Natural progression of cardiac autonomic neuropathy in patients with type 1 diabetes: a four-year follow-up study

Tip 1 diyabetli hastalarda kardiyak otonom nöropatinin doğal gidişi: Dört yıllık takip çalışması

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ABSTRACT

Objective: To determine the prevalence and clinical characteristics of cardiac autonomic neuropathy in type 1 diabetic patients who were followed up for 4 years to shed further light on the natural progression of cardiac autonomic neuropathy.
Methods: It is a prospective cohort observational study, consisted of 57 patients who were originally studied using the standard tests proposed by Ewing and Clarke (1985). At two years follow up, 46 patients were reevaluated, 55 patients from the original study were reevaluated after another 2 years for the 3rd time using the same protocol. The control group comprised 30 age and sex matched healthy volunteers. McNemar test, ANOVA for repeated measurements, paired t test and unpaired t test were used for statistical analyses.
Results: The prevalence of established cardiac autonomic neuropathy (CAN) at the beginning was 14%. Q-Tc intervals were found to be significantly higher in patients with abnormal cardiovascular reflex (CVRs) in the 2nd examination (0.4±0.04 vs 0.5±0.05 sec, p=0.006). Eighteen patients showed deterioration of their CVRs test between 1st and 3rd examination. There was deterioration of their glycemic control guided by glycosylated hemoglobin (8.5±1.4 vs 9.9±1.5%, p=0.05*) and albumin/creatinine ratio (4.4±4.0 vs 28.2±28.0 mg/g creatinine, p= 0.04). On the other hand, 12 patients showed regression of their CVRs test. Only their insulin dose showed significant decrease (1.8±1.3 vs 1.1±0.3 dose/kg, p=0.02).
Conclusion: The prevalence of established CAN in diabetic patients is high at the beginning of the study. Glycosylated hemoglobin, systolic and diastolic blood pressure were significantly increased in diabetics with deterioration of their CAN. However, the dose of insulin was significantly decreased in diabetics with regression of their CAN. *(Anadolu Kardiyol Derg 2011; 11: 224-31)*
Key words: Cardiac autonomic neuropathy, type 1 diabetes, complications, natural history

ÖZET

Amaç: Kardiyak otonom nöropatinin doğal seyrine daha fazla ışık tutmak için 4 yıl boyunca takip edilen Tip 1 diyabet hastalarında kardiyak otonom nöropati sıklığı ve klinik özelliklerini belirlemek.
Yöntemler: Ewing ve Clarke (1985) tarafından önerilen standart testler kullanılarak, ilk olarak çalışılan 57 hastadan oluşan kohort gözlemsel ileriye dönük bir çalışmadır. İki yıllık takipte, 46 hasta yeniden değerlendirildi. Sonraki diğer bir 2 yılda üçüncü kez aynı protokol kullanılarak: Asıl çalışmadan 55 hasta tekrar değerlendirildi. Kontrol grubu, aynı yaş ve cinsiyette 30 sağlıklı gönüllüden oluşmaktadır. İstatistiksel analizler McNemar testi, tekrarlanan ölçümler için ANOVA, eşleştirilmiş ve eşleştirilmemiş t-testleri ile yapılmıştır.
Bulgular: Başlangıçta, kardiyak otonom noröpati (KON) saptanma sıklığı %14'tür. İkinci muayenede Q-Tc aralığı, anormal kardiyovasküler refleksi (CVRs) olan hastalarda anlamlı şekilde daha yüksek bulunmuştur (0.4±0.04 karşın 0.5±0.05 sn, p=0.006). Birinci ve üçüncü muayene arasında on sekiz hasta CVRs testinde bozulma gösterdi. Glikozile hemoglobin rehberliğinde, (8.5±1.4 karşın 9.9±1.5%, p=0.05) glisemik kontrollerinde ve albümin kreatinin oranında (4.4±4.0 karşın 28.2±28.0 mg/g kreatinin , p=0.04) bozulma vardır. Diğer yandan, 12 hasta CVRs testinde gerileme gösterdi. Sadece insülin dozunda anlamlı şekilde azalma oldu (1.8±1.3 karşın 1.1±0.3 doz/kg, p=0.02).
Sonuç: Çalışmanın başlangıcında, diyabetik hastalarda saptanan KON sıklığı yüksektir. Kardiyak otonom nöropatilerinde bozulma olan diyabet hastalarında, glikozile hemoglobin, sistolik ve diyastolik kan basıncı anlamlı olarak yükseldi. Ancak, kardiyak otonom nöropatilerinde gerileme olan diyabet hastalarında insülin dozu anlamlı olarak azaldı. *(Anadolu Kardiyol Derg 2011; 11: 224-31)*
Anahtar kelimeler: Kardiyak otonom nöropati, tip 1 diyabet, komplikasyon, doğal seyir

