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The impacts of poor glycemic control and disease duration on peripheral nerves in children and adolescents with type 1 diabetes mellitus

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Abstract

Objective: To evaluate the risk factors of subclinical neuropathy, and the nerve conduction study (NCS) results in children, and adolescents with type 1 diabetes mellitus (T1DM).
Methods: A total of 81 patients without neuropathy symptoms were studied. Demographical features, pubertal stage, disease duration, NCS results, lipid profile results in the last 2 years, HbA1c results in the last 5 years, and the types of treatments (multiple-dose and insulin pump therapy) were recorded.
Results: The median age was 14 (5) years, 49.3 % (n=40) of the study group was female and 81.5 % (n=66) of the patients were pubertal. Of the patients, 16.04% had abnormal NCS results. There were no significant differences between patients with normal and abnormal NCS results in terms of demographical features, pubertal stage, disease duration, lipid profiles, and dysglycemia. No significant differences were found between the types of treatment in terms of NCS results. The proximal and distal compound muscle action potential (CMAP) amplitudes of the median nerve were significantly lower in patients with poor glycemic control than in those with well-glycemic control. Sensory nerve action potential (SNAP) amplitudes of sural nerve were significantly lower in patients whose disease durations were ≥60 months than in those <60 months.
Conclusions: About a sixth of the T1DM has subclinical neuropathy. CMAP amplitudes of the median nerve are the most affected measurement from poor-glycemic control. Additionally, SNAP amplitudes of the sural nerve are the values most affected by longer disease duration.

Keywords: Diabetic neuropathy, glycemic variability, poor-glycemic control, type 1 diabetes mellitus, children, adolescents

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is a chronic disease with to various complications, including neuropathy, retinopathy, nephropathy, and macrovascular disease.[1] Diabetic neuropathy (DN) is an important complication in patients with diabetes since it is related to mortality, morbidity, and a decrease in the quality of life in patients.[2] DN consists of motor, sensory, autonomic neuropathies and symmetrical distal sensory neuropathy is the most common presentation of DN.[1] Despite the complications including neuropathic pain, foot ulceration, subsequently gangrene, and amputation, the prevalence is often underestimated since it tends to be subclinical in children and adolescents.[3] Disease duration, age, pubertal stage, and glycemic control are the important risk factors. However, subclinical DN has been diagnosed in diabetic children even with excellent metabolic control and short disease duration which suggests the role of genetic susceptibility.[4,5] There are some diagnostic screening tools for the diagnosis of DN such as vibration sensation threshold (VST)[6], measurement of the accumulation of advanced glycation end products (AGES)[7], and tactile perception threshold (TPT).[8] However, nerve conduction study (NCS) is the gold standard diagnostic technique for the diagnosis.[6]

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The term dysglycemia describes hyperglycemia, hypoglycemia, and the degree of fluctuation which is also known as glycemic variability (GV).[9] GV consists of blood glucose variability (reflecting daily or day-to-day blood glucose fluctuations)[10], and hemoglobin-A1c variability (HbA1c-variability) (reflecting visit-to-visit HbA1c changes over longer periods).[11] The best-known pathogenesis of DN is hyperglycemia-induced oxidative stress. However, the effect of GV on diabetic outcomes is still controversial due to inconclusive evidence.[12] Herein, we aimed to evaluate the demographical features, laboratory findings (lipid profiles in the last 2 years, and HbA1c measures in the last 5 years), and NCS results of children, and adolescents with T1DM who have no clinical symptoms of DN.

