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ORIGINAL

THE LINK BETWEEN METABOLIC CONTROL, LENGTH OF ILLNESS AND NEUROPATHY IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES

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Background: Diabetic neuropathy is a clinical or sub-clinical disorder in type 1 diabetes mellitus (T1DM) in the absence of any other causes for peripheral neuropathy.

Methods: This one-year study comprised 69 subjects, children and adolescents with T1DM. The metabolic control of the illness was assessed on the basis of the glycaemia, glycosylated haemoglobin, lipid status, blood pressure, body weight and height and body mass index of the subjects. The data from a questionnaire assessed the frequency of clinical signs of diabetic neuropathy.

Results: The clinical manifestations of diabetic neuropathy were muscular weakness, cramps, paraesthesia, insensitivity to pain, vomiting, diarrhoea, urinary disorders. The subjects with neuropathy had glycaemia of 9.8±1.8 mmol/L and HbA1C 10.6 ± 2.2%, with statistically significantly increased triglyceride levels (t=1.8, p=0.04), systolic and diastolic blood pressure (t=5.4, p <0.001; t=6.4 p<0.001) and BMI (t=2.0, p=0.05). The subjects with T1DM>10 years had significantly more frequent pathological findings of the back of the eye (X2=3,2, p=0,02), with no statistically significant difference in albumin/creatinine (urine). The ROC curve with an analysis of age at the beginning of neuropathy was 11.7 years, with 55% sensitivity and 82% specificity.

Conclusion: Our analysis suggests that there is a significant connection between the metabolic condition and the duration of the illness and the increased frequency of neuropathy in children and adolescents with T1DM.

Aim: To test the hypothesis that metabolic control and length of illness are connected with an increased frequency of neuropathy in children and adolescents with T1DM.

Key words: diabetic neuropathy, children and adolescents with Type 1 diabetes.

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The authors declare no competing interests.

INTRODUCTION

Diabetic neuropathy (DN) is the medical term for progressive damage to the nervous system in patients with T1DM. It is a clinically or sub-clinically evidenced disorder in the absence of other causes for the development of periphery neuropathy [1].

DN is the most frequent chronic complication of diabetes which occurs in up to 50% of patients, without accurate data on its frequency in children and adolescents [2-6]. About 20-30% of patients with T1DM sooner or later develop symptoms of DN [2]. It is the latest recognizable chronic complication of T1 DM, despite its proven negative influence on the quality of life and survival of patients.

DN causes various clinical abnormalities, some of them are clinically manifested others are detectable by various sensitivity tests, and some have not yet been recognized [2,3]. It is classified as peripheral, autonomous, proximal and focal. Peripheral neuropathy causes pain and loss of feeling in the toes and fingers. Autonomous neuropathy causes changes in the function of the intestines and bladder, affects sexual response, and may also affect the heart and control of blood pressure. Proximal neuropathy causes pain in the sides, hips and leads to weakness in the legs. The focal point of neuropathy results in sudden weakness of one or a group of nerves, which causes weakness in the muscles or pain [1-6]. DN manifests in all organs, and the symptoms and signs of the illness may be classified in the following categories: 1) cardiovascular, 2) gastrointestinal, 3) genital-urinal, 4) metabolic 5) vasomotor 6) pupillary [1-3].

In terms of its etiopathogenesis, DN is neurovascular insufficiency, with autoimmune damage and neurohormonal growth factor deficiency [7,8]. Poor metabolic control of the illness in children and adolescents over many years, with hyperglycaemia, high blood pressure, disturbed lipid metabolism and reduced physical activity in those suffering from T1DM lead to diffuse and rapidly progressing damage to the peripheral nerves and small blood vessels [8].

