ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 16, Issue 9, 2023

Online - 2455-3891
Print - 0974-2441

Research Article

NEUROLOGICAL ABNORMALITIES IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

RAKESH JANGIR[1], SENGAR GS[1], TUSHAR DWIVEDI[1], NISHANT ASWANI[2]*

[1]Department of Pediatrics, Sardar Patel Medical College, Bikaner, Rajasthan, India. [2]Department of Pediatrics, American Institute of Medical Sciences, Udaipur, Rajasthan, India.
***Corresponding author: Dr. Nishant Aswani; E mail: nishant_udr@yahoo.co.in**

Received: 15 March 2023, Revised and Accepted: 28 April 2023

ABSTRACT

Objective: The objective of the study is to find out the prevalence of neurological abnormalities in children between 5 and 15 years with type-1 diabetes mellitus (T1DM) of at least 2 years duration and the risk factors associated with the development of neurological abnormalities.

Methods: Hospital-based cross-sectional study on 150 Children of 5–15 years of age having type I diabetes of at least 2 years' duration by simple random sampling fulfilling the inclusion criteria, at Department of Pediatric Medicine, Sardar Patel Medical College and P.B.M. Hospital Bikaner.

Results: Mean age was 10.9±3.6 years, male to female ratio was 1.63:1. The prevalence of peripheral neuropathy was 42.3% when 1 abnormal attribute in at least 1 nerve was considered, it was 7.3% when 2 abnormal attributes in 2 nerves were considered, 4.6% had autonomic neuropathy and 4% had cognitive abnormalities. The peripheral neuropathy was subclinical in a substantial number of cases as up to 39.4% and 39.3% of T1DM cases having peripheral neuropathy had normal neuropathic symptom score and neuropathic disability score, respectively. Female with longer duration of diabetes, higher mean age of diagnosis, and higher mean HbA1c level were significantly more likely to develop peripheral neuropathy.

Conclusion: Neurological complications begin quite early and insidiously in T1DM patients highlighting the importance of early and regular screening by nerve conduction study.

Keywords: Children, Neurological abnormalities, Type 1 diabetes mellitus.

 DOI: http://dx.doi.org/10.22159/ajpcr.2023v16i9.47850. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Among the disorders observed in childhood and adolescence type 1 diabetes mellitus (T1DM) is most common. The cause of type 1 diabetes is unknown, but it is believed to involve a combination of genetic and environmental factors. The notion that DM impacts brain function and structure is not new [1].

It has been reported that the prevalence of subclinical diabetic neuropathy in children with T1DM ranges between 17% and 63% [2]. Although it is well-known that T1DM is associated with neurocognitive impairments [3], there are still some open debates regarding which abilities are impaired, their appearance according to disease acquisition, and their underlying mechanisms [4]. Understanding the full impact of T1DM on the brain, especially in children and adolescents, is a key period for the development of brain matter as well as cognitive functions [5]. Chronic sensorimotor diabetic neuropathy can affect up to 50% of children with poor glycemic control after a long duration of illness if the patients do not receive necessary treatment on time [6].

Diabetic neuropathy can be one of the most frustrating and chronically debilitating complications owing to the associated pain, discomfort, and disability. The use of physiological insulin substituents as well as frequent patient monitoring of blood sugar levels in developed countries had led to good diabetic control which can significantly offset the onset of both neural and vascular complications. However, in the case of resource-poor countries like ours, the management of T1DM still poses major setbacks. An early diagnosis of diabetic neuropathy and the identification of factors predisposing to its development can aid in risk stratification while facilitating the selection of cases requiring targeted interventions. In addition, to date, the studies on the characterization of neuropathy in children are still scarce. The current study, therefore, aims to detect the prevalence of peripheral neuropathy in children with T1DM and associated factors. The cognitive and behavioral impairments associated with T1DM were also studied.