METHODS

Subject selection

We have obtained the approval of the local ethics committee (Date:04/08/2016 No:2016/22-29) outlined in the Second Declaration of Helsinki. Due to the retrospective design, the waiver of consent was not required by the ethics committee. The study was conducted from 2011 to 2016 at Dokuz Eylül University, School of Medicine. Patients who were being followed up by the Pediatric Endocrinology Clinic due to T1DM and whose NCS was performed by the Pediatric Neurology Clinic between 2011 and 2016 were included. Receiving any supplementation such as vitamins, or fish oil, and any medication other than insulin, having clinical symptoms of peripheral neuropathy, and having a history of a disease other than T1DM were the exclusion criteria. NCS results, age, gender, disease duration, pubertal stage, types of insulin treatment, weight, weight-standard deviation score (SDS), height, height-SDS, body mass index (BMI), BMI-SDS, lipid profile results in the last 2 years [low-density lipoprotein 1 and 2 (LDL_{1-2}), high-density lipoprotein (HDL_{1-2}), total cholesterol 1 and 2 (TC_{1-2}), triglyceride 1 and 2 (TG_{1-2})] were reviewed. Pubertal development of subjects was evaluated according to Tanner staging. A testicular volume of ≥4 mL in males and stage 2–5 of breast development in females were considered to be consistent with puberty. To evaluate the relationship between dysglycemia and abnormal NCS results; the mean value of HbA1c (HbA1c-mean), the variability of HbA1c (HbA1c-variability), and the gap between maximum and minimum values of HbA1C ($HbA1c_{max-min}$) in the last five years were recorded. The coefficient variation of HbA1c (HbA1c-variability) is defined as the standard deviation divided by the mean of HbA1c values.[13] A value of HbA1c-mean> 7.5 was considered as poor-control and a value of HbA1c-mean ≤7.5 was accepted as well-control.[14]

Electrophysiological techniques

NCS was performed using Nihon Cohden EMG/EP MEASURING SYSTEM MODEL MEB-9400K SN 80853 2011. In conventional room temperature, sensory and motor nerve conduction studies were performed on both the lower and upper extremities of cases. Unilateral (right side) motor and sensory conductions of the median nerve (MN), unilateral (right side) sensory conductions of the (SN), unilateral (left side) motor conductions of the peroneal nerve were studied as a standard protocol which was constituted for our laboratory. The procedure was performed by the same three experienced pediatric neurologists. An abnormal electrophysiological response was determined as a value below for the age group of lower limit of the normal threshold of amplitude, a value above for the age group of the upper limit of the normal threshold of conduction velocity (CV), or F-wave latency.[15,16] Motor CV of the median and peroneal nerves were determined utilizing standard techniques using surface electrodes. The MN motor CV and compound muscle action potential (CMAP) amplitudes were obtained by stimulating at the wrist and then in the elbow crease anteriorly. Antidromic sensory nerve action potential (SNAP) amplitudes were recorded from the index fingers with ring electrodes at the proximal and distal interphalangeal joints, stimulating the median nerve at the wrist and elbow. The stimulations of the peroneal nerve were made over the midpoint of the anterior aspect of the ankle as the distal point, and either just below the fibula head, behind the fibula head, or in the superior lateral part of the popliteal fossa as the proximal points. The SN was stimulated at the dorsolateral side of the Achilles tendon approximately at the junction of the middle and lower thirds of the leg, the retrograde sensory nerve action potentials were recorded behind the lateral malleolus with surface electrodes (Medelec bar electrodes 18261).

Statistical analysis

The statistical analyses were performed using SPSS version 22 (IBM Corporation, Armonk, NY, USA). Descriptive variables are expressed as

percentages (%), the means ± standard deviation, or medians with interquartile ranges (IQRs) in parentheses. A Chi-squared or Fisher's exact test was used for categorical variables, and Student's t-test or a Mann Whitney U-test for quantitative data following an assessment of normality in a Kolmogorov-Smirnov test. A p-value <0.05 was considered to indicate statistical significance.

RESULTS

The median age was 14 (5) years, 49.3% (n=40) of the study group was female and 81.5% (n=66) of the patients were pubertal. The median and mean T1DM durations were 60 (IQR:70, minimum:3, maximum:168), and 60.17±40.73 months, respectively. The mean weight was 53±15.07 kg, median height was 162.45 (22.7) cm, and median BMI was 20 (22.9). The mean value of the $HbA1c_{mean}$ was 8.35 ± 1.51 (Table 1). Sixty-three percent of the patients were poor-controlled ($HbA1c_{mean}$>7.5%). Of the patients, 16.04% of the patients had abnormal NCS results and 76.9% of them had poor-glycemic control. Forty-six percent of the study group's disease durations were <60 months. There were no significant differences between patients with normal and abnormal NCS results in terms of age, gender, pubertal stage, disease duration, anthropometric measurements, and laboratory results including lipid profiles, $HbA1c_{mean}$, $HbA1c_{variability}$, $HbA1c_{max-min}$. (Table 2). The proximal and distal CMAP amplitudes of the motor MN were significantly lower in the poor-controlled group than in those well-controlled group (Table 3, p=0.02, p=0.02). SNAP amplitudes of the SN were significantly lower in patients whose disease durations were ≥60 months than in those with <60 months (Table 4, p=0.027). Precisely, 15.9% of the patients were treated with insulin pump therapy. There were no significant differences between the types of treatment (multiple-dose and insulin pump therapy) in terms of NCS results (Table 5).

