications [10-12]. The importance of tight glycemic control to mitigate these effects has been confirmed in large prospective studies [7,13]. For these reasons, the pediatric years present a key opportunity for early detection of these processes and for interventions that would prevent or minimize future morbidity.

The aim of the study is to screen the microvascular complications, to define the relationship between the duration of diabetes and the onset of complications in Congolese children, adolescents and young adults with T1DM.

Material and Methods

The study was a clinical hospital based prospective and cross-sectional study carried out at l'Institut du diabète "Maison Bleue" in Brazzaville, Republic of Congo. This is a Non-Governmental Organization (NGO), the only existing center providing ambulatory diabetes care to children and adolescents with diabetes in Brazzaville and its surrounding area. The study was conducted between January and August 2015 (8 months). The research groups included children and adolescents (aged 8 to 19 years), and young adults (aged 20 to 25 years old) with T1DM followed-up at the center; patients with disease duration above 5 years or disease onset during puberty, signed themselves an informed consent (for those aged 18 years and above) or signed by their parents/guardians for those below 18 years. Microvascular complications screening consisted of diabetic neuropathy assessment, a full ophthalmologic examination, and microalbuminuria screening.

Sociodemographic data, especially those relating to age of the patient, level of education of both the patient and the parent/guardian, the socioeconomic status of the family (obtained by using Gayral-Taminh classification [14]) were obtained by using a structured questionnaire. A complete medical history was obtained and a comprehensive physical examination undertaken. Height was determined with a rigid stadiometer against a vertical wall and weight measured using an electronic scale. Body mass index (BMI) was calculated according to the Quetelet equation (Weight (kg)/Height (m^2)). For children and adolescents aged 20 years and below, the BMI for age weight status based on Center for Disease Control (CDC) BMI for age was used for interpreting results and for those above 20 years old the World Health Organization (WHO) International classification [15] of adult patients according to BMI was used. A sexual maturity rating was assessed using Tanner stage [16,17]. Diabetes neuropathy was assessed using the Michigan Neuropathy Screening Instrument (MNSI) [18]. The classification of patients after a full ophthalmologic examination was based on the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales [19] and a new grading system color fundus photographs for diabetic retinopathy (DR) as proposed by Lecleire-Collet A, et al. [20]. Screening of microalbuminuria was performed by the measurement of the albumin to creatinine (A/C) ratio in at least 2 spot urine specimens collected over a period of 6 months by the DCA™ Microalbumin/Creatinine assay and after excluded a urinary infection. Ratios between 30 mg/g and 299 mg/g were defined as microalbuminuria and that equal to 300 mg/g or greater as macroalbuminuria (or clinical albuminuria), and those between 20 mg/g and 29 mg/g as being at risk of developing microalbuminuria; To be considered as positive, two of three specimens collected within a period of 3 to 6 months had to be abnormal [21].

Two tests of glycosylated hemoglobin (HbA1c) were per-

formed for all patients (the first one in January and the second in June), using a 'DCA 2000 advantage' assay. As results are expressed in percentages, the maximum read being 14% (130 mmol/mol), to allow means and SD calculations every result equal or above 14% was considered as 14% (130 mmol/mol). Patients were categorized according to the DCCT standardized classification as follow: optimal control: HbA1c < 7.5% (< 58 mmol/mol); suboptimal control: HbA1c 7.5% to ≤ 9% (58 mmol/mol to 75 mmol/mol); and high risk: HbA1c > 9% (> 75 mmol/mol) [22].

The study received an approval from the National Health Sciences Ethics Committee of Congo (N°056/DGRST/CERSSA). Statistical analysis was performed using Epi Info software version 3.5.1. The quantitative variables were expressed as means and the qualitative variables in percentages. Fisher and the Kruskal-Wallis H tests were used to compare subgroups of patients and a p-value of ≤ 0.05 was regarded as statistically significant. The data reported as mean ± SD for all parameters.