DN in children and adolescents has multiple etiology. There are various different hypotheses, which include: the duration of T1DM, long-term exposure to hyperglycaemia, raised blood pressure, and disturbed lipid metabolism, which together cause what is known as metabolic "blow" to the nerve fibres, and thus neurovascular insufficiency, with various forms of autoimmune damage. It is well-known that hyperglycaemia activates the polyol pathway, which leads to the accumulation of sorbitol and potential changes to the nucleotide adenosine diphosphate which may be a cause of direct neuronal damage and/or a reduced vascularization of the nerves, whilst the activation of protein kinase C leads to vasoconstriction [6]. With the longer duration of T1DM, with increased oxidative stress, the creation of free radicals also increases, and they directly harm the neuronal vascular endothelium [7,8]. In children and adolescent patients with increased anti-bodies titres, various factors may be the trigger for autoimmune mechanisms of nerve damage [9-11]. A reduction in concentrations of neurotrophic growth factor [12] with a lack of essential fatty acids [13] and the formation of the end products of glycosylation [14] also cause a reduction in endoneural vascularization and hypoxia of the nerves, with the destruction of nerve function [6,7]. Many years of exposure to hyperglycaemia, with lipid metabolism disorders and increased blood pressure are directly responsible and involved in the process of the pathogenesis of micro- and macrovascular complications in children and adolescents with T1DM.

Aim of the Study: To test the hypothesis that metabolic condition and the duration of the illness are linked with the increased frequency of neuropathy in children and adolescents with Type 1 Diabetes.

SUBJECTS AND METHODS

Over a period of one year at the Pediatric Clinic and the Clinic for Internal Medicine at the University Clinical Centre (UCC), Tuzla, a retrospective-prospective study was undertaken, encompassing children and adolescents suffering from T1DM. The subjects were selected by the consecutive method, according to the criteria of the World Health Organization for diagnosis of T1DM [15,1]. The criteria for inclusion in this study were: that they suffered from T1DM, that they were aged up to 25 years at the time of the study, that they were receiving insulin and undergoing regular check-ups at the Department of Endocrinology of the Clinic for Children's Illnesses and the Clinic for Internal Medicine at UCC, Tuzla.

The exclusion criteria for the research were: the occurrence of acute and chronic illness (central nervous system, respiratory, cardiovascular, gastrointestinal, genital-urinary system), accompanying systemic illness (lupus eritematodes, juvenile rheumatoid arthritis, type 2 DM), associated liver disease, pregnancy, and use of corticosteroids in treatment of other illnesses.

The criteria for the research were met by 69 subjects, from which two groups were formed according to the duration of T1DM: the test group comprised subjects with T1DM for more than 10 years (N=36) and the control group comprised subjects with T1DM for less than 10 years (N=33). Most of the laboratory tests were performed during previous hospital stays at the Pediatric Clinic and Clinic for Internal Medicine, in the Institute for Biochemistry of the Polyclinic for Laboratory Diagnostics of UCC, Tuzla. For this study the consent of the Ethics Committee of UCC Tuzla was obtained.

Metabolic control of the illness was assessed on the basis of the glycaemia values, average HbA1C values, lipid status, blood pressure, body weight, body height, and body mass index of the subjects taken from their medical history and medical files [16]. Glycaemia was established on the day of the examination, in children by examination of the self-testing log, where all the glycaemia values were recorded as measured on the previous day, whilst in adolescents it was established on the basis of one glycaemia value measured on the day of the test. The HbA1C values and lipid status were assessed on the basis of the mean values of all findings from the medical history and the medical files of the patients.

Blood pressure was measured in supine and sitting positions from both arms using apparatus with a mercury manometer and an armband wide enough to cover at least two thirds of the subject's upper arm. Body weight (BW) and height (BH) were both measured in bare feet and light clothing. After measuring BW and BH, the subject's body mass index was calculated.

By means of a questionnaire, data was obtained on the existence and frequency of clinical signs of neuropathy. The questionnaire data was collected from the parents of subjects up to 18 years of age and from the subjects themselves if they were older than 18. Also, to assess the subjects' neurological complications, the findings were used of examinations by neuro-paediatricians or neurologists, depending on age, in the files and medical history of the children and adolescents with T1DM [17]. Subjects with signs of proximal polyneuropathy were encouraged to undergo ENMG examination by a neurologist, which the subjects refused.