Aim

The objective of the study is to find out the prevalence of neurological abnormalities in children between 5 and 15 years with T1DM of at least 2 years duration and the risk factors associated with the development of neurological abnormalities.

METHODS

Hospital-based cross-sectional study was conducted on 150 Children of 5–15 years of age having type I diabetes of at least 2 years duration by simple random sampling fulfilling the inclusion criteria, at the Department of Pediatric Medicine, Sardar Patel Medical College and P.B.M. Hospital Bikaner. Children between 5 and 15 years with T1DM of at least 2 years duration were included. Children <5 years and more than 15 years, T1DM with a duration <2 years, T1DM on medication predisposing to neurological complications such as chemotherapy, ART, A.T.T, anti-fungal, and anti-epileptic Pre existing neurological disorder, with underlying disorders of peripheral nerves, Not willing to participate were excluded from the study.

Sample size

The prevalence of neurological complications as reported in previous studies varies from 30.00% to 50.00% [7]. An average prevalence of 40.00% was taken for sample size calculation. $n=4pq/d^2$. Taking the allowable error (20.00%) of the reported prevalence of 40% the sample size was calculated to be 150 subjects.

A comprehensive history taking (demographical characteristics, attack of diabetic ketoacidosis, neurological symptoms, sensory and motor involvement), physical examination, and laboratory investigations were carried out and data was collected as per pre-designed pro forma. Neuropathy symptom score (NSS) and neuropathy disability score

(NDS) criteria were used for the diagnosis of diabetic neuropathy [8]. Modified MMSE for use in children as adopted by Jain and Passi was administered to assess the higher mental function [9].

The study was commenced after obtaining clearance from the institutional ethical committee. Informed written consent of the study population was taken.

RESULTS

A total of 150 patients between the ages of 5–15 years with a diagnosis of T1DM were included in our study. The maximum number of cases was in 12–15 years of age group (61.33% cases), followed by 9–12 years (32% cases), while the remaining 6.67% cases were in the age group of 5–9 years. The mean age of our study participants was 10.9±3.6 years. The male-to-female ratio was 1.63:1.The mean age of cases at the time of diagnosis was 7.3±2.7 years. Majority of the cases were having the disease for 4–6 years (48%), the mean duration of T1DM in our cases was 4.2±1.9 years (Table 1).

A majority of cases had normal NSS (72.7% cases). However, the remaining 21 (14%) and 20 (13.3%) patients had 1 and 2 scores of NSS. Majority of cases (66%) had a normal NDS scoring. However, 28% of cases had NDS score 1, while the remaining 6% had NDS score 2 (Table 2).

Ninety-nine cases of T1DM had normal NDS out of which 39.3% had peripheral neuropathy while peripheral neuropathy was present in 45% of cases having abnormal NDS. It suggests that peripheral neuropathy can be present irrespective of NDS score positivity. 109 T1DM patients in our study had normal NSS, out of them 39.4% were found to have peripheral neuropathy and 46.3% with abnormal NSS had peripheral neuropathy in nerve conduction study. Thereby indicating that peripheral neuropathy was occurring in similar proportions without regard to the presence of neuropathy symptoms.

On the basis of the results of the nerve conduction study for sensory and motor nerve neuropathy, the cases were divided into two groups, namely group A and group B. While group A constituted cases without neuropathy on NCV, in group B cases with neuropathy on NCV were included.

The prevalence of peripheral neuropathy, i.e., cases having one abnormal attribute in at least one nerve in NCV in our study was 41.3% (62 out of 150 cases), and on the basis of these results in nerve conduction study displaying 2 abnormal attributes. Only 7.3% of cases were defined as having peripheral neuropathy (Table 3).