Results

A total of sixty-two patients were enrolled in the study, 40 (64.5%) were female (F) and 22 (35.5%) were male (M), an M/F ratio 1:1.8. The age of the participants ranged between 8.25 and 25 years (16.84 ± 3.88). Thirty-one patients had a disease duration below or equal to 5 years (50%) and the remaining thirty-one a disease duration more than 5 years. The mean disease duration was 5.12 ± 3.16 years; the shortest duration was one year and the longest thirteen years. Regarding the glycemic control for the first HbA1c, forty-five patients (72.6%) were classified as high risk, nine patients (14.5%) had suboptimal control and eight (12.9%) had optimal control. For the second test, forty-two patients (67.8%) had high risk, eleven patients (17.7%) had suboptimal control and nine (14.5%) had optimal control. The mean of HbA1c was respectively 10.80 ± 2.80% [5.5%; > 14%] (95 mmol/mol ± 9 [37; > 130]) and 10.62 ± 2.87% [5.1%; > 14%] for the first and the second tests; p-value > 0.5. Four patients (6.4%) out of the sixty-two had diabetic retinopathy (92 mmol/mol ± 9 [32; > 130] (Table 1), thirteen (21%) had positive microalbuminuria, nine (14.5%) were at risk of developing microalbuminuria and in forty (64.5%) patients the two microalbuminuria screening tests performed were negative. None of the patients was found to have clinical albuminuria or overt macroalbuminuria; there was no association (p < 0.05) between disease duration and microalbuminuria (Table 2). One patient (1.6%) had diabetic neuropathy (a total Michigan Neuropathy Screening Instrument score ≥ 2.5), was a male aged 20 years and 7 months with a disease duration equal to 7 years, of a low socioeconomic status, was underweight and was at high risk concerning both HbA1c tests. All patients were on conventional therapy (2 injections per day of premixed insulin 70/30 alone or 2 injections of premixed insulin plus 1 injection of regular insulin per day). The premixed insulin profile was the 70/30. All patients are part of "Life for a child" program, meaning that the program provide for all of them free insulin, some receive fifty strips per month for blood glucose monitoring.

Table 1: Correlation between variables and ophthalmologic examination findings.

		Diabetic retinopathy		
		Absent (n = 58)	**Present (n = 4)**	**p-value**
Gender	Male n (%)	21 (36.2%)	1 (25%)	0.6
	Female n (%)	37 (63.8%)	3 (75%)	
Disease duration	≤ 5 years n (%)	31 (53.4%)	0	0.056
	> 5 years n (%)	27 (46.6%)	4 (100%)	
Socioeconomic status	High n (%)	11 (19%)	0	0.4
	Middle n (%)	28 (48.3%)	2 (50%)	
	Low n (%)	19 (32.7%)	2 (50%)	
SMR (Tanner)	Prepubertal n (%)	3 (5.2%)	0	0.6
	Pubertal n (%)	24 (41.4%)	1 (25%)	
	Adult n (%)	31 (53.4%)	3 (75%)	
BMI	Normal n (%)	42 (72.4%)	4	0.7
	Underweight n (%)	12 (20.7%)	0	
	Overweight n (%)	4 (6.9%)	0	
	Obese n (%)	0	0	
HbA1c-I	High risk n (%)	42 (72.4%)	3 (75%)	0.7
	Suboptimal n (%)	8 (13.8%)	1 (25%)	
	Optimal n (%)	8 (13.8%)	0	
HbA1c-II	High risk n (%)	39 (67.2%)	3 (75%)	0.6
	Suboptimal n (%)	10 (17.2%)	1 (25%)	
	Optimal n (%)	9 (15.6%)	0	

Table 2: Correlation between other variables and microalbuminuria.

		Microalbuminuria			
		Negative (n = 40)	**Positive (n = 13)**	**At risk (n = 9)**	**p-value**
Gender	Male n (%)	16 (40)	5 (38.5)	1 (11.1)	0.23
	Female n (%)	24 (60)	8 (61.5)	8 (88.9)	
Disease duration	≤ 5 years n (%)	19 (47.5)	5 (38.5)	7 (77.8)	0.26
	> 5 years n (%)	21 (52.5)	8 (61.5)	2 (22.2)	
Socioeconomic status	High n (%)	6 (15)	3 (23.1)	2 (22.2)	0.27
	Middle n (%)	19 (47.5)	7 (53.8)	4 (44.5)	
	Low n (%)	15 (37.5)	3 (23.1)	3 (33.3)	
SMR (Tanner)	Prepubertal n (%)	1 (2.5)	1 (7.7)	1 (11.1)	0.51
	Pubertal n (%)	18 (45)	2 (15.4)	5 (55.6)	
	Adult n (%)	21 (52.5)	10 (76.9)	3 (33.3)	
BMI	Normal n (%)	29 (72.5)	10 (76.9)	7 (77.8)	0.43
	Underweight n (%)	8 (20)	3 (23.1)	1 (11.1)	
	Overweight n (%)	3 (7.5)	0	1 (11.1)	
	Obese n (%)	0	0	0	
HbA1c-I	High risk n (%)	25 (62.5)	13 (100)	7 (77.8)	0.008
	Suboptimal n (%)	8 (20)	0	1 (11.1)	
	Optimal n (%)	7 (17.5)	0	1 (11.1)	
HbA1c-II	High risk n (%)	23 (57.5)	12 (92.3)	7 (77.8)	0.02
	Suboptimal n (%)	9 (22.5)	1 (7.7)	1 (11.1)	
	Optimal n (%)	8 (20)	0	1 (11.1)	

