Peripheral Nerve Function Is Increasingly Impaired During Puberty in Adolescents With Type 1 Diabetes

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OBJECTIVE — To evaluate the impact of puberty on peripheral nerve function in adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Of 138 eligible patients with type 1 diabetes, 100 patients (age >9 years and diabetes duration >2 years) attending an outpatient diabetes clinic and 100 age- and sex-matched healthy control subjects took part in this cross-sectional study. Peripheral motor and sensory nerve conduction tests, cardiovascular reflex tests on the autonomic nervous system, and measurements of vibration-perception threshold (VPT) were performed.

RESULTS — Nerve conduction velocity (NCV) in the distal motor and sensory nerves, the motor nerve distal latency, and the sensory nerve action potential (SNAP) amplitude were impaired in the adolescent patients with type 1 diabetes. The deterioration in motor NCV, H-reflex latency, and SNAP amplitude became more conspicuous in late puberty and postpuberty and was related to poor metabolic control. A total of 10 patients had distal diabetic polyneuropathy (DP) neurophysiologically, and these patients had significantly lower heart-rate variation in the deep breathing test than the other patients. Three of the patients with DP had peripheral neurological signs or symptoms. A slight difference in the VPT between the patients and control subjects was observed after puberty.

CONCLUSIONS — Increasing subclinical motor nerve impairment can be detected during late puberty and after puberty, and sensory NCV and SNAP amplitude are reduced in adolescents with type 1 diabetes. Poor metabolic control during puberty appears to induce deteriorating peripheral neural function in young patients with type 1 diabetes.

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Deterioration in nerve segmental myelination and axonal structure, reflected in decreased nerve conduction velocity (NCV) and depressed nerve amplitude, respectively, has been implicated as contributing to the peripheral nerve problems seen in patients with type 1 diabetes. Subclinical diabetic polyneuropathy is not uncommon among young patients with type 1 diabetes. Approximately one-fourth of young patients with a recent diagnosis of this disease have been reported to have pathological findings in the distal nerves, with some improvement in sensory nerve conduction during the remission phase of the disease (1). However, symptomatic distal diabetic polyneuropathy (DP) rarely occurs in children and adolescents with type 1 diabetes (2), but signs and symptoms are more frequent in young-adult patients and are associated with poor glycemic control and long duration of the disease (3).

Height is one of the most important physiological determinants of nerve conduction (NC) because NCV decreases with growth both in patients with diabetes and in healthy subjects (4–6). Poor metabolic control has a negative impact on NCV and on nerve amplitude (4) and is an independent risk factor for symmetric distal DP (7). Puberty is likely to be one of the most critical periods for the development of peripheral nerve dysfunction in patients with type 1 diabetes because of various hormonal changes affecting glycemic control during puberty (8). The Tanner stages of pubertal maturation (9) have rarely been considered in studies on peripheral polyneuropathy in young patients with type 1 diabetes (4,10), and there is a need for additional knowledge of the role of puberty in the development of such abnormalities. The purpose of this cross-sectional study was to assess clinically and neurophysiologically the signs of damage to the peripheral nerve system observed in a large series of adolescent patients with type 1 diabetes in relation to pubertal maturation.

RESEARCH DESIGN AND METHODS

Study population

Of 138 eligible patients with type 1 diabetes at the Pediatric Diabetes Outpatient Clinic at Oulu University Hospital, 101 patients (49 male and 52 female, age >9 years and disease duration >2 years) and 100 healthy adolescents from nearby schools recruited as voluntary control subjects gave their consent or assent to this study. All of the patients with diabetes diagnosed under the age of 15 years living in the district served by the hospital attend the clinic until ages 16–18 years. One of the patients was excluded because of Down syndrome and hypothyreosis. The characteristics of the remaining pa-

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Abbreviations: ANCOVA, analysis of covariance; CMAP, compounding muscle action potential; DL, distal latency; DP, diabetic polyneuropathy; HRV, heart-rate variation; NC, nerve conduction; NCV, NC velocity; SNAP, sensory nerve action potential; VPT, vibration-perception threshold.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Characteristics of the participants*