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Introduction

Though, there are few studies on natural history of cardiac autonomic neuropathy (CAN) in diabetes, the natural history of CAN during long-term follow-up and relationship of CAN with clinical characteristics are not well described. CAN is a severe complication of diabetes, causing death and morbidity and large costs to the welfare system. The mechanisms by which CAN exerts negative influence on quality and length of life are controversial, but many relationships have been found, such as exercise intolerance (1), silent myocardial ischemia (2) and prolongation of the QT interval causing lethal arrhythmias (3). CAN results from damage to the autonomic nerve fibers to the heart, and the earliest indicator of CAN is a decrease in heart rate variation (HRV) during deep breathing, which is easily assessed by a simple bedside test (4).

Most studies concerning CAN in type 1 diabetes mellitus (DM) begin by stating that CAN, although common, is a neglected complication of diabetes, which is often asymptomatic and therefore dangerous. The danger lies in increased morbidity and mortality. Nonetheless, the mortality study showed that the cause of death in type 1 DM is not represented by chronic complications of diabetes, including also CAN, but cardiovascular diseases (5, 6).

The pathological alteration of the nervous system in diabetic patients is extensive and frequently severe. The prevalence of diabetic neuropathy reaches high levels with the evolution of diabetes, often showing frequencies higher than 50% in several groups of patients. The neurological lesion in this pathological situation is extensive in diabetic patient, including widely the peripheral nervous system with its components sensory, motor and autonomic: with typical symptoms and in accordance with the pathogenesis of metabolic origin and/or microvascular disease. The autonomic nervous system is a main regulator of many systems in the human body. Then its lesion can promote significant alterations in the function of the cardiovascular, respiratory, gastrointestinal and urogenital system that can be related to increased mortality (7).

We are aiming to determine:

1. Natural progression of cardiac autonomic neuropathy in a group of type 1 diabetic patients who were followed up for 4 years.
2. Whether the progression of CAN depends on the clinical characteristics of cardiac autonomic neuropathy or other characteristics like insulin dose, blood pressure and their glycemic control guided by glycosylated hemoglobin.

Methods

Patients

The study consisted of 57 patients with type 1 diabetes among those attending to the endocrine clinic in the National Research Centre. The control group consisted of 30 age and sex matched healthy normal volunteers.

The exclusion criteria were as follows:

1. Patients during acute diabetic complications e.g. diabetic ketoacidosis (DKA) or hypoglycemia.
2. Patients suffering from cardiac diseases e.g. congenital, rheumatic heart, left ventricular dysfunction or hypertension.
3. Patients suffering from chronic renal failure and electrolyte imbalance.
4. Patients receiving drugs for cardiovascular disease.
5. Patients younger than six years (in order to be able to perform CVR tests).

Study design and protocol

It is a prospective cohort observational study done after obtaining approval from the local institutional review board and human subjects protection. Written consent was obtained from patients and their parents.

At the beginning of our study, 57 patients were evaluated using a battery of five cardiovascular autonomic tests (Fig. 1).

At two years follow up, 46 patients were reevaluated using the same protocol. Nine patients from the original study could not be located.

At four years follow up, 55 patients from the original study were reevaluated for the 3rd time using the same protocol.

The control group subjects were evaluated only at the beginning of the study by the same protocol.

Electrocardiography (ECG)

Long recording of lead II (on ECG) was done to calculate basal heart rate (HR) and correlated Q-T (QTc) interval by Bazett's formula:

$Q\text{-}Tc = Q\text{-}T / \sqrt{(R\text{-}R)}$ (Normal < 0.45 s)

Cardiac autonomic neuropathy tests

For the diagnosis of CAN we used the standard tests proposed by Ewing and Clarke (8) and the Consensus Statement of the members of the American Diabetes Association and the American Neurological Academy (9). Diagnosis of CAN was made when at least two tests were pathological (8).