Discussion

Glycemic control was exceptionally poor in our study population. This is well documented fact in most of African settings, and especially in adolescents with type 1 diabetes mellitus. The following mean HbA1c from some studies corroborate this statement: 11.2 ± 4.5% (99 mmol/mol ± 26) in Rwanda [23], 13.9% (128 mmol/mol) in Tanzania [24], 11.4% (101 mmol/mol) in Nigeria [12], and an even worse in the Democratic Republic of Congo [25] where only 8% of the study population had a HbA1c below 7% (53 mmol/mol) and in another study in Tanzania [26] where only 5% of the study population reached the target of HbA1c ≤ 7.5% (58 mmol/mol). This picture is different from northern countries (North America, Japan, Australia and Europe) where HbA1c are much better than those encountered in Africa [27-29]. We hypothesized that puberty, gender and insulin type could be the most reasons for this poor control. As shown in the results section, the majority of patients enrolled in this study were in pubertal stages, were females, even if no statistically significant association between the HbA1c level and the gender [p > 0.05] was noted. Studies have shown that glycemic control often deteriorates during adolescence period, adolescents being currently the farthest from achieving HbA1c < 7.5% (58 mmol/mol) and HbA1c levels may be higher than at any other time [30-33]. Patients on premixed insulin (Neutral Protamine Hagedorn and regular insulin) have been found to have poor glycemic control compared with their peers on either insulin analogs or more intensive management of diabetes including insulin pumps [23,26,27,30,34].

Studies from Sub-Saharan Africa dealing with microalbuminuria in children and adolescents are rare. The prevalence of microalbuminuria (21%) in this study was higher than the 12% in Tanzania [24]; similar to those reported in Rwanda [23] and in Congo-Kinshasa [25] (21% and 21.9% respectively). Therefore, this is higher than those in another Tanzanian study [11] and in Nigeria [12] (29.3% and 33.3% respectively). Differences in methodology, age of patients and may be the definition of microalbuminuria may account for these differences. It's well known that increasing age is associated with a higher risk for the development of microalbuminuria [35-37]. On the other side, our results are far high than those found in studies done in western countries [38-40], which are known to have good health care systems, very specialized diabetes care centers and good patients' follow-up. In this study, poor glycemic control (high risk group) was found to have a statistically significant association with the presence of microalbuminuria for the two HbA1c tests done (p < 0.05), supporting the idea that poor glucose control increases the risk of developing microalbuminuria in youths with type 1 diabetes [40-43].

Diabetic retinopathy (DR) is rare in prepubertal children, but it is quite common in young patients with diabetes [44,45] and its prevalence had been found to be high in young adults with longer disease duration [11,46]; it in-

creases in children with onset of the disease after puberty [39,47,48]. However, DR has also been described in children with short disease duration in African children [12].

There are insufficient data on the prevalence and predictors of diabetic peripheral neuropathy among the pediatric population. Furthermore, early detection and good glycemic control have been proven to prevent and delay adverse outcomes associated with diabetic polyneuropathy. Near-normal control of blood glucose, beginning as soon as possible after the onset of diabetes, may delay the development of clinically significant nerve impairment [49]. Very few studies on diabetic neuropathy in children and adolescents had been carried in African region [23,50]; though with different methods in screening neuropathy. In the literature, higher prevalence than that in this study had been reported [34,40,45,51]; Longer duration of diabetes with its sustained impact on peripheral nerves could be an important determinant of diabetic neuropathy. As mentioned early, the wide ranges in the prevalence estimates of diabetic neuropathy among the young in those different studies could be due to the differing criteria and diagnostic tests used to define and characterize diabetic neuropathy.

Although this study failed to demonstrate and to give scientific evidences of the course of these vascular complications, due to a constraint working area (lack of sophisticated diagnostic tools), this study has the merit of pointing a very crucial subject, particularly in these patients mostly from low and middle socioeconomic families. To the best of our knowledge, this is the first study which screen T1DM microvascular complications in Congolese children, adolescents and young adults with diabetes. Successful treatment of type 1 diabetes mellitus, which include improving diabetes care (availability of medical insurance for all, diabetic intensive treatment, analogs insulin, frequent blood glucose monitoring, diabetic education and psychosocial support for patients and parents/guardians), is of particular importance for these patients to reduce, to delay or to prevent the risk of long-term vascular complications.

Conclusions

The high prevalence of early signs of microvascular complications shown in this study, mainly microalbuminuria and in a lesser proportion the presence of diabetes retinopathy in some patients shows the need for early screening of microvascular complications in children and adolescents with type 1 diabetes, especially in poor controlled patients in a constraint setting. These data show that there is a need to improve diabetes care in Congo.

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Author Contribution

S.V.M.M. wrote/reviewed/edited the manuscript, researched data, contributed to discussion; E.B. reviewed the manuscript, researched data and contributed to discussion; F.N.N. reviewed the manuscript, L.C.O.I. contributed to discussion; J.R.M.B. reviewed/edited the manuscript and contributed to discussion; T.N. reviewed the manuscript; F.D.V. edited the first article draft, reviewed/edited the manuscript, he also contributed to discussion; F.C. contributed to discussion, reviewed/edited the manuscript.

Conflict of interest

None.

Guarantor

Dr. Steve Vassili Missambou Mandilou.

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