Statistical analysis was conducted using biomedical application software entitled MedCalc for Windows, Version 114.4 [18]. Numerical data are shown by the central tendency measure and the relevant dispersion measure. To describe the qualitative variables, distribution frequencies were used and the quantitative variables with normal distribution are described by the arithmetic mean and standard deviation. To test the hypothesis between the two groups, the T test and the Mann-Whitney test were used. To test the hypothesis of different frequencies (distribution) of the parameters observed, the $\chi 2$-test was used. Assessment of the diagnostic validity of the tests was conducted by using the Receiver Operating Characteristic Curve - the ROC curve. For the ROC curve obtained, the values under the curve were calculated (Area under curve - AUC) [18].

RESULTS

Table 1 shows the clinical characteristics of all subjects with T1DM.

Table 1. Clinical characteristics of all subjects with T1 DM

Clinical characteristics of subjects with T1 DM (N= 69)	
Gender Male Female	 41 (59.4%) 28 (40.6%)
Age (years; $\bar{x}$ ±SD, range)	17.4±5.2 (4.3-25)
age on onset of T1 DM (years; $\bar{x}$ ±SD; range)	7.7±5.1 (1.4-17.6)
Duration of T1 DM (years; $\bar{x}$ ±SD; range)	9.6±4.6 (1-23.9)
Body weight (years; $\bar{x}$ ±SD; range)	52.7±14.7 (12-90)
Body height (years; $\bar{x}$ ±SD; range)	160.1±16.2 (86.5-180)
(years; $\bar{x}$ ±SD; range)	20.2±3.2 (13-29.7)

Of the total of 69 subjects, 41 were male and 28 female. The average age in the total sample was 17.4 (±5.2) with a range from 4.3 to 25 years. The age at onset of T1DM in all subjects was 7.7 ± 5.1 years, and the average duration of the illness was 9.6±4.6. The average body weight value for all subjects was 52.7±14.7 kg, and body height 160.1±16.2 cm, whilst BMI was in a range of 13-29.7.

In relation to the duration of the illness, the clinical characteristics of the subjects with T1DM are shown in Table 2.

Table 2. The clinical characteristics of the subjects with T1DM in relation to the duration of the illness.

Clinical characteristics of subjects	Duration of T1 DM	
	> 10 years	< 10 years
Number	36	33
M/F	22/14	19/14
Age (years; $\bar{x}$ ±SD)	19.2±4.6*	15.3±5.2
Age on onset of T1DM (years; $\bar{x}$ ±SD)	5.8±4.2**	9.5±5.9
Duration of T1DM (years; $\bar{x}$ ±SD)	13.3±3.0***	5.8±2.4

*t=3.3. p=0.002 **t=3.0. p= 0.004. ***t=11.4. p<0.001

Of the total number of subjects, 36 had T1DM longer than 10 years, and 33 less than 10 years. By the Student t-test the clinical characteristics of the subjects with T1 DM were compared in relation to the duration of the illness. A statistically significant difference was found between the mean values of age but also the age of onset of diabetes in patients with duration of T1DM longer than 10 years in comparison with subjects with a shorter duration of the illness (p=0.002; p=0.004). A statistically significant difference was also found between the duration of T1 DM in patients with longer duration of T1DM in comparison with subjects with shorter duration of the illness (p<0.001).

In Table 3 the frequency of neuropathy (clinical signs) is shown in relation to the duration of T1DM.

Table 3. Frequency of neuropathy (clinical signs) in relation to the duration of T1 DM

Frequency of neuropathy (clinical signs) in relation to the duration of T1 DM.	Duration of T1 DM			
	> 10 years N (%)	< 10 years N (%)	X2	p
Neuropathy	19 (28)	12 (17)	1.27	0.26
No neuropathy	17 (25)	21 (30)		

Neuropathy (clinical signs) in the group of subjects with T1DM > 10 years was found in 19 subjects, and 12 in the group of subjects with a shorter duration of the illness, <10 years. Seventeen subjects had no neuropathy in the group with T1DM > 10 years, and 21 subjects in the <10 years group. No statistically significant difference was found in the frequency of neuropathy in relation to the duration of T1DM.

