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# The correlation of peripheral neuropathy in children suffering from Type 1 diabetes Mellitus (IDDM) with duration of disease and degree of metabolic control by means of electrophysiological methods

Authors
**Dr Sahila Muhammed Kunju[1], Dr S Abdul Gafoor[2*]**
[1]Professor, Department of Physiology, Govt Medical College, Trivandrum
[2]Professor, Department of Physical Medicine and Rehabilitation, Govt Medical College, Kottayam
*Corresponding Author
**Dr S Abdul Gafoor**
Professor & Head, Department of physical Medicine and Rehabilitation, Government Medical College, Kottayam, India
Email: *drsagafoor@gmail.com*

**Abstract**
*Patients with type 1 diabetes develop various complications (micro vascular and macro vascular) that can lead to cardiovascular disease, retinopathy, nephropathy, neuropathy, peripheral vascular disease, and other forms of end-organ damage. Duration and magnitude of hyperglycemia are both strongly correlated with the extent and rate of progression of diabetic micro vascular disease.*
**Objectives:** *To determine the correlation of peripheral neuropathy in children suffering from Type 1 diabetes Mellitus (IDDM) with duration of disease and degree of metabolic control by means of electrophysiological methods.*
**Materials and Method:** *Type 1 diabetic patients attending the Endocrinology outpatient clinic of the SAT Hospital, Thiruvananthapuram were taken as cases. Their detailed history and neurological evaluation are done. All patients undergo electrophysiological evaluation. The results are analysed.*
**Results:** *The degree of nerve abnormality showed correlation with duration of illness and degree of diabetic control. The number of nerves affected by diabetic neuropathy also increased with increasing duration of disease.*
**Conclusion:** *This study emphasizes the need for stricter diabetic control in children with type 1 DM.*
**Keywords:** *Type1 Diabetes Mellitus, Electrophysiological studies, Hyperglycemia.*

## Introduction

Type 1diabetes is characterized by an absolute deficiency of insulin secretion, a generally rapid onset, and a dependence on exogenous insulin at the time of diagnosis. It can present at any age, with over half the cases being diagnosed in childhood. Most cases in children are associated with autoimmune destruction of the pancreatic beta cells. Several genes, especially certain HLA haplotypes, are associated with increased risk of the disease, but environmental factors also play a significant role[1].

In type 1 diabetes mellitus, a genetically susceptible host develops autoimmunity against his or her own beta cells. In most patients, this autoimmune process results in progressive destruction of beta cells until a critical mass of beta cells is lost and insulin deficiency develops. Insulin deficiency in turn leads to the onset of clinical signs and symptoms of type 1 diabetes[2].

At the time of diagnosis, some viable beta cells are still present and these may produce enough insulin to lead to a partial remission of the disease (honeymoon period) but over time, almost all beta cells are destroyed and the patient becomes totally dependent on exogenous insulin for survival. Over time, some of these patients develop secondary complications of diabetes that appear to be related to how well controlled the diabetes has been[2].

It has been recognized for years that the long term complications are a cause of considerable morbidity and mortality worldwide and negatively affect the quality of life in individuals with diabetes with an increase in disability and death. Patients with type 1 diabetes develop various complications (microvascular and macrovascular) that can lead to cardiovascular disease, retinopathy, nephropathy, neuropathy, peripheral vascular disease, and other forms of end-organ damage. Duration and magnitude of hyperglycemia are both strongly correlated with the extent and rate of progression of diabetic microvascular disease[3].

Clinically evident diabetes-related vascular complications may not be common in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of the disease. Childhood and adolescence is a period during which intensive education and treatment may prevent or delay the onset and progression of complications[2].

Diabetic neuropathies constitute a diverse group of conditions. The commonest is a diffuse polyneuropathy which damages distal peripheral nerves, together with the autonomic nervous system.

