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A Study on Clinical Profile of Children with Peripheral Neuropathy and Type 1 Diabetes Mellitus

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ABSTRACT
Attention towards management of Type 1 Diabetes Mellitus and related complications is overshadowed by enormity and exponentially rising incidence of Type 2 Diabetes Mellitus, i.e., an estimated 366 million adult's world-over. In the epidemic of Type 2 D diabetes Mellitus, the rising incidence of type 1 diabetes mellitus among young children and adolescents is not gaining global recognition. The study design was approved by the institutional ethical committee. Informed written consent was obtained from parents/care givers of children before enrollment. History, physical and neurological examination findings were recorded on pre structured and pre-designed profroma. Children with Type 1 Diabetes Mellitus with the duration of disease being at least 5 years were included in the study and were assessed for eligibility. Majority (84.6%) of demyelinating neuropathy was observed in patients with 5-9 years' of disease duration and 100% of motor axonal neuropathy was observed in patients with disease duration of 5-9 years.

INTRODUCTION

Inadequate insulin secretion and/or reduced tissue response to insulin in hormone regulated metabolic pathway results in abnormalities of carbohydrates, lipids and protein metabolism at the cellular level. This state of functional insulin deficiency is termed as Diabetes Mellitus, irrespective of the etiology causing insulin deficiency or its resistance Type 1 Diabetes Mellitus: Due to pancreatic ß-cell destruction, causing absolute deficiency of Insulin, also termed as Insulin dependent diabetes mellitus. Type 2 Diabetes Mellitus: Due to combination of inadequate insulin secretion and resistance to insulin action at the tissue level[1,2]. Attention towards management of Type 1 Diabetes Mellitus and related complications is overshadowed by enormity and exponentially rising incidence of Type 2 Diabetes Mellitus, i.e., an estimated 366 million adults world-over. In the epidemic of Type 2 D diabetes Mellitus, the rising incidence of type 1 diabetes mellitus among young children and adolescents is not gaining global recognition. India shares the highest disease burden in the world with every fifth Type1 DM and every seventh Type 2 DM being an Indian[3,4]. Approximately 80,000 children below the age of 15 years are estimated to develop Type 1 Diabetes annually worldwide. Out of the 4, 90,000 children living with this disorder, 24% are in the European region and 23% in the South-East Asian region. Of the estimated 4, 90,000 children with Type 1 DM, India share the burden of housing 97,700. Chennai has reported an urban incidence of 10.5/100,000 population in 1996. Karnataka state T1DM registry listed an incidence of 3.7/100,000 in boys and 4.0/100,000 in girls[5,6].

MATERIALS AND METHODS

Source of Data: Children with Type 1 diabetes mellitus (with duration >5 years) attending diabetic clinic were enrolled into the study.

Type of Study: Hospital based cross sectional study.

Method of Data Collection: The study design was approved by the institutional ethical committee. Informed written consent was obtained from parents/care givers of children before enrollment. History, physical and neurological examination findings were recorded on pre structured and pre-designed profroma. Children with Type 1 Diabetes Mellitus with the duration of disease being at least 5 years were included in the study and were assessed for eligibility.

Nerve Conduction Study: NCS was performed after explaining the procedure to the parents and the child. It was done by using standard "Allengers Scorpio Electromyography machine". Stimulating electrode was placed on the nerve surface and the response was recorded by placing two electrodes G1 and G2. Median and ulnar nerves from the upper limb and tibial, sural and peroneal nerve from the lower limb were selected. NCS was conducted by the same technician and reporting was done by the same Pediatric neurologist for all 95 patients. At the time of visit, samples for blood glucose, HbA1c, liver function test, urea and creatinine were sent. Along with this, all children were subjected for ophthalmological examination by experienced ophthalmologists to look for diabetic changes. HbA1c reports of previous one year were collected and mean was calculated and were designated, good control, fair control and poor control based on HbA1c range of $\leq$7.5, 7.6-9.9 and $\geq$10 respectively.

Inclusion Criteria: Children diagnosed with Type 1 Diabetes Mellitus with duration of illness >5 years enrolled in Diabetic clinic.

Exclusion Criteria: Children with Type 1 Diabetes Mellitus with history and examination suggestive of other neuropathies:

- Malnutrition.
- Neuromuscular diseases.
- Connective tissue disorders.
- Prolonged hospitalization for any reason.

RESULTS AND DISCUSSIONS

Table 1: Age Distribution of Study Population

Age Group	N	%
6-10 Years	38	40
10-15 Years	37	39
15-18 Years	20	21
Total	95	100

Out of 95 participants, 38(40%) were between of 6-10 years, 37(39%) were between 10-15 years and 20(21%) were between 15-18 year.

Table 2: Sex Distribution of Study Population

Gender	n	%
Male	40	42
Female	55	58
Total	95	100

Out of 95 participants, 40(42%) were males and 55(58%) were females, with male to female ratio of 1:1.3.