DISCUSSION

DN is a serious complication of T1DM which is associated with neuropathic pain, foot ulceration,

Table 1: **Descriptive results of the independent variables**

Age (years) *	14 (5)
Duration of diabetes (months) *	60 (70.50)
Weight (kg) **	53.91 ± 16.04
Weight SDS**	0.31 ± 0.88
Height (cm)*	162.9 (25)
Height SDS**	0.23 ± 1.11
BMI*	20 (5)
BMI- SDS**	0.26 ± 0.84
LDL1** (mg/dL)	91.25 ±33.09
LDL2* (mg/dL)	92 (36.50)
HDL1** (mg/dL)	52.66 ± 10.59
HDL2** (mg/dL)	53.83 ± 9.17
TG1* (mg/dL)	87 (65.50)
TG2** (mg/dL)	120.43 ± 98.20
TC1** (mg/dL)	168.50 ± 38.45
TC2* (mg/dL)	166 (41)
HbA1C- mean** (%)	8.35 ± 1.51
HbA1Cmax-HbA1Cmin** (%)	3.52 ± 1.74
HbA1C-variability *	0.11 (0.07)

IQR: Interquartile Range, SD: Standard Deviation, SDS: Standart Deviation Score, BMI: Body Mass Index, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TG: Triglyceride, TC: Total Cholesterol
*Non-normally distributed data were given as median (IQR).
**Normally distributed data were given as mean (± SD).

Table 2: Clinical and laboratory characteristics of the study group; patients with normal and abnormal NCS results

NCS results n (%)	Normal -68 (83.9%)	Abnormal 13 (16.04%)	p-value
Age (years) *	13.50 (4)	12 (4)	0.456
Gender			0.725
➢ *Female*	33 (48.50%)	7 (53.80%)	
➢ *Male*	35 (51.50%)	6 (46.20%)	
✓ *Prepubertal*	10 (16.70%)	0 (0%)	0.128
✓ *Pubertal*	50 (83.30%)	12 (100%)	
Duration of diabetes (months) *	60 (71.50)	33 (55)	0.420
Weight (kg) **	53.40 ± 16.04	54.66 ± 17.20	0.551
Weight SDS**	0.27 ± 0.79	0.56 ± 1.28	0.683
Height (cm)*	162.45 (25)	159.70 (24)	0.815
Height SDS**	0.17 ± 1.07	0.61 ± 2.38	0.937
BMI*	19.75 (4.85)	21.50 (8.33)	0.279
BMI- SDS**	0.23 ± 0.76	0.37 ± 1.22	0.409
LDL1** (mg/dL)	90 ± 34.05	89.50 ± 26.05	0.437
LDL2* (mg/dL)	92.50 (40.05)	85 (36.25)	0.761
HDL1** (mg/dL)	51.54 ± 10.94	58 ± 5.78	0.297
HDL2** (mg/dL)	53.39 ± 9.51	55.50 ± 6.78	0.859
TG1* (mg/dL)	96 (68.50)	75 (40)	0.925
TG2** (mg/dL)	127.70 ± 102.20	77.75 (±45.04)	0.168
TC1** (mg/dL)	168.58 ± 39.68	167.87 ± 29.32	0.341
TC2* (mg/dL)	166.50 (45.25)	152.50 (50.25)	0.492
HbA1C- mean**(%)	8.31 ± 1.50	8.58 ± 1.61	0.133
HbA1Cmax-HbA1Cmin** (%)	3.57 ± 1.85	3.22 ± 0.93	0.081
HbA1C-variability *	0.11 (0.08)	0.10 (0.03)	0.500

IQR: Interquartile Range, SD: Standard Deviation, SDS: Standart Deviation Score, BMI: Body Mass Index, DN: Diabetic Neuropathy, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, TG: Triglyceride, TC: Total Cholesterol

*Non-normally distributed data were given as median (IQR).