The following cardiovascular reflex (CVR) tests were done in the same sequence:

1) HR response to Valsalva maneuver: The test was performed by the patient blowing into a mouth piece connected to a sphygmomanometer and holding it at a pressure of 40 mmHg for 15 seconds while a continuous ECG was recorded. The maneuver was performed 3 times with interval of one minute in between. The result was expressed as the Valsalva ratio, which is the ratio of the longest R-R interval after the maneuver to the shortest R-R interval during the maneuver. The mean of three Valsalva ratio was taken as the final value (normal Valsalva ratio >1.21, borderline between 1.11 and 1.20, abnormal <1.10).

2) HR variation during deep breathing: The patient sat quietly and breathed deeply at rate of 6 breaths per minute (5 sec-

onds in and 5 seconds out) for one minute. An ECG was recorded throughout the period of deep breathing with a marker used to indicate the onset of each inspiration and expiration. The maximum and minimum R-R intervals during each breathing cycle were measured and converted into beats/minute. The result was then expressed as the mean of the difference between maximum and minimum HRs for the 6 measured cycles in beats / minute (normal response >15 beats/minute, borderline 11-14 beats / minute, abnormal response <10 beats / minute).

3) Immediate HR response to standing: The test was performed with the patient lying quietly on a couch while HR was recorded continuously on ECG machine. The patients were asked to stand up unaided and the point at starting to stand was marked on ECG. The shortest R-R interval at or around the 15th beat and the largest R-R interval at or around the 30th beat after starting to stand were measured with a ruler. The characteristic HR response was expressed by 30: 15 ratio, which is normal if >1.04, borderline between 1.01 and 1.03 and abnormal if <1.0.

4) Blood pressure (BP) response to standing: The test was performed by measuring the patient's BP while he was lying down quietly and again when he stood up. The postural fall in BP was taken as the difference between systolic BP lying and the systolic BP standing (normal response < 10 mm Hg, borderline 11-29 mm Hg , abnormal response > 30 mm Hg).

5) BP response to sustained handgrip: After instructions on using handgrip of an inflated BP cuff, the subject gripped maximally with his dominant arm for a few seconds; this was repeated thrice. The highest of the three readings is called maximum voluntary contraction (MVC). Now the subject was instructed to maintain handgrip steadily at 30% MVC for as long as possible to a maximum of 5 minutes. BP was measured on non- exercising arm and diastolic BP (DBP) was taken at muffling of sound. The BP was recorded 3 times at rest and at intervals of one minute during handgrip. The result was expressed as the difference between the highest DBP during handgrip exercise and mean of 3 DBP readings before handgrip began (normal response > 16 mm Hg, borderline 11-15 mm Hg, abnormal <10 mm Hg).

Laboratory tests

Simultaneously all patients underwent the following tests:

Glycosylated hemoglobin (HbA1c) was done every 3 months by DCA 2000 (Bayer AG, Leverkusen, Germany), based on specific inhibition of latex immunoagglutination using kits provided by Helena Laboratories, Beaumont, TX, USA/ (10).

Screening for microalbuminuria: It was assessed in fresh morning urine samples by measuring albumin / creatinine ratio by enzyme linked immunosorbent assay (ELISA).

Statistical analysis

Statistical analysis were conducted using Statistical Package for Social Science (SPSS) program version 9 (Chicago, Illinois, USA). McNemar test was done for analysis of qualitative data in a follow up study. T-test for dependent variables was also done. Comparison of diabetic patients with control group was done using unpaired t test for independent samples. ANOVA for repeated measurements for comparison of continuous variables in patients with diabetes was also done followed by posthoc analysis (Turkey's test) by using GraphPad Prism version 5 for Windows software (Graphad software, San Diego, California USA).

Results

The study included 57 patients with type 1 diabetes, 27 male and 30 female, their mean age was 12.3±4.1 years (range 8-20 years), mean duration of disease was 5.9±3.7 years (4-15 years) and mean age of onset of disease was 6.4±3.3 years (range 2.5-14 years).

At the beginning of the study, frequencies of symptoms suggestive of cardiac autonomic neuropathy were as follows: urinary symptoms -20.7% , gastrointestinal symptoms -17.2%, blurring of vision -13.8%, palpitations -6.9%, chest pain and loss of sensation -5.2%, postural hypotension, intermittent claudication and paresthesia was 1.7%.

