Evaluation of polyneuropathy and associated risk factors in children with type 1 diabetes mellitus

Hande TÜRKYILMAZ, Orkide GÜZEL, Selvinaz EDİZER, Aycan ÜNALP*
Department of Pediatric Neurology, Dr. Behçet Uz Children's Training and Research Hospital, İzmir, Turkey

1. Introduction
Diabetes mellitus (DM) is a metabolic disorder characterized by anomalies in carbohydrate metabolism. Diabetic neuropathy (DN) is an important complication seen in diabetic patients and is associated with high morbidity and mortality rates in addition to a significant decrease in the quality of life of patients. DN shows itself in heterogeneous clinical manifestations by affecting different nerves, either proximal or distal nerves or sensory, motor, or autonomic nerves. The pathophysiology of DN is multifactorial, i.e. genetic, environmental, behavioral, metabolic, neurotrophic, and vascular factors all play a role in disease development (1,2). The prevalence of DN is reported to be between 28.5% and 50% in various studies. Peripheral neuropathy, especially as a complication of DM, has been extensively studied in adult populations. However, peripheral neuropathy is rarely mentioned in children as a chronic complication of DM, as this condition has a longer latent period during its development. Distal symmetric sensorimotor polyneuropathy is the most commonly diagnosed clinical type of DN. Electrophysiological studies in diabetic patients usually demonstrate nonspecific signs of axonal degeneration in addition to demyelization along nerve segments (3).

The pathophysiology behind DN is not clearly understood except for the marked importance of chronic hyperglycemia, which is thought to be the main culprit in neurovascular damage initiation (4–6). However, the basic pathophysiology of DN is still unknown. Some authors attributed neuropathy to vascular changes (7), while others found no relationship between hyperglycemia and peripheral vascular disease (8). Other studies suggested that mechanical injury (9) and nerve entrapment (10) play prominent roles and are aggravated by vascular factors.

Previous studies usually reported that age, male sex, disease duration, and glycemic control are all factors affecting nerve conduction (8,11). For this reason, our main objective in this study is evaluation of DN incidence rate in children with type 1 DM and determination of the associated risk factors.
2. Materials and methods

2.1. Subject selection

Ethical approval for this study was obtained from the Ethics Committee of Dr. Behçet Uz Children’s Training and Research Hospital. A total of 111 patients, comprising 59 (53.2%) boys and 52 (46.8%) girls, were included in the study. All patients were followed in the Child Neurology and Endocrinology Clinic with a type 1 DM diagnosis. Data from electromyography (EMG) studies of these patients between January 2011 and May 2014 were reviewed in a retrospective fashion. We did not examine B12 levels in this patient group.

2.2. Statistical analysis

Patient age, diabetes duration at the time of EMG implementation, mean HbA1c values, clinical manifestations, frequency of diabetic ketoacidosis, insulin dosage at the time of EMG, neurological examination results, and electrophysiological evaluation results were all recorded. Statistical analysis was performed using SPSS 10.0 for Windows. EMG was performed using Nihon Kohden MEB 9400 EMG equipment. Electrophysiological assessment was done by 2 child neurology specialists in the Dr. Behçet Uz Children’s Training and Research Hospital’s Electrophysiology Laboratory.

Under conventional room temperature settings, sensory and motor nerve conduction studies were performed for both the lower and upper extremities of the patients. The protocol included the unilateral (right side) median, ulnar and sural sensory conductions, and right-side peroneal and tibial motor conductions. Another peripheral nerve involvement, detected in more than two peripheral nerve conduction defects, was used as a criterion for the diagnosis of polyneuropathy detection. Descriptive statistics of patients were recorded. In addition, multiple linear regression analysis was done to assess the possible correlated factors between neuropathy symptoms and body mass index (BMI), EMG results, sex, mean HbA1c, neuropathy period, previous episodes of diabetic ketoacidosis, and insulin requirements.

3. Results

The male-to-female ratio was 1:1.3. Median age of the patients was 138 months, with a range from 39 to 227 months. Fifty-two (46.8%) patients were previously diagnosed with diabetic ketoacidosis, while 48 (43.2%) patients had classical diabetes symptoms and 10 (9%) patients were asymptomatic at diagnosis. At the time of EMG, 79 (71.2%) of the patients had been diagnosed with DM in the last 5 years, 25 (22.5%) patients had been diagnosed within 5–10 years, and 7 (6.3%) patients had been diagnosed more than 10 years previously. Median height was 146 cm (range: 95–186 cm) while median weight was 37 (15–90) kg. Median BMI was 17.9 (11.9–35.1). One hundred (90.1%) patients showed no symptoms of DN while 11 (9.9%) were symptomatic during EMG studies. Forty-seven (42.3%) patients had no history of diabetic ketoacidosis prior to EMG while 53 (47.7%) patients had one, 6 (5.4%) patients had two, 4 (3.6%) patients had three, and 1 (0.9%) patient had four previous diabetic ketoacidosis attacks previously. Twenty-five (22.5%) patients were using insulin at doses lower than 0.5 IU/kg, 59 (53.2%) patients were using doses between 0.5 and 1 IU/kg, and 27 (14.3%) patients were using 1–2 IU/kg insulin. Seventeen (15.3%) patients had median HbA1c levels below 7.5, 25 (22.5%) patients had HbA1c levels between 7.5 and 22.5% patients had HbA1c levels between 7.51 and 9, and 69 (62.2%) patients had HbA1c levels above 9.