**Normally distributed data were given as mean (± SD).

*Non-normally distributed data were given as median (IQR).

**Normally distributed data were given as mean (± SD).

and gangrene. Hence, the present study aimed to evaluate the clinical and laboratory findings of patients with and without subclinical DN, comparison of NCS results according to the types of treatments, glycemic control, and disease duration. The major outcomes of the present study were: *i*) 63% of the patients had poor-glycemic control *ii)*16.04 % of the patients had abnormal NCS results, and 76.9% of them had poor-glycemic control, *iii*) there were no significant differences between patients with normal and abnormal NCS results, in terms of age, gender, pubertal stage, disease duration, anthropometric measurements, lipid profile results, and GV, *iv*) distal and proximal CMAP amplitudes of the motor MN were lower in poor-controlled group (p=0.02, p=0.02), *v*) SNAP amplitudes of the SN were significantly lower in patients with ≥60 months disease duration (p=0.027), *vi)* there were no significant differences between the types of treatment in terms of NCS results.

Various studies reported DN prevalences between 13 and 32.4% (17-19). We found a rate of 16.04% subclinical neuropathy in the current study. This wide range regarding the prevalence of DN in the studies may be related to differences in the study groups' features and designs.

Hyperglycemia leads to elevated levels of

Table 3: Comparison of the NCS results between well- and poor-controlled DM

HbA1C-Mean	Well-controlled (≤7.5) (n=30, 37%)	Poor-controlled (>7.5) (n=51, 63%)	p-value
Proximal CMAP amplitudes of the median nerve**	9.33 ± 2.38	7.47 ± 2.36	**0.020**
Motor Median NCV**	57.14 ± 4.72	55.2 ± 5.97	0.162
Motor Median Proximal latency**	6.88 ± 1.16	7.06 ± 0.97	0.472
Distal CMAP amplitudes of the median nerve**	10.10 ± 1.98	8.51 ± 2.48	**0.020**
Sensory Median NCV**	51.50 ± 5.72	53.6 ± 5.69	0.312
SNAP of the median amplitude**	41.65 ± 20.80	43.4 ± 19.8	0.676
Motor Median Distal Latency*	3.19 (0.47)	3.19 (0.63)	0.746
Peroneal Motor Proximal Latency*	9.85 (2.49)	9.97 (2.03)	0.754
Peroneal Motor Distal Latency*	3.72 (1.11)	3.92 (1.4)	0.322
Peroneal Motor NCV*	51.50 (9.23)	49.8 (8.40)	0.776
Proximal CMAP amplitudes of the peroneal nerve*	2.65 (3.23)	2.56 (2.11)	0.405
Distal CMAP amplitudes of the peroneal nerve*	2.98 (1.90)	3.31 (1.88)	0.929
Sensory Median Distal Latency*	2.30 (0.41)	2.41 (0.44)	0.363
Sensory Sural NCV*	50.80 (10.30)	48.3 (7.78)	0.255
SNAP amplitudes of the sural nerve*	8 (5.18)	10.4 (7.93)	0.289
Sensory sural Distal Latency*	2.70 (0.94)	2.6 (0.82)	0.861

IQR: Interquartile Range, SD: Standard Deviation, CMAP: Compound Muscle Action Potential, NCV: Nerve Conduction Velocity, DM: Diabetes Mellitus, SNAP: Sensory Nerve Action Potential, SNAP: Sensory Nerve Action Potential
*Non-normally distributed data were given as median (IQR).
**Normally distributed data were given as mean (± SD).