	Patients	Control subjects
n	100	100
Sex (M/F)	49/51	49/51
Tanner pubertal stage (M/F)		
I	21 (11/10)	15 (8/7)
II and III	33 (19/14)	30 (18/12)
IV	27 (11/16)	26 (11/15)
V	19 (8/11)	29 (12/17)
Age (years)	13.7 ± 2.0	13.6 ± 2.0
Diabetes duration (years)	7.0 ± 3.5	—
GHb (%)	8.5 ± 1.7	4.4 ± 0.3
GHb in Tanner pubertal stage (%)		
I	7.4 ± 1.3*	4.4 ± 0.2
II and III	8.5 ± 1.4	4.4 ± 0.3
IV	9.2 ± 1.7	4.5 ± 0.4
V	8.7 ± 1.7	4.5 ± 0.4
GHb—2 years (%)	8.5 ± 1.4	—
Insulin dose (IU · kg^{-1} · day^{-1})	0.92 ± 0.20	—
Height (cm)	158.3 ± 10.9	158.6 ± 11.7
Relative height	+0.05 ± 0.93	+0.07 ± 0.82
Weight (kg)	50.7 ± 10.6	50.0 ± 11.0
Relative weight (%)	108 ± 10†	104 ± 11
BMI (kg/m^2)	19.9 ± 2.4	19.2 ± 2.4

Data are *n* or means ± SD. *$P < 0.005$ compared with the other pubertal stages; †$P = 0.016$ (95% CI 0.7–6.5) vs. control subjects.

tients and control subjects are shown in Table 1. All of the patients were receiving intensive insulin treatment, with three to five daily injections. The nonconsenting patients did not differ from the study subjects with regard to long-term GHb or duration of diabetes. The study was approved by the Ethics Committee of the Medical Faculty, University of Oulu, and was carried out according to the provisions of the Declaration of Helsinki.

Study design

Careful assessments of clinical status, including height (mean of three consecutive measurements with a Harpenden stadiometer), weight, Tanner pubertal stage (9), and neurological condition, were performed by one of the investigators (P.H.R.). A standard direct inquiry regarding symptoms and signs of peripheral neuropathy modified from previous recommendations (11,12) was completed at registration for the study. All of the subjects were hospitalized for 22–24 h for the purpose of this study.

A clinical examination, including the sensations of vibration (260 Hz fork), light touch, pain (pinprick), and joint position in the index finger and big toe bilaterally, was carried out. These sensation qualities together with the tendon reflexes in the quadriceps, gastrocnemius, and biceps and triceps surae muscles were classified either as present or absent. The vibration perception threshold (VPT) tests and the cardiovascular reflex tests were performed by one of the investigators (P.H.R.). The NC tests were performed in the Department of Clinical Neurophysiology by skilled technicians who were not aware of the status of the subjects or of any of the other results.

The number of subjects varied slightly among the measurements for a number of reasons, e.g., 1 control subject refused to undergo the NC tests, 2 control subjects had a Martin-Gruber anastomosis in the median nerve, and in 10 patients, the median nerve was not examined. The duration of diabetes (mean and range) did not differ significantly between the pubertal stages: TI, 6.5 years (2.1–10.4); TII and TIII, 6.1 years (2.7–12.5); TIV, 7.9 years (2.2–14.5); and TV, 7.9 years (2.4–15.6). The GHb at various pubertal stages is shown in Table 1. The patients at pubertal stages TII and TIII were significantly older (13.3 ± 1.3 vs. 12.1 ± 1.1 years, $P < 0.001$) and taller (154.7 ± 6.0 vs. 150.8 ± 6.6 cm, $P = 0.015$) than the control subjects, but no such differences were observed at the other stages.

The previously described criterion for peripheral polyneuropathy in diabetes was used: two or more NC tests below the 1st or above the 99th percentile of the control values (13,14).