CVR tests done at the beginning of the study revealed that:

- QTc interval duration was normal in 46 (82.1%) patients and abnormal in 10 (17.9%).
- HR response to deep breathing was normal in 50 (87.7%) patients, abnormal in 3 (5.3%) and borderline in 4 (7%).
- HR response to standing up was normal in 46 (80.7%) patients, abnormal in 4 (7.0%) and borderline in 7 (12.3%).
- HR response to Valsalva maneuver was normal in 50 (87.7%) patients and abnormal in 7 (12.3%).
- Systolic BP decrease with standing was normal in all patients.
- DBP increase with sustained handgrip was normal in 42 (73.7%) patients, abnormal in 7 (12.3 %) and borderline in 8 (14.0%).

The clinical data of patients at the beginning, 2 and 4 years of follow up are presented in Tables 1, 2 and frequencies of abnormal CVRs of patients on three successive examinations with 2 years timely intervals - Tables 3, 4, and Figure 1.

At the beginning, we found that 21 (36.8%) of our patients had abnormalities in CVR tests: 13 (22.8%) with one abnormal test (early involvement), 6 (10.5%) with two abnormal tests (definite involvement) and 2 (3.5%) patients with three or more abnormal tests (severe involvement).

The frequency of abnormal response between 1st and 2nd examination showed regression though not statistically significant in HR response to standing, BP response to handgrip and Q-Tc intervals; while HR response to deep breathing and HR response to Valsalva maneuver remained unchanged.

In addition, the frequencies of abnormal response between 1st and 3rd examinations showed regression in all five CVRs and Q-Tc intervals, however the differences were not statistically significant.

QTc interval duration was found to be statistically significantly higher in patients with abnormal CVRs than those with

Table 1. Comparison between symptoms of autonomic neuropathy of diabetic patients on first and second examinations (2-year interval)

First examination	Second examination				*p
	No		Yes		
	no.	%	no.	%	
Palpations:					
No (n=42)	27	64.3	15	35.7	0.002
Yes (n=4)	2	50	2	50	
Chest pain:					
No (n=43)	37	86.0	6	14	0.1
Yes (n=3)	1	33.3	2	66.7	
Postural hypotension:					
No (n=45)	35	77.8	10	22.2	0.01
Yes (n=1)	1	100	0	0	
Intermittent claudication:					
No (n=46)	43	93.5	3	6.2	
Yes (n=0)	0	0	0	0	
Gastrointestinal symptoms:					
No (n=39)	34	87.2	5	12.8	1
Yes (n=7)	4	57.1	3	42.9	
Urinary symptoms:					
No (n=36)	34	94.4	2	5.6	0.07
Yes (n=10)	9	90	1	10	
Blurred vision:					
No (n=39)	28	71.8	11	28.2	0.6
Yes (n=7)	3	42.9	4	57.1	
Paresthesia:					
No (n=45)	26	57.8	19	42.2	0.0001
Yes (n=1)	1	100	0	0	
Loss of sensation:					
No (n=43)	43	100	0	0	
Yes (n=3)	3	100	0	0	

Data are presented as number/percentage
*McNemar test

Table 2. Comparison between symptoms of autonomic neuropathy of diabetic patients on first and third examination (4-year interval)

First examination	Third examination				*p
	No		Yes		
	no.	%	no.	%	
Palpations:					
No (n=51)	31	60.8	20	39.2	0.0001
Yes (n=4)	1	25	3	75	
Chest pain :					
No (n=52)	41	78.8	11	21.2	0.02
Yes (n=3)	3	100	0	0	
Postural hypotension :					
No (n=54)	47	87	7	13	0.004
Yes (n=1)	0	0	1	100	
Intermittent claudication:					
No (n=54)	51	94.4	3	5.6	0.2
Yes (n=1)	1	100	0	0	
Gastrointestinal symptoms:					
No (n=45)	38	84.4	7	15.6	0.6
Yes (n=10)	6	60	4	40	
Urinary symptoms:					
No (n=43)	41	95.3	2	4.7	0.07
Yes (n=12)	9	75	3	25	
Blurred vision:					
No (n=47)	41	87.2	6	12.8	1
Yes (n=8)	7	87.5	1	12.5	
Paresthesia :					
No (n=54)	33	61.1	21	38.9	0.0001
Yes (n=1)	1	100	0	0	
Loss of sensation:					
No (n=52)	50	96.2	2	3.8	1
Yes (n=3)	3	100	0	0	

Data are presented as number/percentage
*McNemar test

normal CVRs on the 2nd examination (0.5±0.05 sec vs 0.4±0.04 sec, respectively , p=0.006).