Neuropathy is a nonspecific term implying an abnormality of nerve. It is often used synonymously and imprecisely with polyneuropathy or peripheral neuropathy, the latter two being equivalent. Polyneuropathy or peripheral neuropathy identifies a predominantly distal, symmetric, functional abnormality of nerves, that begins in the feet and may gradually ascend. Mononeuropathy indicates the presence of abnormality of a single nerve. Multiple mononeuropathy or mononeuropathy multiplex describes the presence of abnormality of more than one nerve. In this multiple nerves are involved, usually in a random, asymmetric manner.

Peripheral neuropathy is a common complication of T1DM, which increases in frequency with the duration of disease. Contrary to the comparatively extensive studies of diabetic neuropathy in adults, diabetic neuropathy in childhood has not received much attention.

The clinical and economic burden of DPN stems from its central role in the pathophysiology of foot ulceration and lower limb amputation, reduction in quality of life and decreased activities of daily living, and susceptibility to falls and fractures. Intensive glycemic control slows the progression of DPN and may even prevent or arrest its development. Diabetic polyneuropathy is underdiagnosed by both endocrinologists and non endocrinologists. The routine evaluation of DPN is based on patient symptoms and a physical examination, which may include the Semmes-Weinstein monofilament and the 128-hertz tuning fork. However, simple screening methods are of limited value in early neuropathy and in the presence of neurological comorbidities. Nerve conduction studies (NCS) are the most sensitive and specific DPN detection method. Their use is recommended for quantitative confirmation of DPN in clinical practice[4].

Nerve Conduction Studies are the gold standard method for the detection of subclinical DN. Standard nerve conduction studies (NCS) allow the physician to directly measure motor and

sensory nerve function of large fibers involved in position and vibration sensation, deep tendon reflex function, and muscle strength. Small diameter fibers, which convey pain and temperature sensation and autonomic function, are not routinely studied. In diabetes where large fiber nerve function is often impaired, NCS are ideally suited to define the extent and severity of disease[2].

**Objectives of the Study**

To determine the correlation of peripheral neuropathy in children suffering from Type 1 diabetes Mellitus (IDDM) with duration of disease and degree of metabolic control by means of electrophysiological methods

**Materials and Methods**

**Study Design:** The present study is a Hospital Based Cross sectional study done on 48 type 1 diabetic patients who attended the Pediatric Endocrinology clinic at the SAT Hospital, Thiruvananthapuram.

**Study Centre:** Department of Pediatric Neurology, Sree Avittom Thirunal (SAT) Hospital, Thiruvananthapuram, Kerala.

**Study Population:** Type 1 diabetic patients attending the Endocrinology outpatient clinic of the SAT Hospital, Thiruvananthapuram were taken as cases.

**Inclusion criteria**

Children and adolescents between 4 -16 years of age with Type 1 DM, receiving insulin therapy.

**Exclusion criteria**

The subjects with the following conditions were excluded from the study

Evidence of any nutritional deficiencies

Any collagen tissue disease or malignancies

Any other neurological disease in the patient

Any familial or hereditary neurological disease history Ethical approval

Research protocol was submitted to the Human Ethical Committee of the institution. The study commenced after getting the clearance from Human Ethical committee (IEC No: 08/30/2011/MCT). A written informed consent was obtained from parents of all patients included in the study.

**Study Method**

Details regarding the patient were collected which included name, age, gender, permanent address, IP Number, diabetic status, duration of diabetes, any symptoms of neuropathy and other complications of diabetes. These were obtained by an oral questionnaire method, case records and discussion with the concerned physician.

**Clinical evaluation and examination**

In these patients, history of subjective neuropathy symptoms was taken and neurological examination was performed. Informed consent was obtained from the parents of each patient after the procedures were fully explained.

The subjective symptoms included numbness, pain, burning feet, and other types of sensory impairment (touch, pain, and temperature), muscle weakness in the limbs, unsteady walking etc.

All patients underwent clinical neurological examination including the superficial somatic sensations (touch and pain), deep somatic sensations (vibration and joint-position sense) as well as the muscle strength and deep tendon reflexes.

