The Turkish Journal of Pediatrics 36: 97-104, 1994

PERIPHERAL NEUROPATHY IN CHILDREN WITH INSULIN-DEPENDENT DIABETES MELLITUS*

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SUMMARY: Fıçıcıoğlu C, Aydın A, Haktan M, Kızıltan M. (Departments of Pediatrics and Neurology, İstanbul University Cerrahpaşa Faculty of Medicine, İstanbul, Turkey). Peripheral neuropathy in children with insulin-dependent diabetes mellitus. Turk J Pediatr 1994; 36: 97-104.

Peripheral somatic nerve function was studied in 38 unselected diabetic children and 31 age and sex-matched healthy controls. Thirteen of the 38 diabetics had abnormal peripheral somatic nerve function tests (more than 3 SD below the mean for normals). Five of the 13 diabetic children had only abnormal peripheral nerve function (early asymptomatic neuropathy); seven of these 13 were abnormal both in neurologic examination and peripheral nerve function (asymptomatic neuropathy). Only one of the 13 patients showed neuropathic symptoms as well as an abnormal neurologic examination and impaired peripheral nerve function tests (symptomatic neuropathy). Both motor and sensory peripheral somatic nerve abnormalities were related to poor glycemic control (HbA_{1c}) and duration of diabetes. Individual peripheral nerve tests correlated with HbA_{1c} (fibular motor, $p<0.001$; sural sensory, $p<0.05$) or duration of diabetes (fibular motor, $p<0.01$; median motor, $p<0.01$). These results emphasize the importance of metabolic control and duration of diabetes in the pathogenesis of diabetic neuropathy. The findings suggest that peripheral neuropathy is common in young, insulin-dependent diabetics. Being easy to conduct and sensitive, regular follow-up of nervous function test results may help to achieve good metabolic control and prevent diabetic complications. *Key words: Insulin-dependent diabetes, peripheral neuropathy, peripheral somatic nerve tests.*

Diabetic neuropathy is a frequent complication of diabetes mellitus; approximately two out of three adult patients are thought to be affected, even though nerve involvement is often mild and detectable only by electrophysiological tests[1].

The classical signs of peripheral neuropathy are rarely found in children with insulin-dependent diabetes mellitus (IDDM)[2]. The frequency of electrophysiological abnormalities and peripheral neuropathy varies widely, from 9% to 72%, in

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different studies reported on diabetic children[2-9]. These discrepancies can be attributed both to the heterogeneity of cases and the variety of electrophysiological tests; in addition, in none of these papers were there common criteria, accepted by all investigators for the diagnosis of diabetic neuropathy.

Having considered these difficulties, Dyck[10] from the Mayo Clinic suggested some precise criteria for the diagnosis of diabetic neuropathy in 1988.

The aim of this study was to evaluate the prevalence of symptomatic and asymptomatic peripheral neuropathy in an unselected group of children with IDDM by using the minimal criteria suggested by Dyck for the diagnosis of diabetic neuropathy, and to investigate the relation between peripheral neuropathy and some relevant parameters, such as duration of diabetes and metabolic control.

Material and Methods

The study group consisted of 38 children from 3.5 to 18 years of age (mean ± SD: 10.5 ± 3.2) in whom the duration of diabetes ranged from 2 months to 12 years (mean ± SD: 3.1 ± 2.8), and 31 nondiabetic children from 3 to 18 years of age (mean ± SD: 10.2 ± 2.8). The diabetic children were treated with two daily injections of human insulin, the dosage of which was adapted according to blood glucose monitoring with Dextrostix (Ames) and a glucometer. Their normally balanced diets were divided into up to six separate meals. No patients were treated with isoniazid, and none had a history of drug dependence. None of them had a family history of hereditary neuropathic disorders.

HbA_{1c}, as the degree of metabolic control, was measured by the colorimetric technique originally described by Fluckiger et al[11].

Determination of the amplitude, conduction velocity and distal latency of the motor fibers of the fibular and tibial nerves in both lower extremities and of the median and ulnar in one upper extremity, and sensory amplitude conduction velocity and distal latency of the median and sural nerves were made on the patients and healthy children by the same observer with a Medelec MSG electromyograph.

A complete neurological examination was performed by a neurologist on all the children. Muscle strength was evaluated according to the principles suggested by the Medical Research Council. Tendon reflexes were evaluated in biceps brachii, triceps brachii, brachioradialis, quadriceps and gastrocnemius soleus muscles.

Sensory deficit was evaluated at three different points from distal to proximal on each extremity.

Cotton wool was used to assess touch-pressure. Disposable pins and a 25 cm long, 28 Hz tuning fork were used for pain and vibratory sensation testing, respectively.