Table 3: Baseline Characteristics of Study Population (N=95)

Mean Age of Study Population	11.8 years
Mean Age at Onset	5.5 years
Mean Duration of Illness	6.3 years
Retinopathy	Nil
Clinical Neuropathy	Nil

Majority (84.6%) of demyelinating neuropathy was observed in patients with 5-9 years' of disease duration and 100% of motor axonal neuropathy was observed in patients with disease duration of 5-9 years. No significant association could be established. Mean HbA1c values of normal, motor axonal and

Table 4: Distribution of Duration of Illness Between Types of Neuropathy

		Duration Off Illness				
		5-9 Years	10-14 Years	>15 Years	Total	P value
Normal	Count	47	2	0	49	0.285
	% of Total	49.5%	2.1%	0.0%	51.6%	
Motor Axonal Neuropathy	Count	7	0	0	7	
	% of Total	7.4%	0.0%	0.0%	7.4%	
Mild Demyelinating Motor Neuropathy	Count	33	4	2	39	
	% of Total	34.7%	4.2%	2.1%	41.1%	
Total	Count	87	6	2	95	
	% of Total	91.6%	6.3%	2.1%	100.0%	

Table 5: Comparison of Mean HbA1c Values Between Types of Neuropathy

NCV	N	Mean	Min.	Max.
Normal	49	10.88	7.4	14.2
Motor axonal	7	11.17	9.2	13.5
Mild demyelinating motor	39	10.98	8.1	14.3
Total	95	10.9	7.4	14.3

Table 6: Distribution of Glycemic Control Between Types of Neuropathy

		HbA1c (Glycemic Controle)				
		Good control <7.5	Fair control 7.6-9.9	Poor control >10	Total	P value
Normal	Count	1	22	26	49	0.024
	% of Total	2%	44.9%	53.1%	100%	
Motor Axonal Neuropathy	Count	0	1	6	7	
	% of Total	0.0%	14.3%	85.7%	100%	
Mild Demyelinating Motor Neuropathy	Count	0	6	33	39	
	% of Total	0.0%	15.4%	84.6%	100%	
Total	Count	1	29	65	95	
	% of Total	1.1%	30.5%	68.4%	100.0%	

Table 7: Distribution of Types of Neuropathy in Upper and Lower Extremities

	Distribution of Neuropathy				
	Both upper and lower limb	Lower Limb	Upper Limb	Total	P value
Motor axonal neuropathy	0	3	1	4	0.367
	0.0%	12.0%	4.0%	16.0%	
Mild demyelinating motor neuropathy	1	19	1	21	
	4.0%	76.0%	4.0%	84.0%	
	1	22	2	25	
	4.0%	88.0%	8.0%	100.0%	

demyelinating neuropathy were 10.88, 11.17 and 10.98 respectively. Minimum and maximum in axonal neuropathy were 9.2 and 13.5 respectively. In demyelinating neuropathy minimum and maximum were 8.1 and 14.3 respectively. As the glycemic control worsened from good to fair to poor control, proportion of axonal neuropathy increased from 0-14.3-85.7%. A similar increase in proportion of demyelinating neuropathy from 0-15.4-84.6% was observed with p value of 0.024 (<0.05). Out of 25 participants with neuropathy, 22(88%) had lower limb involvement, 2(8%) had upper limb involvement and 1(4%) had both neuropathy in upper and lower limb involvement. Diabetic neuropathy was predominantly seen in lower limb in agreement with theoretical explanation and practical observations reported by clinical studies. Diabetic neuropathy is one of the major complications of type 1 diabetes. Subclinical neuropathy is more common when compared to clinical neuropathy. It affects around 60% of patients with diabetes. Clinical symptoms are rarely seen in patients with Type 1 DM. When tissues are exposed to hyperglycemia, intracellular glucose gets converted to sorbitol, leads to a decrease in the levels of myoinositol causing tissue damage. Hyperglycemia causes glycosylation of protein. Elevated glucose converts myelin to glycosylated myelin, which are endocytosed by macrophage leading to segmental demyelinating. This advanced glycosylated end (AGE) products modify not only myelin, but also tubulin, neurofilaments and actin. This alteration in cytoskeleton causes axonal atrophy, degeneration and impaired axonal transport[7]. Recently it was found that the receptors for AGE (RAGE) interacts with AGEs of peripheral nerve, activates transcription of pro inflammatory genes, which leads to increased oxidative cellular damage. Hyperglycemia causes inflammation of endoneural, epineural and perineural blood vessels leading to ischemia of peripheral nerves. This results in the decrease of motor conduction velocity and axoplasmic transport. Other factors that may contribute to peripheral neuropathy are oxidative stress, genetic variation and autoimmunity[8].

Neuropathy is Defined as Presence of 2 or More of the Following: Neuropathic symptoms decreased distal sensation, decreased or absent ankle reflexes. Confirmation of neuropathy requires nerve conduction studies. In diabetic neuropathy there is an early involvement of small diameter axons, thus skin biopsy

is helpful. Corneal confocal microscopy is a non-invasive method to diagnose neuropathy which is more sensitive than skin biopsy and NCS. Changes can be seen in motor nerve conduction, sensory nerve conduction and F response. Abnormalities are mainly in the form of decrease in amplitude and increase in the latency of motor or sensory action potential depending on site and type of lesion. It was observed that conduction velocity decreased by 0.5m/s/year in diabetics[9]. The main aim of treatment includes glycemic control which reduces the risk and progression of neuropathy. Diet modification and exercise helps in regeneration of small nerve fibers. Some newer drugs like reactive oxygen inhibitors, aldose reductase inhibitors and protein kinase C beta inhibitors are under trial. Pain management includes tricyclic anti-depressants, anti consultants or serotonin norepinephrine reuptake inhibitors. But most commonly used are duloxetine or pregabalin.

CONCLUSION

- As the glycemic control worsened from good to fair to poor control, proportion of axonal neuropathy increased from 0-14.3-85.7%. A similar increase in proportion of demyelinating neuropathy from 0-15.4-84.6% was observed with p value of 0.024 (<0.05).
- Out of 25 participants with neuropathy, 22(88%) had lower limb involvement, 2(8%) had upper limb involvement and 1(4%) had both neuropathy in upper and lower limb involvement.

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