**Touch sensations-** The sense of fine touch was evaluated by touching the skin surface with a wisp of cotton. Crude touch was tested by touching the skin with a blunt object. Tactile localisation was tested by asking the patient to localize the site of touch. Tactile discrimination was tested by asking the patient to discriminate between two points touched simultaneously using a blunt divider as two separate points.

**Pain sensations-** Superficial pain was tested with a pin prick. Deep pain was tested by squeezing the muscles and pinching the tendoachillles.

**Vibration and joint position sense-** The sense of vibration was examined by placing a 128 Hz tuning fork on the malleolus in the lower extremity, and on the projecting bone of radius in the upper extremity. The joint-position sense was also tested by asking the patient to imitate a

movement of a limb on the opposite side of the body with eyes closed.

**Reflexes-** The deep tendon reflexes were obtained from the biceps brachi, triceps brachi and brachioradialis in the upper limb and from the quadriceps (patellar reflex) and gastrocnemius (achilles reflex) muscles in the lower limb. The muscle strength was evaluated in each extremity in the direction from distal toward proximal.

**Neurophysiological examination**

The Nerve conduction study of peripheral nerves involves the transcutaneous stimulation of motor or sensory nerves and recording of the elicited action potentials in the muscle (CMAP) and the sensory nerve (SNAP).

**Nerves studied**

Motor, sensory and mixed nerves can be studied by stimulating the nerve with the recording electrodes placed over the distal muscle, a cutaneous sensory nerve or the entire mixed nerve respectively. The findings of the motor, sensory and mixed nerve studies often complement one another and yield different types of information associated with distinct patterns of abnormalities depending on the underlying pathology. In the present study, the standard nerve conduction measurements were performed on the following nerves

**Right upper limb**

1) Median motor and sensory nerves
2) Ulnar motor and sensory nerves

**Right lower limb**

1) Common peroneal nerve
2) Tibial motor nerve
3) Sural sensory nerve

Studies were performed with a standard technique using surface electrodes. Motor nerve conduction velocity (MCV), CMAP amplitude and distal motor latency (DML) were determined in the motor nerves. Sensory nerve conduction velocity (SCV), peak latency and SNAP amplitude were determined in the sensory nerves.

The results of these motor and sensory nerve conduction studies, expressed as amplitudes, conduction velocities, and latencies, yield certain quantitative information and additional qualitative observations regarding the waveform and dispersion of electrical impulses and provide information that is impossible to obtain from the neurologic examination[12]. At least two abnormal independent neurophysiological nerve parameters in a single nerve were accepted as the criteria for the peripheral nerve involvement.[9]

**Statistical Analysis**

The data was entered into a personal computer and analysed using statistical software, Statistical Package for Social Sciences (SPSS) version[17].

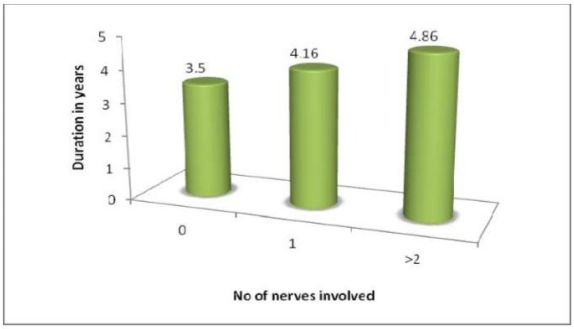
For the analysis, p value <0.05 was considered to be significant. For analysis, the diabetic cases were divided into 3 groups according to their duration of illness - Group 1 <2 years, Group 2 - 2-5 years and Group 3 > 5years. 25% of the patients were in Group 1, 37.5% in Group 2 and 37.5% in Group 3. Mean duration of illness was 3.9 years in the cases. Out of the 48 patients, 18 (37.5%) were found to have peripheral neuropathy as determined by means of electrophysiological method. Of these, only 6(12.5%) had associated symptoms.