The mean values of CVRs tests of patients at the beginning, 2nd and 4th years of follow-up compared to control group are presented in Table 5.

Eighteen patients of the original studied group showed progression (deterioration) of their CVR test between 1st and 3rd examinations. There were deterioration of their glycemic control guided by HbA1c and albumin / creatinine ratio ($p \leq 0.05$ for both). On the other hand, 12 patients of the original studied group showed regression of their CVR test. Their HbA1c showed inconsistent pattern, only their insulin dose showed significant decrease ($p<0.05$) (Table 6).

Discussion

At the beginning, we found that 21 (36.8%) of our patients had abnormalities in CVR tests, 13 (22.8%) with one abnormal test (early involvement), 6 (10.5%) with two abnormal tests (definite involvement) and 2 (3.5%) with three or more abnormal tests (severe involvement). The prevalence of established CAN is 14%.

The overall prevalence of abnormal CVR in our study is nearly similar to that of Paries et al. (11), Who found that prevalence of CAN varies between 20% to 70% of diabetic subjects. Also Pavy-Le et al. (12), reported a prevalence of 12.3%. On the contrary, Aman et al. (13) reported 0% prevalence of abnormal CVR tests.

Table 3. Comparison of cardiovascular reflex (parasympathetic and sympathetic) variables of diabetic patients on first and second examination (2-year interval)

First examination	Second examination						*p
	Normal		Abnormal		Borderline		
	no.	%	no.	%	no.	%	
QT interval:							
Normal (n=39)	31	79.5	8	20.5	0	0	0.6
Abnormal (n=7)	5	71.4	2	28.6	0	0	
Heart rate response to deep breathing (E/I ratio):							
Normal (n=41)	35	85.3	2	4.9	4	9.8	
Abnormal (n=3)	1	33.3	2	66.7	0	0	0.5
Borderline (n=2)	2	100	0	0	0	0	
Heart rate response to standing up (30/15 ratio):							
Normal (n=37)	35	94.6	1	2.7	1	2.7	
Abnormal (n=5)	5	100	0	0	0	0	0.07
Borderline (n=4)	4	100	0	0	0	0	
Heart rate response to Valsalva maneuver:							
Normal (n=40)	33	82.5	7	17.5	0	0	0.07
Abnormal (n=6)	1	16.7	5	83.3	0	0	
Systolic blood pressure decrease with standing:							
Normal (n=46)	46	100	0	0	0	0	
Abnormal (n=0)	0	0	0	0	0	0	
Diastolic blood pressure increase with sustained handgrip:							
Normal (n=33)	26	78.8	4	12.1	3	9.1	
Abnormal (n=7)	6	85.7	1	14.3	0	0	0.5
Borderline (n=6)	5	83.3	0	0	1	16.7	

Data are presented as number/percentage
*McNemar test

Table 4. Comparison of cardiovascular reflex (parasympathetic and sympathetic parameter) variables of diabetic patients on first and third examination (4-year interval)

First examination	Third examination						*p
	Normal		Abnormal		Borderline		
	no.	%	no.	%	no.	%	
QT interval:							
Normal (n=46)	42	91.3	4	8.7	0	0	0.3
Abnormal (n=9)	9	100	0	0	0	0	
Heart rate response to deep breathing (E/I ratio):							
Normal (n=48)	37	77.1	7	14.6	4	8.3	
Abnormal (n=4)	3	75	1	25	0	0	0.2
Borderline (n=3)	1	33.3	1	33.3	1	33.3	
Heart rate response to standing up (30/15 ratio):							
Normal (n=45)	36	80	9	20	0	0	
Abnormal (n=6)	4	66.7	2	33.3	0	0	0.6
Borderline (n=4)	2	50	0	0	2	50	
Heart rate response to Valsalva maneuver:							
Normal (n=48)	35	72.9	13	27.1	0	0	0.1
Abnormal (n=7)	5	71.4	2	28.6	0	0	
Systolic blood pressure decrease with standing:							
Normal (n=55)	55	100	0	0	0	0	-
Abnormal (n=0)	0	0	0	0	0	0	
Diastolic blood pressure increase with sustained handgrip:							
Normal (n=42)	37	88.1	5	11.9	0	0	
Abnormal (n=8)	7	87.5	1	12.5	0	0	-
Borderline(n=5)	5	100	0	0	0	0	

Data are presented as number/percentage
*McNemar test

The discordance between different investigators may be related to the different criteria used to diagnose and classify neuropathy and because the prevalence of neuropathy may be influenced by age, duration of diabetes and type of diabetes (14).

