

Cardiac Autonomic Dysfunction in Children and Adolescents with Type 1 Diabetes Mellitus

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Introduction: Autonomic neuropathy is less well documented in children with type 1 diabetes mellitus and has received less attention than other diabetic complications. Sudden death and cardio-respiratory arrest in patients with type 1 and type 2 diabetes mellitus have been attributed to cardiac autonomic dysfunction.

Aim: The aim of this study was to determine the prevalence of autonomic neuropathy in a cohort of children and adolescents with type I diabetes and to examine the relationship between this complication, and duration of diabetes and degree of glycemic control.

Material and Methods: Seventy-six type 1 diabetic children and adolescents below age 18 years of age, and 76 non-diabetic school children, matched for age and sex, had their cardiac autonomic nerve function assessed using four autonomic function tests. Namely the respiratory sinus arrhythmia test; the Valsalva ratio test; the heart rate response to standing, and the blood pressure response to standing. The first three are tests of parasympathetic function, while the last one is a sympathetic function test.

Results: The diabetic patients had a median age of 12 years and their median duration of diabetes mellitus was 43 months. They showed a significantly higher resting heart rate and a significant drop in systolic and diastolic blood pressures upon standing compared to the control group. The duration of diabetes mellitus showed linear correlation to the symptoms of autonomic dysfunction.

Conclusion: We conclude that cardiac autonomic neuropathy is not rare in young diabetic patients of relatively short duration of illness where glycemic control is less than optimal. Such tests may serve as long-term prognostic indicators in diabetic patients.

Keywords: autonomic neuropathy, peripheral neuropathy, glycemic control, Middle East

Introduction

About 13% of patients with type 1 diabetes mellitus develop diabetic neuropathy as a result of damage to peripheral and/or autonomic nerves¹. This complication is usually described in adult patients with type 2 diabetes mellitus after several years of illness and often in the presence of poor metabolic control. It is less well documented in children with type 1 diabetes mellitus who have relatively short duration of disease (<7 years). Because the symptoms of autonomic neuropathy are insidious in onset and difficult to recognize, it has received less attention than other diabetic complications. However, although it is not usually life threatening, diabetic autonomic neuropathy (DAN) may be associated with substantial morbidity²⁻⁴. Sudden death and cardio-respiratory arrest in patients with type 1 and type 2 diabetes mellitus have been attributed to cardiac

autonomic dysfunction⁵. Evidence of autonomic neuropathy in those patients has been considered a sensitive indicator of increased risk of mortality and morbidity⁶. The development of some simple tests of autonomic nerve function have helped in the assessment of patients complaining of clinical features that may be attributed to autonomic dysfunction as well as in the assessment of asymptomatic subjects. These tests also have a predictive and prognostic value in the clinical evaluation of such patients.

The aim of this study was to determine the prevalence of autonomic neuropathy in a cohort of children and adolescents with type I diabetes and to examine the relationship between this complication, and duration of diabetes and degree of glycemic control. Four autonomic nerve function tests were used. Additional objective was thus to assess which one of these tests was the most predictive and correlates best with the clinical symptoms and signs of autonomic neuropathy.

Subjects and methods

The study is one of a series of studies that address complications in young patients with type 1 diabetes. The patients were seen regularly at the pediatric diabetes outpatient clinic of Sultan Qaboos University Hospital in Muscat, Sultanate of Oman, for clinical evaluation and insulin prescription on monthly basis. The cohort

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included 76 children and adolescents below the age of 18 years with type 1 (insulin-dependent) diabetes mellitus. The period of data collection was between September 1997 and August 2006. All patients were treated with a premixed of short and intermediate-acting human insulin (Mixtard Novo) given in two daily doses. The data recorded included clinical presentation, duration of diabetes, dose of insulin per kg/day, family history of diabetes, and frequency of ketoacidosis and severe hypoglycemia. The onset of diabetes was noted on the day of commencement of insulin therapy. The glycated hemoglobin (HbA1c) concentration was measured every two months and the average of one-year readings was used to reflect the degree of glycemic control. The reference value for non-diabetic subjects in our hospital is less than 6.2 %. Severe hypoglycemia was defined as an episode that required assistance from another person or hospital care and DKA was rated significant only when confirmed and treated in a hospital. The mean number of such episodes in the year preceding the study was utilized for data analysis. Seventy-two non-diabetic school children matched for age and sex were recruited to serve as controls. Independent evaluation of each patient to ascertain the presence of other late-onset diabetic complications was carried out using standardized ophthalmoscopy and retinal photography for retinopathy, serum creatinine and 24h urinary protein concentration for nephropathy, and clinical evaluation and nerve conduction for peripheral neuropathy.