Methods

Motor nerve conduction

The compound muscle action potential (CMAP) of the right median nerve was obtained on the abductor pollicis brevis, the nerve being stimulated supramaximally at the wrist 65 mm above the recording electrode and at the elbow. The peroneal nerve CMAP was recorded on both sides on the extensor digitorum brevis muscle after supramaximal stimulation at the ankle 75 mm above the recording electrode and at the popliteal fossa. The distal latency (DL) of the CMAP was measured from the onset of the stimulus to the initial CMAP negative deflection.

Sensory nerve conduction

The sensory nerve action potential (SNAP) of the median nerve was measured by the antidromic technique on the index finger, with ring electrodes placed 2.5 cm apart. The sural SNAPs were recorded behind the lateral malleolus, with stimulation applied 14 cm proximal to the recording electrode.

H-reflex

The H-reflex was measured on the soleus muscle by stimulating the tibial nerve at the popliteal fossa using a 0.5-ms stimulus duration and a slow stimulus frequency. As an oligosynaptic reflex, the H-reflex represents the afferent nerve impulses in the sensory fibers extending from the muscle spindles and efferent nerve impulses in the α-motor axons, including the reflex arch of the sensory dorsal root, spinal cord, and motor ventral root. The H-reflex latency difference (total H-reflex latency minus latency from the popliteal fossa to soleus muscle) reflects the functioning of the proximal part of the tibial nerve.

F-wave

The F-wave of the peroneal nerve was obtained by supramaximal stimulation at the popliteal fossa. The shortest F-wave latency of 16 responses was selected.

Table 2—*Conduction velocity in the motor and sensory nerves, and the sensory nerve amplitude in patients and control subjects*

	Peroneal	Sural	Median		Sural
	Motor NCV (m/s)	Sensory NCV (m/s)	Motor NCV (m/s)	Sensory NCV (m/s)	SNAP amplitude (μV)
Patients	47.5 ± 3.1 (100)	47.2 ± 3.7 (100)	55.4 ± 3.8 (90)	50.1 ± 4.9 (89)	28.8 ± 1.1 (100)
Control subjects	51.0 ± 3.0 (98)	49.2 ± 3.6 (99)	59.0 ± 3.5 (96)	52.1 ± 3.5 (99)	35.8 ± 1.5 (99)
Difference	3.5 (2.7–4.4)	2.0 (0.9–3.0)	3.6 (2.6–4.7)	2.0 (0.8–3.3)	7.0 (3.5–10.6)
P	<0.0001	0.0004	<0.0001	0.002	<0.0001

Data are means ± SD (*n*) and the difference (95% CI) of the mean NCV or SNAP amplitude between the patients and control subjects. Results of the right extremities (arm and foot) are shown.

Cardiovascular reflex tests

Heart-rate variation (HRV) in a 10-min resting state and the heart-rate response (maximum/minimum) to deep breathing for 60 s and to active standing (30:15) were determined after a 30-min rest in a quiet room.

VPT

Two consecutive readings of VPT were performed at 63, 125, 250, and 500 Hz with a Vibrometry system 9589 (15) on the second metacarpal and first metatarsal bones. The sense of vibration was reported by pressing a button and holding it down until the vibration disappeared, and the perception graph was marked as a vibrogram (dB, 10^{-6} m/s^2). The mean of the two readings was taken as the VPT.

Laboratory methods

GHb was analyzed by high-pressure liquid chromatography (nondiabetic range 4.0–6.0%). The mean of the GHb values measured at regular visits over the preceding 2 years (one to three measurements per year) was taken to present the long-term GHb.

Statistical analysis

The NC tests were adjusted for the mean height and skin temperature for the entire group or in the pubertal stages, depending on the setting. The adjusted means (SD) were calculated using the analysis of covariance (ANCOVA), and the means were compared using the unpaired Student's *t* test. The 95% CI was estimated for each difference between two means. The percentiles of the normal values were calculated by regression analysis. Two-way ANCOVA was performed to relieve the possible interaction of puberty and diabetes on NC studies. Linear multiple regression analysis was performed to assess the independent associations of numerous variables with NC tests. The statistical tests were performed with SPSS 9.0 software (SPSS, Chicago, IL). $P < 0.05$ was considered statistically significant.