intracellular glucose in nerves. When the normal glycolytic pathway is saturated, extra glucose is shunted into the polyol pathway and converted to sorbitol and fructose by the aldose reductase and sorbitol dehydrogenase enzymes. Accumulation of these metabolites leads to toxicity by decreasing the levels of nerve myoinositol, and membrane Na^+/K^+-ATPase activity. Moreover, hyperglycemia causes glycosylated myelin which is endocytosed by macrophages. Additionally, AGEs disrupt the structure of tubulin, neurofilament, and actin. Therefore, axonal atrophy, degeneration, and impaired axonal transport occur. Since the receptor for AGEs (RAGE) exists in peripheral nerves, AGE interaction with RAGE activates the transcription of proinflammatory genes and leads to increased cellular oxidative stress, which causes nerve dysfunction.[20-23] Although antioxidant enzyme systems ensure reducing cellular oxidative stress, patients who have antioxidant enzyme genetic variations may be susceptible to early DN.[24] Previous studies reported that poor-glycemic control, longer duration of disease, high GV rates, height, and pubertal stage are the risk factors for DN.[19,25-30] Albers *et al*. found a significant relationship between $HbA1c_{mean}$ and DN during the epidemiology of diabetes interventions and complication (EDIC) study.[31] In a prospective study including a 10-year follow-up by Hajas *et al*., long-term poor glycemic control, disease duration, and age were the determining factors for DN.[32] In another prospective study, sustained hyperglycemia and disease duration were found as risk factors for DN.[18] In a cross-sectional study by Moser *et al*., no association was found between HbA1c, diabetes duration, age, pubertal condition, height or cholesterol, and DN.[33] In a study by Barkai *et al*., poor-glycemic control and pubertal development were found to be contributors to the pathogenesis of DN.[34]

Table 4: Comparison of the NCS results between long- (≥60 months) and short (<60 months) DM duration disease

Disease duration	Disease duration < 60 months (n=36, 46%)	Disease duration (≥60 months) (n=45, 54%)	p-value
Proximal CMAP amplitudes of the median nerve**	7.70 ± 2.21	8.41 ± 4.35	0.260
Motor Median NCV**	54.69 ± 5.12	56.72 ± 5.92	0.155
Motor Median Proximal latency**	7.05 ± 0.99	6.89 ± 1.18	0.550
Distal CMAP amplitudes of the median nerve**	8.99 ± 2.74	9.52 ± 2.74	0.440
Sensory Median NCV**	52.26 ± 5.18	52.95 ± 5.85	0.440
SNAP amplitudes of the sural nerve**	40.70 ± 19.80	40.20 ± 20.10	0.790
Motor Median Distal Latency*	3.24 (0.58)	3.16 (0.61)	0.116
Peroneal Motor Proximal Latency*	9.92 (2.56)	9.95 (2.38)	0.617
Peroneal Motor Distal Latency*	3.65 (1.21)	3.85 (1.25)	0.492
Peroneal Motor NCV*	48.70 (7.40)	51.35 (10.88)	0.407
Proximal CMAP amplitudes of the peroneal nerve *	2.42 (2.54)	2.65 (2.15)	0.394
Distal CMAP amplitudes of the peroneal nerve*	3.30 (1.75)	3.02 (2.11)	
Sensory Median Distal Latency*	2.50 (0.51)	2.35 (0.39)	0.281
Sensory Sural NCV*	50.90 (8.50)	47.75 (8.60)	0.396
SNAP amplitudes of the sural nerve*	11.30 (6.75)	8.85 (5.78)	**0.027**
Sensory sural Distal Latency*	2.51 (0.81)	2.73 (0.95)	0.179

IQR: Interquartile Range, SD: Standard Deviation, CMAP: Compound Muscle Action Potential, NCV: Nerve Conduction Velocity,
DM: Diabetes Mellitus, SNAP: Sensory Nerve Action Potential, SNAP: Sensory Nerve Action Potential
*Non-normally distributed data were given as median (IQR).
**Normally distributed data were given as mean (± SD).

In a prospective study including 144 newly diagnosed diabetic children, low sensory CV were found at the time of the T1DM diagnosis in 25% of the patients. Repeated examinations showed the improvement of the sensory CV over the first 2 years and there was a correlation between low motor CV and glycemic control.[35] In a cross-sectional study including 111 diabetic children, a correlation was found between poor metabolic control, diabetes duration, number of ketoacidosis attacks and DN.[19] There are few studies regarding the relationship between GV and DN and the results are conflicting. Xu *et al*. reported an association between DN and GV in well-controlled patients with type 2 diabetes mellitus (T2DM).[36] However, some researchers considered GV as a side effect of endogenous systems regarding glucose homeostasis that leads to glucose fluctuation. Therefore it was suggested that GV is a result of diabetic complications rather than a direct reason for diabetic complications.[36,37] In the present study, no significant differences were found between the patients with normal and abnormal NCS results, in terms of age, disease duration, weight, height, pubertal stage, BMI, lipid profile results in the last 2 years, $HbA1C_{mean}$, $HbA1C_{variability}$, and $HbA1C_{max-min}$. The lack of relationship in the present study may be associated with younger age and a small number of patients with subclinical DN. Cross-sectional design