Cardiac autonomic nerve function was assessed by four standard physiologic tests: the respiratory sinus arrhythmia test (RSA); the Valsalva ratio test (VR); the heart rate response to standing (30:15 ratio), and the blood pressure response to standing (Postural BP). The first three are tests of parasympathetic function, while the last one is a sympathetic function test. The patients were left to lie down supine for half an hour of rest before the tests were performed. During this time their medical history was recorded including details of symptoms suggestive of autonomic neuropathy, and a thorough physical examination was performed. None of the patients had clinical evidence of any intrinsic heart or respiratory disease nor were any of them on any medication that might affect their cardiovascular system.

Statistical analysis

Student's t-test was used to compare the mean of each test result between the groups.

Linear and multiple regression analysis were computed using the SPSS statistical software to examine the correlation between the duration of diabetes and the degree of glycemic control, and the presence of autonomic dysfunction. The predictive value of each test in relation to the symptoms and signs of DAN was also tested. Level of statistical significance was set at $p < 0.05$.

Results

Fifty-one patients (67.1%) had no symptoms i.e. asymptomatic diabetic (AD), ten patients (13.2%) reported symptoms of diabetic peripheral neuropathy (DPN), eight patients (10.5%) had symptoms of diabetic autonomic neuropathy (DAN), and seven patients (9.2%) showed symptoms and signs of both peripheral and autonomic diabetic neuropathy (DPAN). The most common symptoms of peripheral neuropathy reported were numbness and tingling sensation mainly in the feet together with pain described as pins and needles that were persistent. For the possibly autonomic neuropathy, the most common symptoms reported in order of frequency were: postural dizziness, sweating abnormalities, nausea, nocturnal diarrhea, epigastric fullness, gustatory sweating, vomiting and constipation. All were reported to be persistent and somewhat troublesome. None of the patients showed any gross neurological signs.

There was no significant statistical difference between the diabetic patients and the control subjects regarding median age, mean weight, mean height, and the average supine blood pressure (table 1). However, in the group of diabetic patients 23 subjects (30%) were below the third percentile for weight, and 19 subjects (25%) were below the third percentile for height, according to Tanner standards⁷. In the control group 11 subjects (14.5%) were below the third percentile for weight and 9 subjects (11.8%) were below the third percentile for height. The resting heart rate of the diabetic children was significantly higher than that of the control group ($P < 0.05$). Table 2 compares the results of the autonomic function tests between the different groups. It illustrates significant differences between the two groups in the heart rate response to standing (30:15 ratio), and postural B.P tests. The details of the results of the autonomic function tests are shown in table 3. There was a significant lowering of both systolic and diastolic blood pressures upon standing ($P < 0.01$) in the postural B.P. test. The other two tests (RSA and

Table 1: Characteristics of the control and diabetic subjects

		Control n = 76	Diabetic Subjects n = 76	P Value
Age <years>	Mean ± S.D.	12.6 ± 2.6	12.8 ± 2.5	NS
	Range	7 - 16	7 - 17	
Sex	Male	38	39	NS
	Female	38	37	
Weight (kg)	Mean ± S.D.	39.36 ± 15	34.20 ± 10	NS
	Range	20 - 70	21 - 73	
Height (cm)	Mean ± S.D.	145.6 ± 15.2	143.07 ± 12.16	NS
	Range	116 - 165	120 - 166	
Resting heart rate (beats/min)	Mean ± S.D.	83 ± 9	90 ± 12	<0.05
Resting Supine BP (mmHg)				
Systolic	Mean ± S.D.	107.3 ± 11.4	110.8 ± 13.3	NS
Diastolic	Mean ± S.D.	67.3 ± 8.7	68.2 ± 12.9	

Table 2: (Mean ± S.D.) of the autonomic function tests

	Respiratory Sinus arrhythmia (R) beats/min	Valsalva ratio (V.R)	Heart rate response to standing (30:15 ratio)	Blood pressure response to standing (Postural B.P) Systolic Diastole mmHg	
Control n=76	30.3 ± 6.6	1.7± 0.5	1.2 ± 0.3	+3.4±7.6	+4.8±10
Asymptomatic diabetic (A.D) n=51	27.9 ± 12.7	2.0± 0.5	1.2 ± 0.2	-8.3±9.6	-3.4±14
Diabetics with peripheral neuropathy (D.P.N) n=10	25.7 ± 10.2	1.7± 0.6	1.3 ± 0.2	-3.1±6.1	-0.1±8.3
Diabetics with Autonomic neuropathy (D.A.N) n=8	28.5 ± 10.3	1.8± 0.3	1.2 ± 0.1	-0.8±10.5	-0.1±6.2
Diabetics with both peripheral & autonomic neuropathy (D.P.A.N) n=7	25.9 ± 11.7	2.1± 0.6	1.0 ± 0.05	-8.1±9.9	-6.3±7.5

Table 3: Statistical comparison of the results of the autonomic function between the different groups.