RESULTS — Motor and sensory NCV and SNAP amplitude were symmetrically impaired in the diabetic patients compared with the control subjects (Table 2). Also, the H-reflex latency (28.3 ± 0.2 vs. 27.0 ± 0.1 ms, CI 0.5–2.1, $P = 0.002$, right tibial nerve) and the F-wave latency (38.1 ± 0.4 vs. 36.3 ± 0.4 ms, 0.7–3.0, $P = 0.002$, right peroneal nerve) were prolonged in the patients versus the control subjects.

The difference between the patients and control subjects increased with pubertal maturation in the H-reflex latency difference (Table 3) and in the peroneal NCV but not in the median NCV (Fig. 1). The sural SNAP amplitude was lower in the patients than in the control subjects after puberty (26.0 ± 1.1 vs. 32.2 ± 1.4, CI 2.6–10.2, $P < 0.001$, right sural nerve), whereas the median SNAP amplitude did not differ significantly between the patients and control subjects ($P = 0.096$). A significant interaction of diabetes and puberty with the peroneal NCV ($P < 0.05$) and the H-reflex latency difference ($P < 0.05$) was observed in the patients (two-way ANCOVA).

A significant correlation was observed between long-term GHb and puberty ($r = 0.36$, $P < 0.001$) and between GHb and duration of diabetes ($r = 0.34$, $P = 0.001$) but not between puberty and diabetes duration ($P = 0.092$). An independent association of long-term GHb ($\beta = -0.22$, $P = 0.03$) and diabetes duration ($\beta = -0.25$, $P = 0.013$) with peroneal NCV ($R^2 = 0.15$) and GHb ($\beta = -0.23$, $P = 0.031$) with median motor NCV ($R^2 = 0.05$) was observed in a multiple stepwise regression model including pubertal stage, diabetes duration, long-term GHb, sex, and age at diagnosis as independent variables.

DP was detected neurophysiologically in 10 patients (5 male and 5 female): 1 prepubertal, 3 pubertal, and 6 postpubertal. Of these 10 patients, 7 (3 male and 4 female) had symmetrically reduced peroneal NCV, including 3 patients with persistent numbness of the legs or symmetric loss of deep tendon reflexes in the lower

Table 3—*H-reflex latency difference (milliseconds) in the tibial nerves*

	Tanner pubertal stages			
	TI	TII and TIII	TIV	TV
Right tibial nerve				
Patients	21.3 ± 0.2	23.0 ± 0.3	25.6 ± 0.4	26.4 ± 0.5
Control subjects	21.4 ± 0.4	22.3 ± 0.2	24.1 ± 0.3	24.7 ± 0.3
Difference	–0.1 (–0.9–0.7)	0.7 (0.05–1.5)	1.5 (0.4–2.5)	1.7 (0.7–2.7)
P	0.76	0.037	0.006	0.0012
Left tibial nerve				
Patients	21.5 ± 0.2	23.0 ± 0.4	25.9 ± 0.5	26.6 ± 0.5
Control subjects	21.6 ± 0.4	22.0 ± 0.3	24.0 ± 0.3	24.7 ± 0.3
Difference	–0.1 (–0.9–0.8)	1.0 (0.1–1.9)	1.9 (0.6–3.1)	1.9 (0.8–3.0)
P	0.88	0.032	0.0041	0.0009

Data are means ± SD and the difference (95% CI) of the mean H-reflex latency difference between the patients and control subjects.