The most common clinical manifestations of diabetic neuropathy in our subjects are shown in Figures 1a and 1b, and they were: muscle weakness, cramps, paraesthesia, insensitivity to pain, vomiting, diarrhoea, urinary disorders and other problems.

The parameters of metabolic control in relation to the presence or absence of neuropathy are shown in Table 4.

The group of subjects with signs of neuropathy had statistically significantly higher triglyceride values, and higher systolic and diastolic blood pressure and BMI in comparison with the subjects without neuropathy.

The microvascular complications in children and adolescents in relation to the duration of T1DM are shown in Table 5.

A high ratio of albumin/creatinine (urine) was found in 18 subjects with T1DM >10 years, and in 16 subjects with shorter duration, <10 years. In all subjects with high values of albumin/creatinine ratio (urine) no statistically significant difference was found in relation to the duration of T1DM. Twenty-two subjects with T1DM >10 years had pathological findings from the examination of the back of the eye, as did 8 subjects with T1DM < 10 years. Nineteen subjects with T1DM >10 years had neuropathy, as well as 12 subjects with T1DM < 10 years. No statistically significant difference was found in relation to the duration of T1DM (95% CI: 0.4-1.18).

The duration of T1DM in children and adolescents needed for development of neuropathy was 11.7 years (Figure 2).

DISCUSSION

Our analysis suggests that there is a significant connection between the metabolic condition and the duration of the illness and the increased frequency of neuropathy in children and adolescents with T1DM. With the average age of our subjects of 17.4 (±5.2) years, 31 (44.92%) had clinical signs of DN, and 36 (52.17%) had had T1DM for more than 10 years.

Karawanaki et al, in their research, showed that DN occurs more often in children with onset of T1DM at a young age [19].

The most common clinical manifestations of DN in our subjects were in the form of muscle weakness, cramps, paraesthesia, insensitivity to pain, vomiting, diarrhoea and urinary disorders. These symptoms were most frequent in children and adolescents with longer duration of T1DM >10 years, albeit without statistical significance, but also with the fact that signs of DN were present in both groups of subject regardless of the duration of DM.

The possible reasons for the occurrence of DN in our subjects are closely related to the poor metabolic control of the illness for many years, which is shown by the average mean blood glucose levels of 9.8 ± 1.8 mmol/L

Table 4. Parameters of metabolic control in relation to the presence or absence of neuropathy

Parameters of metabolic control	Neuropathy		t	p
	Present	Absent		
BS	9.8±1.8	10.3±1.6	1.16	0.25
HbA1C	10.6±2.2	10.1±2.4	0.81	0.38
Triglycerides	1.7±1.4	1.2±0.8	1.84	0.04*
Cholesterol	4.9±1.1	4.5±1.2	1.31	0.19
LDL	3.0±0.8	2.9±1.0	0.63	0.53
HDL	1.2±0.3	1.1±0.4	1.17	0.25
Blood pressure (systolic)	120±2.3	117±2.3	5.40	<0.001
Blood pressure (diastolic)	80±1.5	76±3.2	6.40	<0.001
BMI	21.1±3.3	19.6±3.0	2.05	0.05

Key: BS– blood sugar; HbA1C – haemoglobin A1C; LDL – low density lipoproteins; HDL - high density lipoproteins; BMI – body mass index

Table 5. Microvascular complications in children and adolescents in relation to the duration of T1DM

Microvascular complications	Duration of T1 DM		X2	p
	> 10 years N=36	< 10 years N=33		
raised albumin/creatinine in urine N (%)	18 (50)	16 (48.5)	0	1
Pathological finding from examination of back of eye N (%)	22 (61)	8 (24)	3.2	0.02
Neuropathy present, N (%)	19 (53)	12 (36)	1.27	0.26

and average mean values of HbAlC 10.6 ± 2.2%. Various studies, with DCCT as the leading one amongst them, have shown that optimal glycaemic control is one of the main factors affecting the occurrence of DN [1,18,19]. In its early stages, improvement was clinically evident in autonomous neurological dysfunction in patients after a few days on intensive insulin therapy. Vinik et al. examined the effect of HbA1C values on autonomous nerve function in children and adolescents with T1DM [13]. According to that study, it is clear that high levels of HbA1C are in direct correlation with the occurrence of DN in children and adolescents [18], which is also confirmed by our research. Wherret and Danneman arrived at similar results [19], which altogether supports the notion that the stabilization of DN, or the prevention of any further progression, depends primarily on optimal glycaemic control of the illness.