Out of the 18 patients with abnormal nerve conduction in this study, 10 were females and 8 were males. No significant difference was found in the incidence of the two. Previous studies have revealed that diabetic males have a higher tendency toward decreased NCVs than diabetic females. 17, 165 The effect of the sex hormone on glucose metabolism might play a role while the thicker subcutaneous fat of females might account for lower amplitude. [20]

Relation between duration of diabetes and number of nerves involved

| Number of nerves involved | Duration in years | | | | | | Total | |
|---|---|---|---|---|---|---|---|---|
| | <2 | | 2-5 | | >5 | | | |
| | N | % | N | % | N | % | N | % |
| 0 | 8 | 66.7 | 15 | 71.4 | 7 | 46.7 | 30 | 62.5 |
| 1 | 2 | 16.7 | 5 | 23.8 | 6 | 40.0 | 13 | 27.1 |
| 2 | 1 | 8.3 | 1 | 4.8 | 2 | 13.3 | 4 | 8.3 |
| 3 | 1 | 8.3 | 0 | 0 | 0 | 0 | 1 | 2.1 |
| Total | 12 | 100.0 | 21 | 100.0 | 15 | 100.0 | 48 | 100.0 |

Number of nerves involved with increasing duration of disease




The number of nerves involved increased with increasing duration of disease. Those patients with involvement of > 2 nerves had a mean duration of illness of 4.86 years.

Correlation between duration of disease and nerve Conduction Parameters

| Nerve conduction parameter | r | p |
|---|---|---|
| Median Motor - Distal Latency | 0.295* | 0.042* |
| Median Motor – NCV | -0.216 | 0.141 |
| Median Motor – Amplitude | 0.033 | 0.822 |
| Median Sensory -Peak Latency | -0.011 | 0.943 |
| Median Sensory –Amplitude | -0.154 | 0.295 |
| Median Sensory – NCV | -0.134 | 0.365 |
| Ulnar Motor - Distal Latency | 0.009 | 0.949 |
| Ulnar Motor - NCV | 0.097 | 0.510 |
| Ulnar Motor - Amplitude | 0.007 | 0.961 |
| Ulnar Sensory - Peak Latency | -0.117 | 0.429 |
| Ulnar Sensory - Amplitude | -0.176 | 0.231 |
| Ulnar Sensory – NCV | -0.201 | 0.172 |
| CPN - Distal Latency | -0.145 | 0.327 |
| CPN - NCV | -0.297* | 0.041* |
| CPN - Amplitude | 0.109 | 0.462 |
| Tibial nerve - Distal Latency | -0.081 | 0.582 |
| Tibial nerve- NCV | -0.304* | 0.036* |
| Tibial nerve - Amplitude | -0.242 | 0.098 |
| Sural Sensory - Peak Latency | -0.020 | 0.903 |
| Sural Sensory- Amplitude | 0.143 | 0.385 |
| Sural Sensory – NCV | -0.045 | 0.782 |

Correlation between HbA1c and Nerve Conduction Parameters

| Nerve Conduction Parameter | r | P |
|---|---|---|
| Median Motor - Distal Latency | 0.296* | 0.041 |
| Median Motor – NCV | -0.207 | 0.157 |
| Median Motor – Amplitude | 0.029 | 0.847 |
| Median Sensory -Peak Latency | -0.273 | 0.061 |
| Median Sensory –Amplitude | 0.189 | 0.197 |
| Median Sensory – NCV | 0.013 | 0.932 |
| Ulnar Motor - Distal Latency | 0.168 | 0.254 |
| Ulnar Motor - NCV | -0.322* | 0.026 |
| Ulnar Motor - Amplitude | 0.093 | 0.531 |
| Ulnar Sensory - Peak Latency | -0.128 | 0.385 |
| Ulnar Sensory - Amplitude | 0.111 | 0.451 |
| Ulnar Sensory - NCV | -0.229 | 0.117 |
| CPN - Distal Latency | 0.147 | 0.318 |
| CPN - NCV | -0.296* | 0.041 |
| CPN - Amplitude | 0.044 | 0.765 |
| Tibial nerve - Distal Latency | 0.207 | 0.158 |
| Tibial nerve - NCV | -0.208 | 0.157 |
| Tibial nerve – Amplitude | -0.164 | 0.267 |
| Sural Sensory- Peak Latency | -0.352* | 0.028 |
| Sural Sensory- Amplitude | -0.019 | 0.910 |
| Sural Sensory - NCV | 0.068 | 0.675 |

**Discussion**

In the present study, we found neuropathy in the lower extremity in 11 patients while that in the upper limb was in 10 patients. Of all the nerves, the sural sensory nerve was the most frequently affected (18.8%).