During EMG, 84 (75.7%) of the patients were unremarkable and 19 (17.1%) patients were diagnosed with sensorial neuropathy in addition to 3 (2.7%) patients with motor neuropathy and 5 (4.5%) patients with sensorimotor neuropathy. The incidence rate of symptomatic DN was 13.5% and the incidence rate of DN diagnosed with EMG was 22.5%.

Following multiple linear regression analysis that included EMG results, sex, median HbA1c levels, diabetes duration, number of prior diabetic ketoacidosis episodes, daily insulin requirement level, presence of neuropathy symptoms, and BMI, a positive correlation was found between DN and diabetes duration (P = 0.002) and between DN and number of previous diabetic ketoacidosis episodes (P = 0.03) (Table). No significant positive relationship was detected for sex, BMI, daily insulin requirement, or DN symptom presence.

4. Discussion

Epidemiologic and clinical features show substantial differences among countries and populations in type 1 DM. The primary goal in type 1 DM management is to prevent and control micro- and macrovascular complications by achieving good glycemic control. It has been long known that there is a positive correlation between diabetes duration and DN prevalence (5,6). Clinical neuropathy is rarely diagnosed in pediatric populations, despite the fact that subclinical neuropathy is quite common, especially in adolescent patients. Nerve conduction studies are the

<table>
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<th>Parameter</th>
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<tr>
<td>HbA1c level</td>
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<tr>
<td>Duration of diabetes</td>
<td>0.002</td>
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<tr>
<td>Number of diabetic ketoacidosis</td>
<td>0.037</td>
</tr>
<tr>
<td>Symptoms of neuropathy</td>
<td>0.986</td>
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gold standard in the detection of DN on the subclinical level. Likewise, our study revealed a positive correlation between diabetes duration and DN (P = 0.002)

Şimşek et al.'s study reported that DN patients tended to be significantly older than the control group (patients without DN). Mean diabetes duration was significantly longer in patients with DN in comparison with controls, as well. There was no significant difference detected in mean HbA1c levels in the past year in DN patients when compared to controls (8). Their results are in accordance with our study findings, which showed no relations between HbA1c levels and DN.

The incidence rate of symptomatic DN was 13.5% in our study. The same rate for DN diagnosed by EMG was calculated as 22.5%. Höllner et al. reported that incidence as 15% in symptomatic DN cases and 38% in DN cases diagnosed by EMG. Their conclusion was that in type 1 DM seen in children and adolescents, diabetic neuropathy has a higher prevalence rate; however, the majority of cases remain subclinical. For this reason, routine nerve conduction velocity (NCV) assessment for DN seems to be beneficial in those patient groups (4). In the EURODIAB study, DN prevalence as diagnosed by electrophysiological studies was 23.5% in 276 children with type 1 DM (5). Our study results seem to be compatible with the results of previously published studies found in the literature. Therefore, we can argue that it is crucial to screen children with type 1 DM for DN, even if they are asymptomatic.

In our study, DN was diagnosed in 3 cases a month after type 1 DM diagnosis was made. Marcus et al. found a significant correlation between NCV and duration of the disease; however, there were a few exceptions. A male patient with a disease duration of 15.5 years had normal NCV results despite showing signs of clinical neuropathy. In addition, two other patients, one with absent reflexes whose DM diagnosis was relatively fresh and one patient diagnosed with diabetes 2 months earlier without neuropathic findings, showed low NCV results. In the former case, one can explain that that decrease in NCV is caused by acute metabolic changes, as suggested by Gregersen; however, in the other patient, one would expect these changes to have returned to the normal range within 2 months (10,13). For this reason, more extensive studies with larger series are necessary on this subject.

Hansen et al. proved that high blood glucose levels for several years is the major factor in the development and progression of microvascular complications related with type 1 DM. Controlling mean blood glucose levels significantly reduces the risk of diabetic microvascular complications. A curve-linear relationship is present between HbA1c levels and DN progression (7). In a more recent study, early defects in NCV could be used as a predictive factor in DN development. However, HbA1c still remains the strongest predictor during the early years of the disease (10). Gregersen and Chantraine also found greater NCV reduction in their younger patients and reported that the change was bigger during the first year of the disease (14,15).