Symptoms suggestive of CAN were less reported compared to the frequency of CAN diagnosed by CVR tests. In our study urinary symptoms were found in 20.7% of patients, gastrointestinal symptoms - 17.2%, blurring of vision - 13.8%, palpitations - in 6.9%, chest pain and loss of sensation - 5.2%, postural hypotension, intermittent claudication and paresthesia - 1.7%. These findings are in accordance with previous studies (12) and support the fact that many diabetics with CAN are asymptomatic.

Khoharo et al. (14), reported the following finding among their 49 diabetic patients with symptomatic autonomic neuropathy, postural hypotension in 67%, diarrhea in 49% , gustatory sweating in 37%, bladder paresis in 6%, gastroparesis in 4% and cardiorespiratory arrest in 4%. The different frequencies of autonomic symptoms between our study and that of Khoharo et al. (14) may be explained by the older age and longer duration of their patients.

The major observation in this study is the regression of symptoms over the 4 years follow-up period: palpitations, postural hypotension, and paresthesia significantly decreased on the second examination, while on the third examination, statistically significant increase in frequency of palpitations and postural hypotension was found, however frequency of chest pain and paresthesia was statistically significant decreased.

In the current study, although HR response to standing and BP response to handgrip showed regression in diabetics studied over time, the others (HR response to deep breathing and HR response to Valsalva maneuver) showed stationary response but

Table 5. Comparison of cardiovascular reflex (parasympathetic and sympathetic) variables between diabetic patients and control group

Variables	Diabetic patients			Controls (n=30)	**F	**p
	First examination (n=46)	Second examination (n=46)	Third examination (n=46)			
Heart rate response to deep breathing (E/I ratio), betas/min	23.5±9.2*	24.4±10.5*	22.7±12.7*	31.3±8.5	0.43	0.6
Heart rate response to standing up (30/15 ratio)	1.1±0.2	1.2±0.2	1.1±0.1	1.2±0.2	1.02	0.2
Heart rate response to Valsalva maneuver, beats/min	1.6±0.4	1.5±0.3	1.5±0.4	1.6±0.3	1.4	0.2
Systolic blood pressure decrease with standing, mmHg	-3.2±5.9	-1.4±7.4	-3.7±8.8	-0.5±3.9	2.1	0.1
Diastolic blood pressure increase with sustained handgrip, mmHg	23.2±10.7	25.5±10.4	25.5±11.9	23.5±10.1	0.7	0.6

Data are presented as mean±SD

*-unpaired t test - p<0.05 in comparison with controls

**ANOVA for repeated measurements for comparison of continuous variables in diabetic patients in 1st, 2nd and 3rd measurements

Table 6. Comparison of clinical and laboratory data of diabetic patients who had progression and regression of cardiovascular reflexes on 1st and 3rd examinations

Variables	First examination (n=18)	Third examination (n=18)	*p
A - Patients with progressive cardiovascular reflexes			
Glycosylated hemoglobin, %	8.5±1.4	9.9±1.5	0.05
Albumin/creatinine ratio, mg/g creatinine	4.4±4.0	28.2±28.0	0.04
Insulin dose /kg	2.5±4.6	0.9±0.3	0.2
Systolic blood pressure, mmHg	106.5±16.4	115.0±12.1	0.01
Diastolic blood pressure, mmHg	69.1±10.5	78.1±10.5	0.005
B - Patients with regressive cardiovascular reflexes	**First examination (n=12)**	**Third examination (n=12)**	***p**
Glycosylated hemoglobin, %	8.9±1.5	9.4±1.4	0.4
Albumin/creatinine ratio, mg/g creatinine	7.9±8.7	23.0±29.3	0.2
Insulin dose /kg	1.8±1.3	1.1±0.3	0.02
Systolic blood pressure, mmHg	104.6±19.4	115.8±20.2	0.1
Diastolic blood pressure, mmHg	75.8±14.1	83.3±10.7	0.08

Data are presented as mean±SD
*Paired t test for dependent samples

it was statistically not significant. Our findings regarding stationary response to Valsalva maneuver consistently overtime was the same as in Ducher et al. study (15), who reported that Valsalva ratio is highly susceptible to changes of autonomic function over time and is evidently robust against longitudinal measurement effects in spite of being difficult to perform in young children and requires considerable efforts and cooperation.