In diabetic neuropathy, the lower extremities are affected more frequently than the upper extremities. It is a form of polyneuropathy starting from the lower extremities and progressing slowly. Distal nerves are more affected than proximal nerves[8,9].

The prominence of peripheral nerve dysfunction in the lower extremity is related with the length of these nerves. All the necessary proteins which are synthesized in the cell body are transmitted to distal parts of the nerves by axoplasmic flow and maintain the anatomic and functional integrity of the nerve. The interruption of axoplasmic flow which can occur in the early part of the disease itself is more prominent in long nerves than in short nerves. Also, nerve conduction velocity was found to be reduced at the rate of 2.4

Relationship between duration of diabetes and neuropathy

Out of the 48 patients, 13(27.1%) had abnormal nerve conduction in only 1 nerve,4 (8.3%) had abnormal nerve conduction in 2 nerves and 1(2.08 %) had abnormalities in 3 nerve

In the present study there was a definite increase in the number of nerves involved with the duration of the disease.

The mean duration of illness of the patients in this study was 3.9 years while the mean duration of illness of children with peripheral nerve involvement was 4.8 years. The patients who had involvement of more than two nerves had a mean duration of disease of 4.86 years.

Correlation was found between the following factors and the duration of illness:

1) Duration of illness and distal latency of the median motor nerve.
   Pearson's correlation coefficient r =.295. p = 0.042
2) Duration of illness and NCV of the common peroneal nerve.
   Pearson's correlation coefficient r = -0.297. p=0.041
3) Duration of illness and NCV of the tibial nerve.
   Pearson's correlation coefficient r = -0.304. p=0.036

In the present study a significant correlation was found between:

1) HbA1c and distal latency of the median motor nerve
   Pearson's correlation coefficient r =0 .296, p = 0.041
2) HbA1c and NCV of the ulnar motor nerve
   Pearson's correlation coefficient r = -0.322 , p = 0.026
3) HbA1c and NCV of the common peroneal nerve
   Pearson's correlation coefficient r = -0.296. p=0.041
4) HbA1c and peak latency of the sural nerve
   Pearson's correlation coefficient r= -0.352. p=0.028

Progression of DN is related to glycemic control in both type 1 and type 2 diabetes[11,12]. Poor metabolic control is a major determinant of the damage to peripheral and autonomic nerve function in young type 1 diabetics[3,13]. The finding of this study emphasizes the importance of high glycaemic levels in determining the initial electrophysiological alterations of the nerve fibers while still in the subclinical stages.

Increased activity of the polyol pathway and an altered myoinositol metabolism within the nerve cell provides the most accredited hypothesis in explaining diabetic neuropathy and, therefore good metabolic control improves nervous cell metabolism.

Lowering levels of HbA1c retards the deterioration in both NCV and symptoms and signs of neuropathy. The magnitude of the reduction is such that it has been proposed that clinically overt diabetic neuropathy may even be prevented. The strongest predictor for the development of a clinical neuropathy is HbA1c during the first years of the disease. HbA1c should ideally be at 7% or lower to decrease the risk of nerve damage by more than 50%, which stresses the importance of good metabolic control during the early years of diabetes[14].

## Conclusion

The degree of nerve abnormality showed correlation with duration of illness and degree of diabetic control which further emphasizes the need for stricter diabetic control in children with type 1 DM.

The number of nerves affected by diabetic neuropathy also increased with increasing duration of disease.

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