Sense of joint position was tested by manually displacing the great toe or finger.

The findings of the neurologic examination were scored as to neurological symptoms and neurological disability[10].

Criteria for diagnosis and staging of diabetic neuropathy (Table I):

Table I: Staging of Diabetic Neuropathy

	EMG*	NE**	NS***
Stage 0-No Neuropathy	−	−	−
Stage Ia-Early Asymptomatic Neuropathy	+	−	−
Stage Ib-Asymptomatic Neuropathy	+	+	−
Stage II-Symptomatic Neuropathy	+	+	+
Stage III-Disabling Neuropathy	+	+	++

* EMG-Electromyography.
** NE-Neurologic examination.
*** NS-Neuropathic symptoms.

Stage 0-No Neuropathy :

Stage I a-Early Subclinical (asymptomatic) Neuropathy: abnormality of amplitude or nerve conduction (more than 3SD below the mean for normals) or distal latency (more than 3SD above the mean for normals) of one or more attributes in two or more nerves and not due to a disease other than IDDM or to faulty electrode placement or low nerve temperature.

Stage I b-Subclinical (asymptomatic) Neuropathy: abnormalities both of peripheral nerve test and neurologic examination (abnormality of one or more of muscle strength, tendon reflexes or sensation, judged to be due to diabetic neuropathy).

Stage II-Symptomatic Neuropathy: two or more abnormalities of nerve conduction, neurologic examination or neuropathic symptoms. Neuropathic symptoms present but of lesser severity than in Stage III.

Stage III-Disabling Neuropathy: two or more abnormalities of peripheral nerve test, neurologic examination or neuropathic symptoms. Disabling neuropathic symptoms present.

Analysis : Standard statistical tests were used throughout. Results in the text are expressed as mean ± standard deviation.

Results

Glycemic Control : In the 38 diabetics, the mean HbA_{1c} was 14.4±4.7% (range: 7.8-21). There was a significant correlation between plasma glucose and HbA_{1c} ($r=0.65$, $p<0.001$).

Clinical Features : With one exception, no patients had symptoms of somatic neuropathy and only eight showed abnormal clinical findings; seven had diminished and one had absent tendon reflexes. Three had general muscle weakness and one had diminshed pin-prick sensation to the level of the ankles. All eight of these patients had abnormal results of peripheral electrophysiologic nerve tests in two or more nerves (Table II).

Table II: Frequency of Symptoms and Signs of Peripheral Neuropathy in Diabetic Children (n = 38)

Symptoms/Signs	n	%
Decreased deep tendon reflexes	7	18.4
Absent deep tendon reflexes	1	2.6
Muscle weakness	3	7.8
Paresthesia/pain/cramp	1	2.6
Loss of pain sensation	1	2.6
One or more signs and/or symptoms	8	21

Peripheral Somatic Nerve Tests : The mean amplitude, nerve conduction velocity and distal latency values in diabetic children were slower than those in the normal control group. However, the difference was statistically significant only for fibular nerve amplitude; fibular, tibial and median nerve motor conduction velocity (MCV) and distal latency; and sural and median nerve sensory conduction velocity (SCV), amplitude and distal latency (Table III).

One of the 38 diabetic children studied satisfied our criteria and was diagnosed as having symptomatic diabetic neuropathy, giving a prevalence of 2.6%. Seven other patients (18.4%) had both abnormal peripheral somatic electrophysiologic nerve test results in two or more nerves and pathologic findings in the neurologic examination (asymptomatic neuropathy). Five of the 38 diabetic children diagnosed as having early subclinical neuropathy had only abnormal electrophysiological test results in one or more attributes of two or more nerves.

The diabetic patients with asymptomatic and symptomatic neuropathy had a statistically significant longer duration of diabetes and higher HbA_{1c} value than those of the non-neuropathic children (Table IV).

The correlation between conduction velocities and the duration of diabetes and HbA_{1c} are presented in Table V.

The duration of diabetes showed a strong correlation with median and fibular motor conduction velocities ($r = 0.44$; $p < 0.01$, $r = 0.42$; $p < 0.01$), but there was no correlation with median and sural sensory conduction velocities.