Patients & control	Test	P value
Control vs A.D	Resting Heart Rate	P < 0.05
	Postural B.P (S)	P < 0.005
Control vs D.A.N	Resting Heart Rate	P < 0.05
Control vs D.P.A.N	30:15 Ratio	P < 0.05
	Postural B.P (S)	P < 0.005
	Postural B.P (D)	P < 0.01
A.D vs D.P.A.N	30:15 Ratio	P < 0.01
D.P.N vs D.P.A.N	30:15 Ratio	P < 0.005
D.A.N vs D.P.A.N	30:15 Ratio	P < 0.005

B.P (S): Systolic blood pressure, B.P (D): Diastolic blood pressure

VR) showed insignificant differences between the diabetic and the control groups ($p = 0.5$).

There was a positive correlation between duration of diabetes mellitus and prevalence of neuropathy in this group of patients ($r = 0.84$ $p < 0.001$). The mean duration of diabetes in months \pm standard deviation was 17 ± 16 for the A.D., 23 ± 17 for D.A.N., 32 ± 33 for the D.P.N. and 67 ± 30 for the D.P.A.N. group. The number of autonomic neuropathy symptoms reported in each patient correlated significantly only with the duration of his diabetes mellitus ($r = 0.56$). Also the systolic drop in blood pressure was significantly correlated to the diastolic drop in the postural B.P. test ($r = 0.623$).

Discussion

Although autonomic neuropathy is a result of multi-system pathology, the usage of cardiovascular reflex tests has been shown to correlate well with all symptoms of autonomic neuropathy⁸. An elevated resting heart rate in our diabetics compared to the control is in agreement with findings by Storstein and Jervell¹¹. This reflects parasympathetic cardiac nerve involvement, as during quiet non-stressed supine position there is little cardiac sympathetic activity¹². Cardiac parasympathetic activity may be diminished in diabetes even before clinical symptoms of autonomic neuropathy are evident. An association between objectively defined diabetic neuropathy and elevated resting heart rate has been observed¹³. The resting heart rate was not significantly elevated in the D.P.N. and D.P.A.N. groups compared to the control. This may reflect the natural history of cardiac autonomic neuropathy in which an early

parasympathetic impairment may elevate the heart rate, but as the duration of the diabetes increases, as in the two groups above mentioned, sympathetic involvement occurs that may relatively slow the heart rate¹⁴. The heart rate elevation to standing (30:15 ratio) depends upon an intact parasympathetic supply to the heart. Loss of the ability to increase heart rate upon standing was observed to occur even within one year of diagnosing diabetes¹⁵. The fact that heart rate failed to increase in DPAN groups although they suffered from postural hypotension in comparison to the control and they had greater blood pressure fall may indicate a defect in the baroreceptor reflex arch as suggested by Hilsted¹⁶. Postural hypotension is the most significant clinical expression of autonomic neuropathy to affect the cardio-vascular system. The postural BP test may be significantly altered even in asymptomatic diabetics¹⁷. In our study the commonest symptom of autonomic neuropathy reported was postural hypotension. The asymptomatic diabetic (AD) group had significantly altered postural BP test compared to the control $P < 0.005$. Sympathetic activity impairment failing to increase the total peripheral resistance appears to be the primary cause since parasympathetic outflow to the heart is not required for normal postural adaptation¹⁸. The duration of diabetes mellitus correlated well with autonomic symptoms. This is in agreement with Weinberg and Pfeifer who showed resting heart rate and duration of diabetes were predictive of having symptoms of autonomic neuropathy¹⁹.

We may conclude that the resting heart rate, in addition to the heart rate response to standing, and the blood pressure response to standing autonomic function tests are easy to perform even on children. They require minimal cooperation by the subjects as compared to the other tests. Even

in asymptomatic diabetics and with relatively short duration of diabetes autonomic neuropathy could be diagnosed by these tests and they gave an idea about the severity of autonomic dysfunction. It may be possible for any clinician to perform them as they may help in the assessment and management of his diabetic patients.

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