Table 1: Distribution of cases according to age

Sociodemography	Number of patients (n=150), n (%)
Age distribution (years)	
5–9	10 (6.67)
>9–12	48 (32)
>12–15	92 (61.33)
Gender	
Male	93 (62)
Female	57 (38)
Duration of diabetes (years)	
2–4	41 (27.3)
>4–6	72 (48)
>6–8	37 (24.7)

Autonomic neuropathy was present in 4.8% of cases having peripheral neuropathy (group B) while it was present in 4.5% of cases who did not have peripheral neuropathy (group A). There was no statistically significant difference in the prevalence of autonomic neuropathy in group A and group B. In our study, cognitive dysfunction was present in 4% of cases. Maximum prevalence was in >5–8 years of age group.

The mean age of cases without neuropathy was 10.2±3.4 years, while that of cases with neuropathy was 11.6±4.2 years (p=0.07). The prevalence of neuropathy was significantly more in females (50.8%) as compared to male (35.8%), DM patients (p=0.03). In group A, positive family history was found in 7.9% of cases. While in group B (children with peripheral neuropathy), family history was present in 19.3% of cases (p=0.0001). The anthropometric parameters were comparable between the two groups of patients (with neuropathy vs. without neuropathy) (Table 4).

The mean duration of T1DM in group A was 3.6±2.6 years, while that in group B was 4.3±2.1 years (p=0.04). While the mean age of diagnosis of T1DM was 6.4±2.6 years in group A, in group B it was significantly higher with the mean duration being 7.1±2.9 years. (p=0.03). The mean Hb1ac level was also significantly higher in children having peripheral neuropathy (8.6±2.4%) than in those who did not (7.3±1.5%). There was a significantly positive association between high Hb1ac levels and the presence of neuropathy (p=0.001) (Table 4). Other laboratory parameters including serum urea, creatinine, and ESR were comparable between the two groups. No significant association of peripheral neuropathy was found between mean urea, creatinine, and ESR value in our study.

66 (44%) patients required ≤1 U/kg/day insulin for the management of their T1DM, while the remaining 84 (66%) cases required 1–2 U/kg/day insulin. The requirement of insulin in patients from groups and group B was similar and comparable with no significant difference. The Chi-square statistic was 0.9032 and the p=0.34 (Fig. 1).

In our study, in patients with neuropathy the following percentage of changes were seen: Median nerve (motor branch) - There was 50% rise in mean distal latency, 12.5% fall in peak amplitude and 24.16% fall in mean velocity in patients with neuropathy. Common peroneal nerve - There was 16.12% rise in mean distal latency, 14.29% fall in peak amplitude, and 21.55% fall in mean velocity in patients with neuropathy. Ulnar nerve - There was 36.84% rise in mean distal latency, 5.19% fall in peak amplitude, and 13.79% fall in mean velocity in patients with neuropathy. Median nerve (sensory branch) - There was 41.37% rise in mean distal latency, 9.01% fall in peak amplitude, and 24.19% fall in mean velocity in patients with neuropathy. Sural nerve - There was 63.37% rise in mean distal latency, 10.88% fall in peak amplitude, and 10.30% fall in mean velocity in patients with neuropathy. Over all greatest change was seen in the distal latency of sural and motor branch of the median nerve (Table 5).

DISCUSSION

Considering a single abnormal attribute in at least 1 nerve, the observed prevalence of subclinical neuropathy in our cross-sectional study was

Table 2: Neuropathy symptom score, neuropathy disability score

NSS	Peripheral neuropathy present, n (%)	Peripheral neuropathy absent, n (%)	Total	p
NSS normal	43 (39.4)	66 (60.6)	109	0.64
NSS abnormal	19 (46.3)	22 (53.7)	41	
Total	62	88	150	
NDS				
NDS normal	39 (39.3)	60 (60.7)	99	0.57
NDS abnormal	23 (45)	28 (55)	51	

NSS: Neuropathy symptom score, NDS: Neuropathy disability score

high. The prevalence of peripheral neuropathy with NCV in our study was 42.3% (62 out of 150 cases). Similar results have been reported by Barbosa *et al*. with a reported prevalence of diabetic neuropathy in T1DM being 42.8% [10]. While Maahs *et al*. have reported the prevalence of diabetic neuropathy to be 22.7% which, was significantly lower than ours, the results of Miralles-García *et al*. are similar to ours with 54% prevalence rate [11,12].