Table 5: Comparison of the NCS results between the types of treatments (multiple-dose insulin therapy and insulin pump therapy)

Treatment type	Multiple-dose therapy (n=69, 85.1%)	Insulin pump therapy (n=12, 14.9%)	p-value
Proximal CMAP amplitudes of the median nerve**	8.25 ± 2.41	9.15 ± 2.82	0.684
Motor Median NCV**	55.2 ± 5.11	60.09 ± 4.83	0.074
Motor Median Proximal latency**	6.94 ± 0.99	7.10 ± 1.39	0.344
Distal CMAP amplitudes of the median nerve**	9.46 ± 2.82	9.71 ± 1.46	0.729
Sensory Median NCV**	53.25 ± 5.65	51.20 ± 6.32	0.409
SNAP of the median amplitude**	42.55 ± 19.54	41.3 ± 28.96	0.509
Motor Median Distal Latency*	3.19 (0.53)	3.14 (1.61)	0.712
Peroneal Motor Proximal Latency*	9.97 (2.11)	9.80 (5.30)	0.839
Peroneal Motor Distal Latency*	3.80 (1.10)	4.15 (4.80)	0.100
Peroneal Motor NCV*	50.00 (9.23)	49.60 (7.15)	0.607
Proximal CMAP amplitudes of the peroneal nerve*	2.40 (2.33)	3.52 (5.72)	0.221
Distal CMAP amplitudes of the peroneal nerve*	3.03 (1.82)	4.12 (5.01)	0.199
Sensory Median Distal Latency*	2.35 (0.45)	2.4 (0.60)	0.712
Sensory Sural NCV*	50.00 (8.13)	50.30 (13.85)	0.851
SNAP amplitudes of the sural nerve*	10.50 (7.03)	9.30 (15.00)	0.925
Sensory sural Distal Latency*	2.62 (0.83)	2.78 (0.83)	0.521

IQR: Interquartile Range, SD: Standard Deviation, CMAP: Compound Muscle Action Potential, NCV: Nerve Conduction Velocity,
DM: Diabetes Mellitus, SNAP: Sensory Nerve Action Potential, SNAP: Sensory Nerve Action Potential
*Non-normally distributed data were given as median (IQR).
**Normally distributed data were given as mean (± SD).

and different contributing factors like genetic variations of antioxidant enzyme systems may also be the other causes. Repeated electrophysiological examinations yearly, and long-term follow-up of patients may show a relationship.

In a prospective cohort study including 38 children and adolescent with T1DM, results of NCS were evaluated at baseline and 5 years after the diagnosis. By the time, the most significant changes were found in the tibial sensory nerve.[17] In a 24-year prospective cohort study including 32 newly diagnosed diabetic adults, rapid decline was observed in the poorly-controlled group for sural sensorial NCV (three-folds) and peroneal motor NCV (six-folds).[38] In the present study, proximal and distal CMAP amplitudes of the MN were statistically lower in poorly-controlled group than in those well-controlled. The hypothesis is known as the "double crush", proposed that the MN might become more susceptible to pressure effects in the carpal tunnel (CT) when underlying DM, rheumatoid arthritis, obesity, heavy manual work, and previous injury to the wrist.[39] In a study by Horinouchi *et al*. including 187 diabetic adults, the study group was subdivided into four subgroups; *i)* patients without median neuropathy and diabetic polyneuropathy (n=71), *ii)* patients with median neuropathy and without diabetic polyneuropathy (n=25), *iii)* patients with median neuropathy and diabetic polyneuropathy (n=55), *iv)* patients without median neuropathy and diabetic polyneuropathy (n=36). They found significantly longer values of F-wave latencies and lower values of CMAP, SNAP, nerve CV in patients with median neuropathy and diabetic polyneuropathy subgroup than in those without diabetic polyneuropathy. It was suggested that median neuropathy with diabetes could be attributed to an impairment of axonal function at common entrapment sites. Thus, median