Our study also points out the significance of high triglyceride levels in the occurrence of DN, whilst the other parameters of lipid profile (cholesterol, LDL, HDL and RISK) did not have any statistically significant link with DN. Other authors have also points out that poor metabolic control is connected to high levels of triglycerides [20], so Martinez et al. point out that disturbed lipid metabolism is linked with poor metabolic control and longer duration of the illness. Disturbed lipid metabolism, with frequently high values of triglycerides and LDL, combined with many years of hyperglycaemia, leads to cardiovascular and vasomotor manifestations of DN in later years of life [21].

High levels of both systolic and diastolic blood pressure had a statistically significant effect on the occurrence of DN in our study, similar to the studies by Marcovecchio et al., who found that average blood pressure values were significantly higher in sick children with expressed neuropathy, due to increased cardiac output and increased peripheral vascular resistance [22]. According to research by Polish authors, high blood pressure is a direct sign of increased risk for development of microvascular complications in children and adolescents with T1DM [23]. Marcovecchio et al. showed that children and adolescents with T1DM and sub-clinically manifested neuropathy have more sensitive alpha adrenergic receptors and more expressed vasoconstriction of the blood vessels [22]. Krause et al found that the regular oscillations of blood pressure in children and adolescents with T1DM recorded a significantly greater rise during the day, whilst during the night they were significantly reduced [24]. Since in children and adolescents with T1DM blood pressure is often high or within the upper limits of the reference values, increased sensitivity to alpha adrenergic and baro receptors may be one of the reasons for abnormal blood pressure values and may cause the earlier occurrence of DN in children and adolescents.

The BMI was statistically significantly different in the group with DN with an average mean value of 21.1 ± 3.3, in comparison with the group without DN, whose average values were 19.6 ±3.0. Higher BMI values are mainly manifested at the onset of DM and are associated with younger age, whilst in later phases of DM, if they are higher they are a parameter of poor metabolic control of the illness [22-24]. Patients on intensive insulin therapy mainly have lower BMI values [25,1].

Alongside DN, in terms of other chronic complications of DM, no statistically significant difference was found in our patients in the albumin/creatinine (urine) ratio in relation to the duration of T1DM, whilst there was an evident difference in the frequency of pathological findings of the back of the eye [26,27]. Chronic complications of T1DM, one of which is neuropathy, are frequently asymptomatic in the early stages, and when they become symptomatic it is difficult to halt their progression [28]. In view of the fact that the earliest signs of chronic complications begin early on in childhood, they speed up with the onset of puberty and with longer duration of T1DM, and they are already manifest when the illness has been present for longer than 10 years, it is necessary to act in good time in the sense of attaining optimal metabolic control of the illness, correct diet, and increased physical activities in children and adolescents.

On the basis of the appearance and assessment of the ROC curve (Figure 2) it was calculated that the criterion for discriminating between our subjects in terms of neuropathy and normal findings was 11.7 years, with sensitivity of 55% and specificity of 82%, and this is an important parameter in the future prevention and treatment of children and adolescents with T1DM, and opens the possibility of further research.

CONCLUSION

The summarized results obtained from our analysis suggest that there is a significant connection between the metabolic condition and the duration of the illness with an increased frequency of neuropathy in children and adolescents with T1DM. Early reports unwittingly perhaps exaggerated links between the metabolic status of children with T1DM and attributed less importance to the duration of the illness. We found that the age for discriminating between our subjects in terms of neuropathy and normal findings was 11.7 years, which is an important parameter in the future prevention and treatment of children and adolescents with T1DM, and opens the possibility of further research.

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