Table III: Mean Electrophysiological Measurements and Significance

	Nerves	Normal n: 31	Diabetic n: 38	Significance
Compound muscle action potential amplitude CMAP (millivolts)	Fibular	4.6 ± 1.8	3.5 ± 2	$p<0.01$
	Tibial	6.05 ± 2.5	6.17 ± 2.4	NS*
	Median	8.24 ± 3.7	8.97 ± 3.2	NS
	Ulnar	7.3 ± 3	7.1 ± 2.4	NS
Motor Conduction Velocity MCV (m/s)	Fibular	48.5 ± 6	43 ± 7.5	$p<0.001$
	Tibial	45.7 ± 5.4	40.8 ± 6.5	$p<0.001$
	Median	56 ± 5.7	52.2 ± 8.7	$p<0.05$
	Ulnar	56.5 ± 9	52.3 ± 9.4	NS
Distal latency (m/s)	Fibular	3.5 ± 1.1	4.5 ± 1.4	$p<0.001$
	Tibial	3.3 ± 0.7	4.3 ± 1.4	$p<0.001$
	Median	2.75 ± 0.4	3.2 ± 0.7	$p<0.001$
	Ulnar	2.3 ± 0.4	2.6 ± 0.8	NS
Sensory nerve action potential amplitude SNAP (microvolts)	Sural	18.1 ± 4.6	14.3 ± 5	$p<0.001$
	Median	69.6 ± 20.2	54.8 ± 17.8	$p<0.01$
Sensory conduction velocity SCV (m/s)	Sural	54.3 ± 3.7	50.1 ± 5.7	$p<0.001$
	Median	59.5 ± 8.9	54.6 ± 9.5	$p<0.05$
Distal latency (m/s)	Sural	3.45 ± 0.6	4.32 ± 1.1	$p<0.001$
	Median	2.8 ± 0.36	3.17 ± 0.6	$p<0.05$

* NS: not significant.

Table IV: Mean Value of HbA_{1c} and Duration of Diabetes in Diabetic Subjects with and Without Neuropathy

	Group with Asymptomatic-Symptomatic Diabetic Neuropathy n = 13	Group Without Diabetic Neuropathy n = 25	Significance
HbA_{1c} (%)	20.7 ± 4.9	13.9 ± 3.8	$p<0.001$
Duration of diabetes (yr)	6.1 ± 3.4	2.3 ± 2.1	$p<0.001$

Poor balance of diabetes, based on HbA_{1c}, also correlated with fibular motor conduction velocity ($r=0.75$; $p<0.001$) and sural sensory conduction velocity ($r=0.31$; $r<0.05$); however, no correlation was found between HbA_{1c} and median motor and sensory conduction velocities.

Table V: Correlation of Nerve Conduction Parameters with HbA_{1c} and Duration of Diabetes

	Correlation Coefficient	Significance
Duration of diabetes		
Median, MNCV	0.44	$p<0.01$
Fibular, MNCV	0.42	$p<0.01$
Median, SNCV	0.20	NS*
Sural, SNCV	0.18	NS
HbA_{1c}		
Median, MNCV	0.22	NS
Fibular, MNCV	0.75	$p<0.001$
Median, SNCV	0.21	NS
Sural, SNCV	0.31	$p<0.05$

* NS: not significant.

Discussion

The present study investigated peripheral neuropathy in IDDM. We found that 12 of the 38 diabetic children (31.5%) had subclinical neuropathy and confirmed that impaired peripheral nerve function is not a rare complication of diabetes in childhood.

Studies of peripheral somatic nerve function have been reported in diabetic children before, but the results are difficult to compare with ours because wide age ranges were included, either motor or sensory conduction studies alone were evaluated, variations in normal values throughout the childhood period were not taken into account, and a variety of diagnostic criteria were used.

Our findings are not concordant with those reported by Hoffmann[12], whose relative data emphasize a strong contrast between adult and child populations, and who concludes that peripheral neuropathy is a rare complication in children.

Despite the strict diagnostic criteria used in our study, the following investigators have reported data which agree with this study: Eeg-Olofsson et al[2] 9%, Gamstrop et al[3] 10%, Kaar et al[4] 30%, Lawrence at al[5] 19%, Young et al[6] 72%, Dorchy et al[7] 36%, Eng et al[8] 30%, Gallai et al[9] 32%, Marcus et al[13] 25%, and Hoffmann et al[14] 40%.

We have shown that disturbances of motor and sensory peripheral somatic nerve function in young, type 1 diabetics are related to both glycemic control, as assessed by HbA_{1c}, and the duration of diabetes.

In diabetic children, those with definite evidence of peripheral neuropathy have been shown to have a longer duration of diabetes. A correlation was found between abnormal fibular and median motor conduction velocities and the duration of diabetes, but not between sural and median sensory conduction velocities and the duration of diabetes.

In many studies reported, it was found that the longer the duration of diabetes, the higher the frequency of peripheral neuropathy[2-4,8,13,14]. Although this correlation is clear in the adult population, it was not possible to find any relation between diabetic neuropathy and the duration of diabetes in some of the studies reported on children[6,7,9].