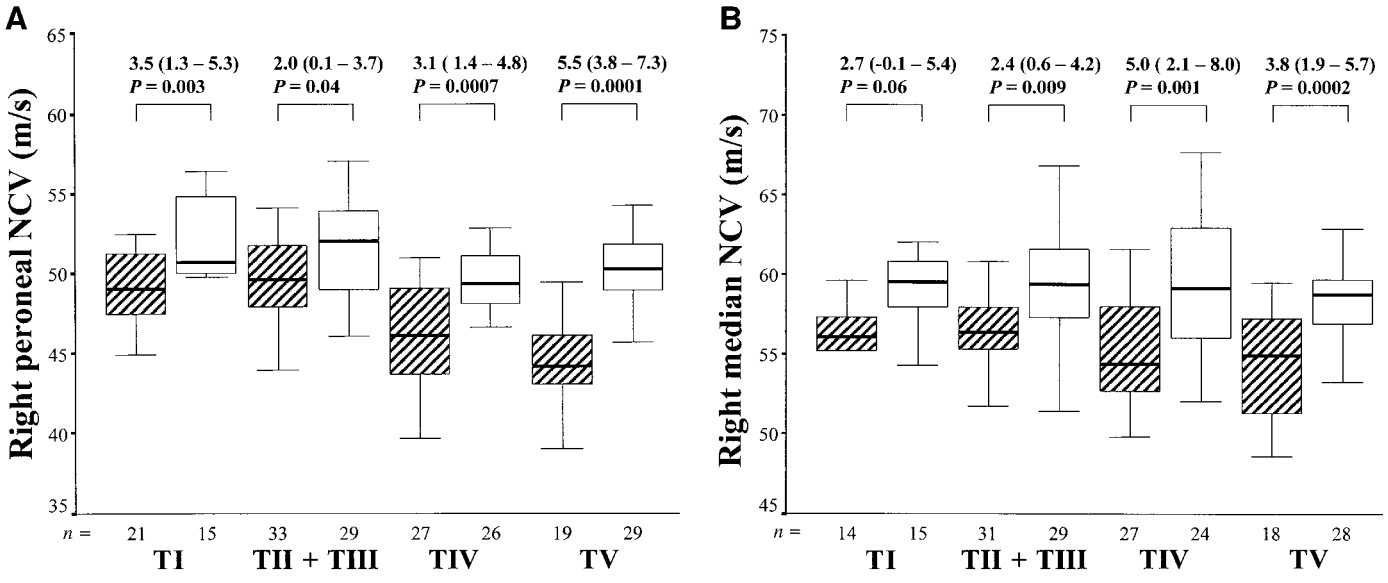

Figure 1—*Box plots of the right peroneal* (A) *and right median* (B) *NCV in the patients* (▨) *and control subjects* (□). *TI, TII and III, TIV, and TV are the Tanner pubertal stages. The mean difference of the NCV between the patients and control subjects (95% CI) and the* P*-values are shown above the box plots.* n = *the number of the patients at various pubertal stages.*

extremities. These 10 patients with DP had a higher GHb (9.9 ± 1.8 vs. 8.3 ± 1.2%, CI 0.8–2.5, $P < 0.001$) and a longer duration of diabetes (10.8 ± 3.2 vs. 6.6 ± 3.3 years, 2.0–6.4, $P < 0.001$) than the patients without DP. The HRV in response to deep breathing was lower in these patients than in those with no DP (1.43 ± 0.14 vs. 1.57 ± 0.15, 0.04–0.24, $P = 0.006$), whereas the other cardiovascular tests did not show any significant differences.

There was a slight tendency for an increase in VPT with puberty in the patients, and a significant difference was observed relative to the control subjects after puberty at 250 Hz in the left leg ($P < 0.05$) (data not shown).

The questionnaire on symptoms of peripheral neuropathy was completed by 76 patients and by all of the control subjects. In addition to the three patients with symptomatic DP, nine patients without DP had peripheral neurological symptoms (tingling or numbness). None of the patients had any loss of the sense of light touch, pain, or joint position. All of the 24 patients who did not complete the questionnaire had normal vibration sense, whereas 2 patients (with DP) had absent joint reflexes in the lower extremities. Of these 24 patients, 5 had DP neurophysiologically, but they had no symptoms when asked afterward. One control subject had occasional numbness of the soles of the feet but no signs of DP, and the NC tests were normal.