Children with type 1 DM frequently have nerve conduction anomalies without showing any clinical neuroapathy at the time of their diagnosis. The frequency of any anomalies attributed to nerve conduction increases over a 5-year follow-up period. Moreover, duration of the disease and poor glycemic control also are proven to be important risk factors over 5 years as related to the development of subclinical neuropathy (14).

We could not find a correlation between DN incidence rates and mean HbA1c levels. Another multicentric study done in Turkey on pediatric DM patients also did not report a direct relationship between type 1 DM and HbA1c or the incidence rate of neuropathy (8). According to the results of the mentioned study, higher HbA1c levels might increase the incidence of neuropathy if it goes on for a long time.

The EURODIAB study results suggest that, following adjustment for other risk factors and diabetic complications, duration of diabetes, current HbA1c values, changes in HbA1c values during the follow-up period, BMI, and smoking remain independently associated with neuropathy incidence rates. This prospective study also indicated that, apart from glycemic control, the incidence of neuropathy is partially associated with relatively modifiable cardiovascular risk factors that include raised triglyceride levels, BMI, smoking, and hypertension (5). Five years later, in addition to diabetes duration and HbA1c, nephropathy, retinopathy, or a clinical diagnosis of neuropathy was also associated with low NCV and response amplitudes. On the other hand, that study did not find any association with high blood pressure, lipid levels, BMI, waist-to-hip ratio, smoking, or alcohol consumption (11). In the Rochester Diabetic Neuropathy Study, the major risk factors for DN were determined to be poorly controlled diabetes; duration of diabetes, smoking, hypertension, and dyslipidemia were also listed as other risk factors (9). All those mentioned studies were performed with adult patients in a prospective fashion. We were not able to determine serum lipid levels in our patients because of our study’s retrospective status.

We managed to find a positive correlation between DN and diabetic ketoacidosis, which signifies poor management of DM. This finding is compatible with the findings of Marcus et al. (12), Gregersen (13), and Gamstorp et al. (16). Diabetic control assessment is arbitrary, regardless of which criteria are used. Very few if any children can achieve "perfect control", i.e. return to a normal metabolic state. In diabetes, the general
breakdown of normal metabolism might play a major part in DN, and in addition acute changes in motor nerve conduction velocity (MNCV) with use or withdrawal of insulin support this suggestion, as seen in Gregersen’s study (13). Moreover, such a breakdown can be used to explain Ellenberg’s (17) group of patients and our one newly diagnosed patient with very low MNCV in addition to MNCV levels lower than normal ranges in most diabetics. However, it is not able to explain the relatively normal MNCV in some patients with longer diabetes durations.

Hyllienmark et al. reported that nerve dysfunction seen during early periods of the disease is a predictor of clinical neuropathy that might develop several years later. Decreases in baseline peroneal NCV, median NCV, and sural sensory nerve action potential were associated with a significantly increased risk of developing clinical neuropathy in an average of 13 years following initial electrophysiological examination. Forward logistic regression model analysis showed a positive predictive value of an early decrease in peroneal NCV, even when long-term HbA1c levels were accounted for. This unique result once more emphasizes the importance of the role of early NCV measurements in young diabetic patients. The strongest predictor for the development of a clinical neuropathy was poor metabolic control during early periods of the disease (i.e. up to baseline examination) (10).

Samahy et al. suggested that patients with poor glycemic control had longer disease durations, higher diabetic ketoacidosis frequency, and diabetic microvascular complications. These results indicated that, although the majority of patients were on intensive insulin therapy, poor glycemic control was relatively common and diabetic microvascular complications were observed (12).

The main factor that determined the severity of DN course was the age of DM onset. This shows the significance of more accurate control since the DN development risk is higher in children with DM onset at age 12–13. During early stages of DM, conductivity through peripheral nerves correlated with glycosylated hemoglobin and with the frequency of hypoglycemic states (18).

All of our findings suggest that poor metabolic control, especially during early periods of the disease, is a major risk factor for neuropathy development, independently of whether patients are treated with conventional or intensive therapy for the condition. Contrary to intensive therapy from disease onset with reasonably good metabolic control, clinical neuropathy was still seen in 15% of the patients with type 1 DM following an average of 20 years.

In summary, early detection of children and adolescents with suspected NCV anomalies is essential to plan all appropriate measures to be taken for preventing DN development. It is especially important to perform nerve conduction studies for patients who have had long diabetes durations and previous diabetic ketoacidosis episodes. We strongly believe that new studies, especially prospective models with long-term evaluations, would be beneficial in understanding NCV in children with type 1 DM.

References