Gallai et al[9] explained this discrepancy by the shorter duration of diabetes in a juvenile population, which obviously does not permit a correlation to be verified due to the limited number of years in question.

The level of HbA_{1c} was also higher in diabetic children with peripheral neuropathy than in children without neuropathy.

The motor conduction velocity of the fibular nerve and sensory conduction velocity of the sural nerve were dependent on the balance of diabetes based on HbA_{1c}.

In light of these findings, the motor abnormalities we have demonstrated in the median and fibular nerves are related predominantly to the duration of diabetes and are probably permanent because of repeated metabolic insults over the years; on the other hand, abnormalities in sensory conduction of the sural nerve although electrophysiologically similar, may still be reversible, and hence correlated only with the HbA_{1c}.

The data found in our study confirm the importance of hyperglycemia in the etiology of diabetic neuropathy and point to the net combined effects of metabolic control and the duration of diabetes.

In electromyographic (EMG) studies; amplitude indicates axonal function, whereas motor and sensory conduction velocity measurements reflect predominantly Schwann cell damage.

In our study, although we could not find any denervation finding such as fibrillation, the measurements of sensory and motor potential amplitudes in the lower extremities were decreased when compared with those of the control group. We also found a marked decrease in motor and sensory conduction velocities. Our results therefore imply that there is little axonal but extensive Schwann cell malfunction in young diabetic patients who are free of clinically detectable neuropathy.

In conclusion, according to our data it is possible to suppose that diabetic neuropathy is not a rare complication of diabetes in children and that the reduction

of amplitude, conduction velocity and distal latency values is influenced by the degree of glycemic control and the duration of diabetes.

Being easy to conduct and sensitive, peripheral nerve tests may be suggested for diabetic children at regular intervals after the onset of the disease in order to achieve good metabolic control and to find and follow abnormalities in peripheral nerve function.

REFERENCES

1. Canal N, Comi G, Saibene V, et al. Relationship between peripheral and autonomic neuropathy in insulin dependent diabetes: a clinical and instrumental evaluation. In: Canal N, Pozza G, (eds) Peripheral Neuropathies. Amsterdam: Elsevier North Holland Biomedical 1978: 247-253.
2. Eeg-Olofesson O, Petersen I. Childhood diabetic neuropathy: a clinical and neurophysiological study. Acta Paediatr Scand 1966; 55: 163-176.
3. Gamstorp I, Shelburne SA, Engleson G, et al. Peripheral neuropathy in juvenile diabetes. Diabetes 1966; 15: 411-418.
4. Käär ML, Saukkonen AL, Pitkänen M, Akerblom HK. Peripheral neuropathy in diabetic children and adolescents. A cross-sectional study. Acta Paediatr Scand 1983; 72: 373-378.
5. Lawrence DG, Locke S. Neuropathy in children with diabetes mellitus. Br Med J 1963; 5333: 784-785.
6. Young RJ, Ewing DJ, Clarke BF. Nerve function and metabolic control in teenage diabetics. Diabetes 1983; 32: 142-147.
7. Dorchy H, Noel P, Kruger M, de Maertelaer V, Dupont E, Toussaint D, et al. Peroneal motor nerve conduction velocity in diabetic children and adolescents. Relationships to metabolic control, HLA-DR antigens, retinopathy, and EEG. Eur J Pediatr 1985; 144: 310-315.
8. Eng GD, Hung W, August GP, Smokvina MD. Nerve conduction velocity determinations in juvenile diabetes continuing study of 190 patients. Arch Phys Med Rehabil 1976; 57: 1-5.
9. Gallai V, Firenze C, Mazzotta G, Del Gatto F. Neuropathy in children and adolescents with diabetes mellitus. Acta Neurol Scand 1988; 78: 136-140.
10. Dyck PJ. Detection, characterization and staging of polyneuropathy: assessed in diabetics. Muscle Nerve 1988; 11: 21-32.
11. Flückiger R, Winterhalter KH. In vitro synthesis of hemoglobin A_{1c}. FEBS Lett 1976; 71: 356-360.
12. Hoffman J. Peripheral neuropathy in children with diabetes mellitus. Acta Neurol Scand 1964; 40 (suppl.8): 1-66.
13. Marcus J, Ehrlich R, Kelly M, Murphy EG. Nerve conduction in childhood diabetes. Can Med Assoc J 1973; 108: 1116-1119.
14. Hoffman WH, Hart ZH, Frank RN. Correlates of delayed motor nerve conduction and retinopathy in juvenile-onset diabetes mellitus. J Pediatr 1983; 102: 351-356.