However, most of the recent studies have considered at least 2 abnormal attributes of 2 nerves to define peripheral neuropathy. On the basis of these results in a nerve conduction study displaying 2 abnormal attributes only 7.3% of cases were defined as having peripheral neuropathy. This finding is similar to Hajas *et al*. who had reported 2 or more abnormal attributes in 2 nerves in 17.7% of cases [13].

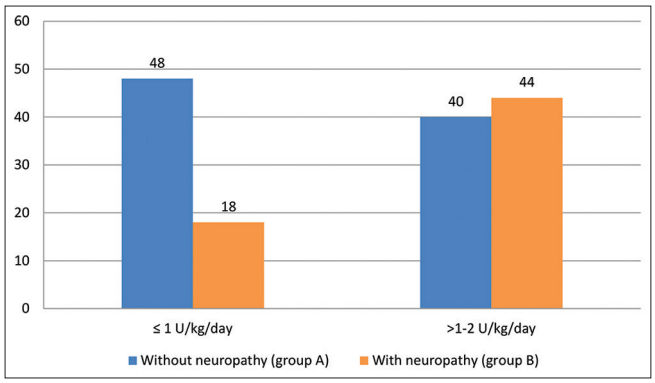

Fig. 1: Peripheral neuropathy in relation to daily insulin requirement

Table 3: Prevalence of nurological abnormality

Peripheral neuropathy	Number of cases (%)
One abnormal attribute in at least one nerve in NCV	
Absent (Group A)	88 (58.7)
Present (Group B)	62 (41.3)
2 abnormal attribute in at least 2 nerves on NCV	
Absent	139 (92.7)
Present	11 (7.3)
Autonomic neuropathy	
Present	7 (4.6)
Absent	143 (95.4)
Cognitive dysfunction (abnormal MMSE score according to age)	
>5–8 years (9)	1 (11)
9–11 years (46)	1 (2.1)
>12 years (95)	4 (4.25)

NCV: Nerve conduction velocity, MMSE: Mini-mental state examination

In this study, the delays in distal latencies were highly significant in group B with neuropathy when compared to group A. These results are in accordance with the findings of Shrivastava *et al*. who found a significant correlation between the duration of type 1 diabetes and prolongation of P100 latencies [14]. The reduction in mean amplitude values was also highly significant in group B when compared to group A in our study. These results are compatible with the findings of Shrivastava *et al*.[14] and Gupta and Deshpande [15].

Majority of the attributes in electrophysiological study of nerves were abnormal in cases having peripheral neuropathy. A maximum percentage rise in distant latency was observed in the sural nerve (63.64%) followed by the median nerve (50%). Maximum percentage falls in nerve conduction velocity (NCV) was observed in the median nerve (24.6%) and common peroneal nerve (21.5%). A maximum percentage fall in peak amplitude was observed in common peroneal nerve (14.29%) in cases with peripheral neuropathy. Mean peak amplitude did not significantly differ between group A and group B except in common peroneal nerve.

In agreement with previous studies, all the NCS indices in our study showed compatible changes in patients with diabetic neuropathy, namely lower velocities and higher latencies of both sensory and motor nerves [16]. According to Hajas *et al*., DPN was diagnosed in 24% with 17.8% TIDM children having subclinical neuropathy [13]. Their study showed a significant decrease in velocity and amplitude of the tibial motor, peroneal motor, and sural sensory nerves. In our study we observed that out of total of 150 patients studied, the most commonly affected nerve was a common peroneal nerve in 37 (24.7%) cases, followed by the ulnar nerve in 14 (9.3%) cases, sural nerve in 11 (7.3%) cases. The motor branch of the median nerve was affected only in 6 (4%) cases, while 5 (3.3%) cases had involvement of the sensory branch of the median nerve.

