CARDIAC AUTONOMIC NEUROPATHY IS HIGHLY PREDICTIVE FOR SURVIVAL IN CHILDREN WITH MAURIAC SYNDROME

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Introduction. Diabetic autonomic neuropathy (DAN) is highly predictive for subsequent mortality of the patients. The main reason for death is terminal renal insufficiency. Asymptomatic DAN can be establish by testing heart rate (HR) and HR variability (HRV) at rest and during sympathetic and vagal stimuli. Worsened HRV is related to the cardiac autonomic neuropathy (CAN).

Objective. To assess asymptomatic CAN and its predictive value for survival in children with diabetes and Mauriac syndrome.

Material and methods.

Twelve children (7 boys, 5 girls) with Mauriac syndrome (growth retardation, hepatomegaly and delayed puberty) were included in a cross-sectional study for CAN. Ten of them were born between 1980-1987 and two children in 2001 and 2005.

Time-domain (HR and coefficient of variation of HR) and Frequency-domain analysis with total power (TP) of HRV and low/high frequency ratios (LF/HF) were performed. They were based on R-R intervals of electrocardiograms in children under 18 years of age. The results were compared to 346 age/sex matched controls and 204 diabetic children with normal growth. The diabetics were divided in to a groups based on their metabolic control. First five groups had no late complications, but differed with their mean values of long lasting HbA1c: 7,8,9,10 and >10% respectivelly. Sixth group consisted of 30 children with poor control (HbA1c>10%) and microangiopathy. The children with Mauriac syndrome presented the last 7th subgroup in the study.

Deviations out of referent 25–75 percentiles or ± 2 SDSs were accepted as abnormal for HR and HRV at rest and during respiratory and orthostatic stimuli.

Results.

Mean age of children with Mauriac syndrome at diagnosis of diabetes was 3.4±2.5 years (8 months to 8.3 years); mean age at the investigation 15.3±2.7 years (9.7 to 17.9); diabetes duration 12.1±3 years (7.6 to 15.9); mean growth retardation was -3,27 ± 0.92 SDS (Table 1). These children had significantly younger age at diagnosis and longer duration of diabetes than others, p<0.05.

Most children with Mauriac syndrome had one or more late chronic complications, but initial nephropathy dominated in all of them at the time of the study for CAN.

Table1. Clinical characteristics of children with Mauriac syndrome

Patient	Date of birth	Age at diagnosis	Age at investigation	Diabetes duration	Height SDS	Pubertal stage (Tanner)
1. D.T.	1985	2.6	17.8	15,2	-2.8	4
2. D.G.	1984	8.1	17.4	9,3	-3,0	3
3. E.P.	1984	1.5	16.7	15,2	-5,7	1
4. K..R.	1982	2.2	9.9	7,6	-3,7	1
5. L.D.	1981	0.7	16.1	15,2	-4,0	2
6. L.U.	1984	1	17	15,9	-2,5	4
7. L.T.	1986	2.8	16.3	13,3	-2,9	2
8.R.G.	1980	1.1	16.4	15,1	-3.5	2
9. T. M.	1985	8.3	17.9	9,6	-2	4
10. T.D.	1987	5.1	15.2	10,0	-2.32	2
11. G.Z.	2005	1.9	11	7	-3.81	1
12.A.M.	2001	4	14	8	-3.43	1

All children with Mauriac syndrome showed significant deviations out of referent values for HR and HRV at rest and differed significantly in their mean SDSs from children with normal growth (Fig.1 and Fig.2).

Fig.1. Mean SDSs for HR, significantly higher in the 7th group of children (Mauriac syndrome), compared to children with normal growth, p<0.05.

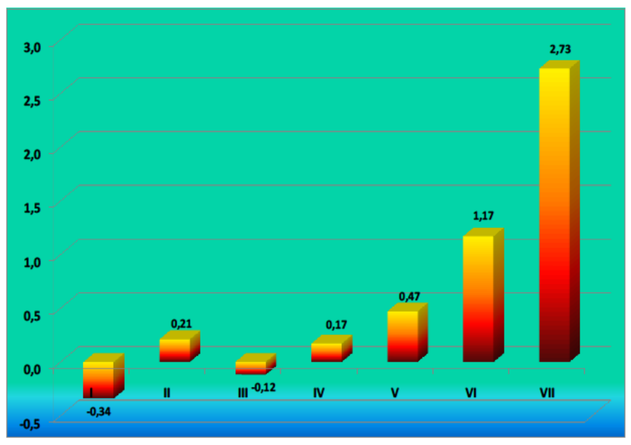
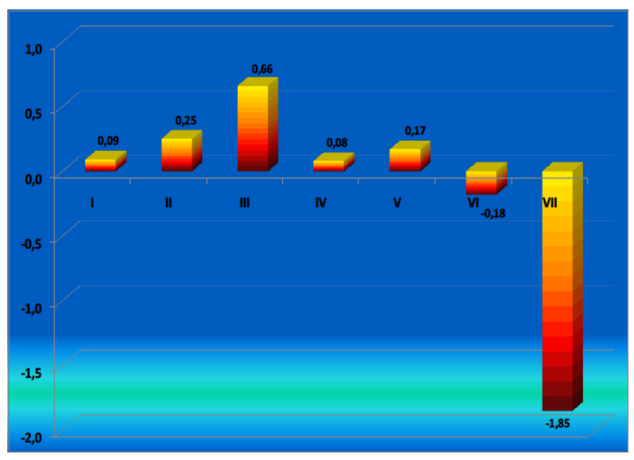