Valsalva is a complex test, it encompasses a complex reflex arch involving both sympathetic and parasympathetic pathways to the heart, sympathetic pathways to the vascular tone and baroreceptors in the chest and lungs. It is reasonable that the Valsalva index is affected after total and significant autonomic nervous system damage, which occurred over the 4 years period in the study .

The Valsalva and sustained handgrip test depend on patient effort and compliance. The postural fall of BP may be unreliable as in people with diabetes it varies throughout the day, being linked to the timing of insulin injections and patients with fluid retention may have extensive autonomic damage but without postural hypotension. Assessment of HR associated with deep breathing requires special equipment that indicates depth and cycle of breathing. In addition, it has been recommended by diabetologists that the use of lying to standing HR change is clinically acceptable (16, 17).

New methods that are non-invasive and independent of patient cooperation are preferable in the diagnosis of CAN but still require further research to understand their sensitivity and specificity in risk stratification for CAN (17).

Postural dizziness, like in previous reports, was far less frequent (10.3%) and did not correlate with a greater postural drop in BP, which suggests that severe sympathetic dysfunction is a rare complication in comparison to parasympathetic dysfunction (11).

Karamitsos et al. (18) demonstrated progression of CAN significantly during the 2 years subsequent to its diagnosis . However, Scaramuzza et al. (19), did not find any significant abnormality in CVR test either at 1st examination or at 18 months follow-up.

Based on our finding of the impaired HR response to deep breathing and to Valsalva maneuver, we can suggest that cardiac parasympathetic damage occurs earlier in the course of diabetes than the extracardiac sympathetic one or it may be because the HR tests are rather more sensitive than the BP tests.