neuropathy in patients with diabetes may lead to a misdiagnosis of diabetic involvement of MN in diabetic patients with isolated carpal tunnel syndrome (CTS).[40] The view of Hourinouchi et al. may be valid for adults since CTS is a common disorder in adults and most of the precipitating factors are present in many adults with CTS. However, CTS is a rare entity in children and has a considerable variety of related diseases such as skeletal dysplasias, trauma, mucopolysaccharidosis, and mucolipidosis. In the present study, none of the patients have an underlying disorder except for T1DM. The precise mechanism of the frequent occurrence of CTS in DM is unclear. However, hyperglycemia-induced edema of the MN, increased sensitivity to exogenous trauma, nerve myelin ischemia, and axonal injury appear to be the probable causes.[41] In a cohort study by Arnold et al., a pattern of change that was consistent with axonal depolarization, which may occur in the context of dysfunction of the energy-dependent axonal Na^+/K^+a-ATPase, or microvascular perfusion abnormality was found in patients with T1DM.[42] Additionally, previous studies demonstrated that Na^+/K^+-ATPase dysfunction led to the intra-axonal accumulation of Na^+, axonal swelling, structural change, and subsequently, apoptotic processes and axonal loss occurred by the reversal of Na^+/Ca^+-exchanger. In contrast to the T1DM, minimally axonal dysfunction was demonstrated in patients with T2DM, even with similar disease duration and glycemic control.[43] Moreover, alteration in Na^+/K^+-ATPase and biophysical changes were not well-understood in T2DM.[44] Therefore, the causes of prominent axonal dysfunction in the MN may be explained by hyperglycemia-induced axonal edema due to Na^+/K^+-ATPase dysfunction in T1DM, increased sensitivity to exogenous trauma, and pressure in the CT. We suggest that in the presence of underlying poor-controlled T1DM, motor fibers of the MN may become susceptible to pressure effects in the CT. It should be emphasized that this condition is different from the CTS since sensory fibers are affected first and the change in CV tends to precede a change of the amplitude recorded potential in CTS.[45] Suljic *et al*., demonstrated that amplitudes and mean CV were significantly lower, and distal latency and F-latency were significantly longer in the motor MN in patients T1DM than in those with T2DM.[46] Diabetes type may also have a contribution to which nerve become susceptible to be affected more. Maybe, the difference between the diabetes types is related to the actual disease durations. While the time between disease onset and diagnosis is short in T1DM, it is longer in T2DM. There are studies indicating that SN involvement is more frequently seen in T2DM. In a study by Maruboyina et al., all patients (10 patients with <10 years of T2DM, 10 patients with ≥10 years of T2DM) showed a decrease in CV and amplitudes and an increase in latency of SN when compared to the healthy controls. Moreover, the values were altered in the longer disease duration group.[47] Similarly, in the current study, the SNAP amplitudes of the SN were the most affected values from the disease duration. The results of the previous studies and the current study give rise to the thought that the type of diabetes and age may have a contribution to which nerves become more susceptible to be affected.

There are studies indicating that insülin pump therapy is related to lower levels of DN compared to multiple-dose therapy.[47,48] However, Christensen *et al*. found no relationship between DN and types of treatment in young adults with T1DM.[49] In the current study, there were no significant differences between the types of treatment in terms of NCS results. The lack of relationship may be related to the small number of patients receiving insulin pump therapy in the present study. Also, methodological differences and different sample sizes between the studies may be the other causes.

The current study is the first study investigating the relationship between demographical features, detailed long-term laboratory results including GV and NCS results in children and adolescents without any DN symptoms. Being a 3rd level center that follows up a large number of T1DM patients and having NCS experience allowed us to examine a large number of T1DM patients' NCS. However, the small number of patients with abnormal NCS results was a limitation in the present study. Also, performing NCS for only four nerves, the absence of the electromyographic examination, and the retrospective design were the other limitations.

We conclude that the CMAP amplitudes of the MN are the most affected measurement from poor-glycemic control. The probable causes are increased susceptibility of the MN to the pressure in the CT in the presence of underlying poor-controlled T1DM. The SNAP amplitudes of the SN are the values most affected by longer disease duration. Long-term prospective studies with repeated NCS examinations including analyzing antioxidant gene variants with different types of diabetes are needed to clarify the thought that the

type of diabetes and age may have a contribution to which nerves become more susceptible to be affected.

DISCLOSURE

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