The patients with neuropathy in our study were older, had a longer duration of TIDM and low body mass index (BMI). Mean blood glucose and HbA1c level was high among those with neuropathy. The predictors for neuropathy that were considered in our study were age, sex, weight, height, hypoglycemia at evaluation, abnormal renal function test, ESR, and family history of diabetes. The acquaintance of predictors for DPN is clinically valuable because it provides a window of opportunity for prevention and delaying the occurrence of these complications. Considering 1 abnormal attribute of at least 2 separate nerves, a statistically significant relation between neuropathy and predictors could not be established. However, with 2 abnormal attributes for 2

Table 4: Analysis of cases with and without neuropathy

Variable	Without neuropathy (Group A)	With neuropathy (Group B)	p
Mean age (years)	10.2±3.4	11.6±4.2	0.07
Gender			
Males (n=93)	60 (68.18)	33 (53.22)	0.03
Females (n=57)	28 (31.82)	29 (46.78)	
Family history			
Present (n=19)	7 (7.9)	12 (19.3)	0.0001
Absent (n=131)	81 (92.1)	50 (80.7)	
Mean weight z score±SD	29.66±7.34–0.5±1.3	28.07±7.21–0.7±1.5	0.41
Mean height (m)	1.3 (0.8–1.6) ±0.5	1.2 (0.9–1.6) ±0.6	0.22
Mean BMI (kg/m^2)	18.9±1.8	19.4±1.9	0.13
BMI range (kg/m^2)	13.8–22.9	14.3–23.7	0.22
Clinical parameters			
Mean duration of diabetes (years)	3.1±1.6	3.9±2.1	0.04
Mean age of diagnosis	7.4±2.6	7.5±2.9	0.03
Mean HbA1c levels (%)	11.5±1.5	12.7±2.4	0.001
Mean RBS (mg/dL)	189±45.8	221±51.2	0.03

RBS: Random blood sugar, HbA1c: Hemoglobin A1C, BMI: Body mass index, SD: Standard deviation

Table 5: Electrophysiological profile of patients with and without neuropathy

Variable	Without neuropathy (Group A)	With neuropathy (Group B)	p
Motor			
Median nerve			
Mean distal latency	2.6±0.6	3.9±0.8 ms	0.001
Mean peak amplitude	12.8±2.6 mV	11.2±3.1 years	0.31
Mean velocity±SD (m/s)	68.7±5.9	52.1±8.2	0.03
Common peroneal nerve			
Mean distal latency	3.1±1.8	3.6±2.7 ms	0.01
Mean peak amplitude	4.2±1.7 mV	3.6±3.1 years	0.04
Mean velocity (m/s)	54.3±10.8	42.6±7.9	0.02
Ulnar nerve			
Mean distal latency	1.9±0.3	2.6±1 ms	0.004
Mean peak amplitude	7.7±1.5 mV	7.3±1.3 years	0.21
Mean velocity (m/s)	58.7±6.8	50.6±13.9	0.03
Sensory			
Median nerve			
Mean distal latency	2.9±1.1	4.1±1.2 ms	0.001
Mean peak amplitude	12.2±3.1 mV	11.1±3.5 years	0.23
Mean velocity (m/s)	67.8±7.7	51.4±9.5	0.02
Sural nerve			
Mean distal latency	1.1±0.3	1.8±0.8 ms	0.001
Mean peak amplitude	14.7±3.8 mV	16.3±4.2 years	0.09
Mean velocity (m/s)	108.7±74.1	97.5±80.2	0.30

SD: Standard deviation

separate nerves the neuropathy was significantly associated with BMI i.e., children with subclinical neuropathy in our study had lower BMI. This disparity could be due to the smaller sample size of the study population. As with our study, Unnikrishnan *et al*. and Amutha *et al*. did not report any significant association between any of the risk factors and DPN [17,18]. Similarly, a study by Toopchizadeh *et al*. in their study had a longer duration of diabetes and high HbA1c in patients with neuropathy compared to those without neuropathy, but this difference was not statistically significant [19].