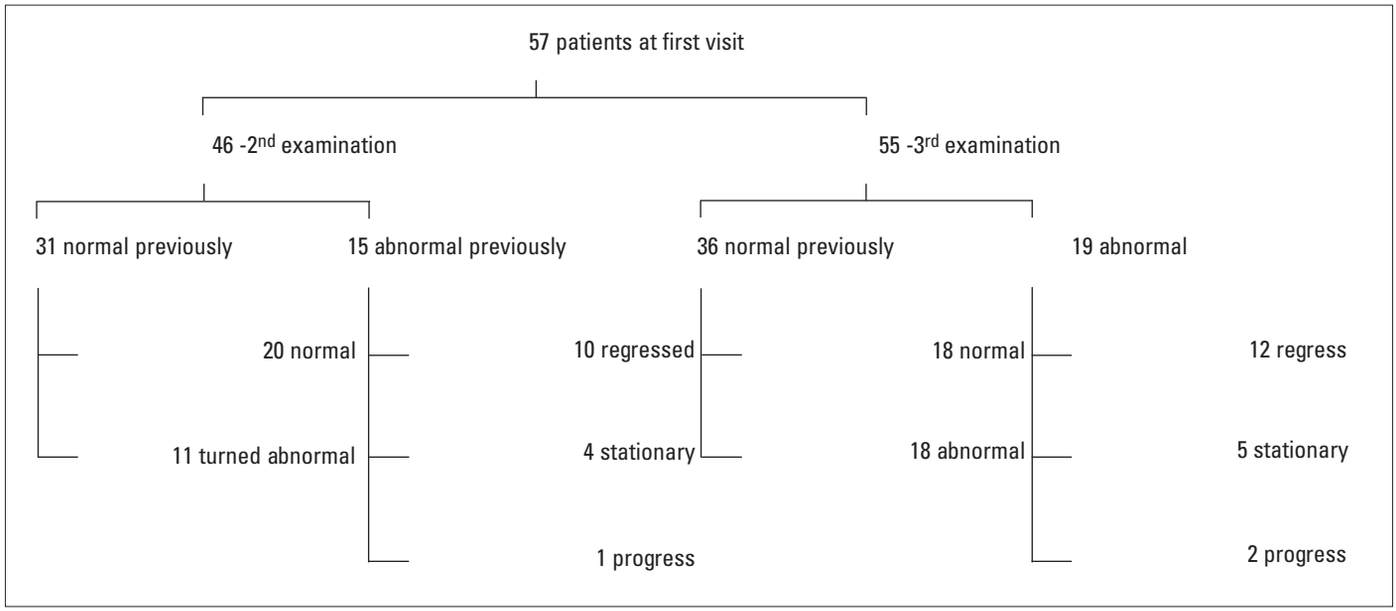

Figure 1. Flow chart of patients enrollment and follow-up

In the current study, HR response to standing up was significantly higher on the second examination than on the first and third examinations, but it was not significant compared with the control group. No significant difference was found between the remaining four CVR tests in either the three examinations or in comparison with the control group.

No significant difference in HbA1c was observed in the group of diabetics with improvement of their CVRs but it is of interest to note that those diabetics with deterioration of their CVR tests showed also deterioration of their glycemic control. Our findings are consistent with those of Vinik et al. (20), who found that the prevalence of CAN progressively increases in a direct proportion to age, duration of DM and poor glycemic control.

Cardiac autonomic function was preserved with HbA1c <8.4%, whereas cardiac autonomic dysfunction was impaired in the group with HbA1c >8.4 % (21). Optimized glycemic control seems to slow down the impairment in CAN function tests in type 1 diabetic patients (11).

In addition, it is worthy to note that the insulin dose was significantly decreasing in a group of diabetics with regression of their CAN, which may be related to a better glycemic control.

On trying to correlate other clinical and laboratory data to progression or regression of abnormality of CVRs, we found that glycosylated hemoglobin, systolic and diastolic BPs were significantly increased in diabetics with deterioration of their CAN. However, the dose of insulin was significantly decreased in diabetics with regression of their CAN.

The CAN probably contributes to the worse prognosis of the coronary heart disease and of the heart failure in type 1 and type 2 diabetic patients. For diabetologists, the nervous complications of diabetes are the result of an increase influx of glucose to the neuronal and endothelial cells. Evidence shows that, with the aim of preventing these complications, the diabetic patients should receive a precocious diagnosis and be instructed for having a good metabolic and BP control. Use of angiotensin converting enzyme inhibitors and beta- adrenergic blockers are probably of impact in the prevention of the cardiac autonomic complications of diabetes (22).

In the current study, Q- T intervals was found to be statistically significantly higher in patients with abnormal CVRs than those with normal CVRs on the 2nd examination.

The main finding of 23-year follow-up study (23) was that in subjects with type 1 diabetes QTc, but not resting HR was associated with an increased risk of all-cause mortality and mortality due to cardiovascular and cardiac disease.

Pappachan et al. (24), reported that higher CAN scores correlated with longer QTc intervals (correlation=0.73; p<0.001).

CAN is common in long standing type-1 diabetics and results in prolonged QTc interval that may increase susceptibility to cardiac arrhythmias and even death. Intensive glycemic control improves the cardiac autonomic nerve functions (14). However, measurements of QTc interval are easily obtained without the need for patient compliance, and QTc analysis is a simple, inexpensive, and noninvasive test that could be used to stratify the death risk in diabetic patients (25).

Study limitations

There are several limitations of our study:

1- Follow- up leads to loss of patients either due to deaths or to loss of interest to do follow-up.
2- CVR tests cannot be performed in patients younger than six years.
3- Autonomic tests results may depend on patients' cooperation and / or on peripheral sensitive neuropathy.

Conclusion

Prevalence of established CAN in diabetic patients is high at the beginning of the study. Our data suggest that Valsalva-stimulated HR response is highly susceptible to the presence of autonomic dysfunction over time. Glycosylated hemoglobin, albumin/creatinine ratio, systolic and diastolic BP were significantly increase in diabetics with deterioration of their CAN. However, the dose of insulin was found to significantly decrease in diabetics with regression of their CAN.

We recommend, routine assessment of CVRs of patients with diabetes especially over 5 years duration on yearly basis and proper glycemic control to prevent development of diabetic complications or ameliorate the pre- existing complication. BP measurement both supine and standing in the routine follow up visits and hypertensives should be closely monitored and controlled to avoid progression of nephropathy and neuropathy.

Conflict of interests: None declared.

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