Fig.2. Mean SDSs of Coefficient of variation of HRV at rest significantly lower in 7th group (Mauriac syndrome), compared to the children with normal growth, p<0.05



The most sensitive frequency domain analysis outlined significantly not only 7th, but 6th group from the other diabetic children (Fig.3 and Fig.4). Suppressed respiratory arrhythmia was expressed by low TP and high LF/HT ratio

Fig.3. Mean SDSs of TP of HRV at rest significantly lower in 6th and 7th group, compared to the first five diabetic groups, p<0.05

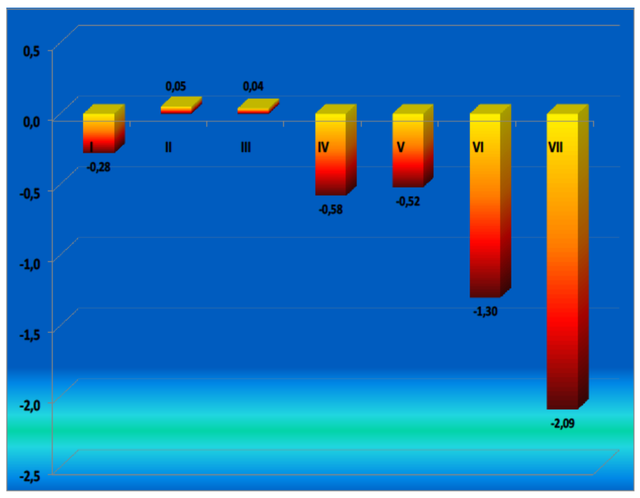
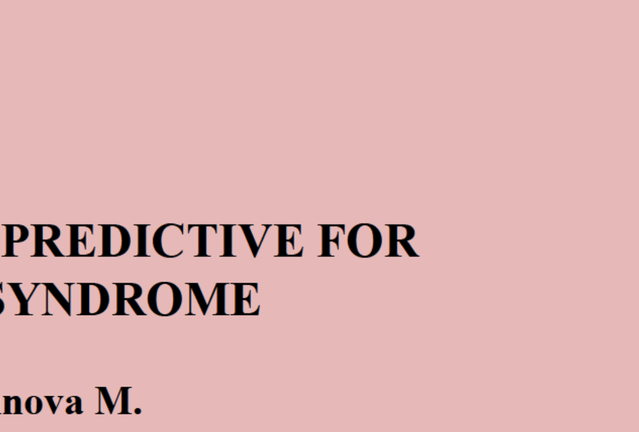
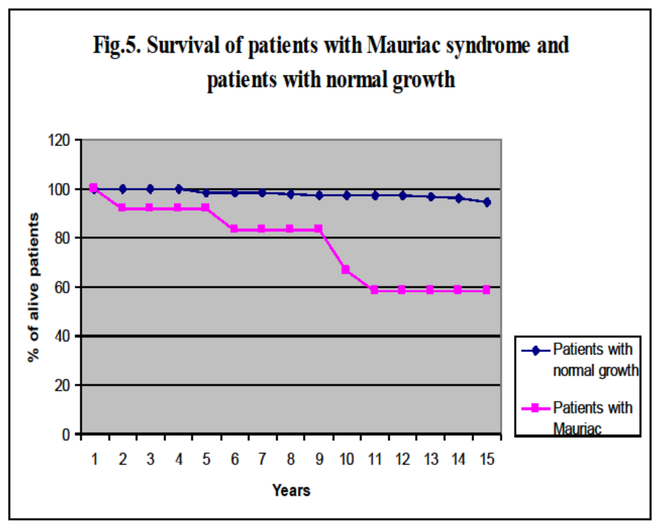


Fig.4. Mean SDSs of LF/HF ratio, significantly elevated in 6th an 7th groups, compared to the first five groups, p<0.05



In 2015 the mortality among all diabetic patients was investigated, including the group of Mauriac patients. Overall mortality in the patients with normal growth was 12 out of 204 patients (5.8%). All but one were from the groups with poor metabolic control (HbA1c>9%). Among children with Mauriac syndrome 5 out of 10 who were born before 1987 year died between 2001 and 2010 with overall mortality 42% (Fig.5).

Fig.5. Survival of patients with Mauriac syndrome and patients with normal growth



Disscussion.

In our cross-sectional study asymptomatic CAN, expressed with significant tachycardia at rest and lowered respiratory arrhythmia was available in children with poor metabolic control that have one or more late complications. They were diagnosed with most sensitive frequency domain analysis. Less sensitive time domain analysis outlined only significantly children with Mauriac syndrome from the others. Irrespective of methods of investigation HR and HRV in children with Mauriac syndrome showed the most severe impairment of HR and HRV.

Conclusions.

Children with Mauriac syndrome developed asymptomatic cardiac autonomic neuropathy before age of 18 years together with initial nephropathy and other late complications. Early age of diabetes and chronic insulin deficiency with persisting hyperglycemia were the most important risk factors for poor prognosis.

CAN predicted poor survival and early death among patients who developed Mauriac syndrome in their childhood.

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