In other Indian studies, Ramachandran *et al.* and Kumar *et al*. showed the statistically significant relationship of the duration of disease, glycemic control, and hypertension with DPN [20,21]. There was a significant correlation of neuropathy in our study with a longer duration of T1DM, high Hb1ac levels, early age of onset of T1DM, and high RBS levels. These results were contrasting with the observation of Walter-Höliner *et al*. who discovered that NCV and the presence of clinically evident DPN were not significantly associated with age, sex, duration of diabetes, BMI, HbAlc level, LDL or HDL levels, levels of vitamin B12 and E [22].

Unikrishnan *et al.* had 535 TIDM patients with the mean age at diagnosis 12+5.4 years, 53% being male. Mean HbAlc level was 9.3 2.3%. The mean BMI was 17.4+4.3 kg/m^2 [18]. Amutha *et al*. enrolled 108 patients with TIDM with mean age of 18.8=6.2 years, mean age at diagnosis of 17+4.3 years, and mean duration of TIDM 2.2+3.7 years with a mean HbAlc level of 10.3+2.9% [17]. While in our study the sample size was almost similar to Amutha *et al*. with a significantly younger mean age.

The duration of DM and mean HbA1c levels was higher in most of the studies than what we observed in our study group [20]. However, the mean Hb1ac level of Unnikrishnan *et al*. and Amutha *et al*. was comparable with our study population [17,18]. However, these studies had a mean duration of diabetes greater than our cohort, the reason may be that they had included children and adolescents with at least 5 years of DM.

Our analysis also revealed that cognitive impairments in T1DM patients were minimal. Only 4% of cases had an abnormal MMSE. Maximum prevalence was in >5–8 years. A handful of reports have found evidence of central nervous system involvement for T1DM-affected children. In their studies, Wilkinson *et al*. and Greig *et al*. found minor cognitive impairment in patients affected with T1DM [23,24]. Although unlike previous reports there was no significant association of cognitive impairment with diabetic neuropathy in our work.

Clinically, white matter hyperintensity has been reported to play an important role in cognitive dysfunction and prevalent neuropathies in T1DM patients. In our study, the MMSE score was normal in 95.92% cases. This result is contrasting with Ding *et al*. who reported significantly lower scores for MMSE on orientation and language of T1DM patients than those of healthy controls [25].

Autonomic neuropathy can be one grave consequence of uncontrolled T2DM. It can lead to resting tachycardia, silent myocardial ischemia, and arrhythmia. It may be detected by evaluating resting tachycardia, loss of sinus arrhythmia, and heart rate response to Valsalva maneuver. In our study, only 4.67% of cases had autonomic neuropathy with 4 patients in group A and 3 in group B. Similar results have been reported by Khoharo *et al*. [26].

CONCLUSION

The peripheral neuropathy was subclinical in a substantial number of cases as up to 39.4% and 39.3% T1DM cases having peripheral neuropathy had normal Neuropathic symptom score and neuropathic disability score, respectively. The prevalence of Autonomic neuropathy and cognitive abnormalities was found to be 4.6% and 4%, respectively. Longer duration of illness, female sex, family history of diabetes, and higher mean HbA1c level were significantly related to a higher prevalence of peripheral neuropathy. The study suggests that neurological complications begin quite early and insidiously in T1DM patients highlighting the importance of early and regular screening by nerve conduction study.

ACKNOWLEDGMENT

We are so thankful to everyone who provided encouragement and support throughout the study.

AUTHORS' CONTRIBUTION

All the authors have contributed equally.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR'S FUNDING

The authors hereby declare that no financial support was taken from anyone for this research, authorship or publication of this article.

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