CONCLUSIONS — This cross-sectional study demonstrates a progressive reduction in peroneal NCV in late-pubertal and postpubertal adolescents with type 1 diabetes. However, distal sensomotor polyneuropathy with signs and symptoms does not seem to appear until after puberty. A close association was observed between neuropathy and long-term poor metabolic control, and the adolescent patients with distal polyneuropathy also had signs of autonomic nerve dysfunction. In addition to pathologically retarded nerve conduction observed in the distal nerves, we also detected dysfunction in the proximal nerve tract, reflected by the H-reflex latency in the patients. The present data represents an unselected clinical population of adolescents with type 1 diabetes and a control population well matched for age and sex. This is one of the largest studies on distal diabetic neuropathy in adolescent patients with systematically performed pubertal staging of both the diabetic patients and control subjects.

Subclinical distal DP has been reported to occur in 9–68% of children and adolescents with type 1 diabetes (16–18). This wide variation may at least partly be caused by the variable definition of peripheral neuropathy and the number of variables included in the definition of neuropathy in general. Variations in age, number of control subjects, and degree of matching between patients and control subjects may also contribute to the variability in the results regarding distal diabetic neuropathy in adolescents.

Our observation that the motor nerves of the lower extremities are most often affected in adolescents with diabetes is supported by previous data (2,17), although diabetes also affects less myelinated sensory nerve fibers early in the course of the disease (1). The finding that the adolescent patients with distal DP also had parasympathetic nerve dysfunction is in line with previous results in adult patients (3,19) and supports the observation of distal neural damage in diabetic polyneuropathy. The fact that only a few of the adolescent patients had signs or symptoms of distal nerve dysfunction is in accordance with some previous reports (2,17) showing that only ~4% of the children or adolescent patients with type 1 diabetes had symptoms or signs consistent with clinical neuropathy. However, abnormal deep tendon reflexes and signs of DP are already detectable in one-fifth of all young and otherwise healthy adult diabetic patients (3).

Puberty impairs insulin action both in patients with type 1 diabetes and in healthy adolescents (8), and our findings are largely in accordance with the obser-

vation that poor metabolic control is the most important prognostic factor for neuronal dysfunction both in adolescent (2,20) and adult patients (7,21). The peripheral and autonomic nerve fibers of pubertal and postpubertal patients with diabetes may be the most vulnerable to nerve demyelination and axonal damage caused by poor metabolic control induced by the pubertal hormonal changes (8) and presumably also by poor motivation for self-care during puberty. Relatively long duration of diabetes may partly explain the progressive nerve dysfunction also seen in this series because diabetes duration has been observed to relate to neuronal dysfunction in patients >18 years of age (21).

Although functional changes in the peripheral large myelinated nerve fibers were already detectable before puberty and during pubertal maturation, a slight difference in VPT between the patients and control subjects was observed only after puberty. VPT reflects the functioning of the large nerve fibers, and VPT has been observed to increase in children and adolescents with type 1 diabetes relative to healthy control subjects, particularly after puberty (22). However, some reports have failed to detect any obvious increase in VPT in patients with autonomic or peripheral nerve dysfunction (23). Differences in methodology between these reports may account at least in part for the conflicting results regarding the sense of vibration. Unfortunately, we did not have any data on cold or warm thresholds, which are useful in the assessment of the function of small nerve fibers. That function has also been shown to deteriorate in adolescent patients with type 1 diabetes, and such measurements can be used to identify subclinical DP (24).

The metabolic milieu brought about by poor glycemic control during puberty may have a worsening effect on peroneal nerve conduction velocity and H-reflex, although such dysfunction is rarely symptomatic in adolescence. Intensive insulin treatment has been shown to effectively preserve peripheral nerve function in patients with type 1 diabetes, and this effect seems to be most apparent for motor nerves, both in patients with and without neuropathy (25). The increasing impairment of nerve function with puberty in our adolescent patients receiving intensive insulin treatment nevertheless stresses the need for improved metabolic control of diabetes during this critical phase of growth and development.

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