DISTAL POLYEUROPATHY IN NON-INSULIN DEPENDENT DIABETES MELLITUS

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Summary

Pattern of peripheral neuropathy in 838 subjects of NIDDM, (478 males and 360 females) varying in age from 25 years to 65 years has been analysed. The study was conducted over 3 years (1984 to 1986). Distal polyneuropathy was encountered in 64% ($p<0.05$) being more frequent in advanced age ($p<0.001$), and the long duration of diabetes (16 to 20yrs.) ($p<0.05$). Autonomic neuropathy was a common accompaniment (43%). Patients on low caloric diet had higher incidence of polyneuropathy while the blood sugar level had no direct relationship. Elevated serum triglycerides and low HDL cholesterol was associated with higher incidence of polyneuropathy. Large Vessel Disease (LVD) in the form of Peripheral vascular disease (P.V.D.) was found in 34.9%, Cerebrovascular accidents (C.V.A.) in 31% and Ischaemic Heart Disease (I.H.D.) in 32.2% cases of polyneuropathy. S.V.D. in the form of Retinopathy, nephropathy was detected in 24.36% and 62.35% respectively. Presence of distal polyneuropathy even after glycaemic control (180 out of 296 eases—60.80%) makes us feel that polyneuropathy be regarded as a component rather than a complication of diabetes.

Introduction

Diabetes melltus is a systemic disorder characterised by metabolic abnormalities and angiopathy[3],[3,4,5,9]. The relationship between degree of glyceamic control and development of long term complications poses an intriguing though vital question. Of these the neurolgical complications contribute to the major cause of disability,[4],[7,8,18] and a number of theories have been proposed for their pathogenesis. The magnitude of morbidity calls for reassessment of the situation and hence this study.

Material and Methods

838 cases of NIDDM attending the diabetic clinic Department of Medicine, Medical College, Jabalpur between Oct. 1984 to Apr. 1986 comprised the

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material of this study. Subjects underwent detailed clinical workup including Body Mass Index (B.M.I.) (kg/m^2), hypertension labelled as per WHO criteria (BP>160/95)[5,19]. A thorough neurological assessment was made. Polyneuropathy was regarded as bilateral loss of ankle jerks or gross sensory deficit in both feet as per WHO criteria (multinational study). P.V.D. was labelled with positive history of intermittent claudication or frank absence of peripheral pulsation[19]. Changes in fundi were confirmed by an Ophthalmologist. A 75 gm O.G.T.T. was carried out and diagnostic criteria of WHO was adopted[19]. Blood Glucose was estimated by the ortho-toludine method, while Glycosylated Haemoglobin (HbA1C) by modified chemical method of Fluckiger and Winterhalter [16,17]. Serum triglycerides, total serum cholesterol, HDL cholesterol and serum creatinine were determined in the fasting state. Proteinuria was assessed by estimating the 24 hr. urinary protein excretion by the Sulphosalicylic acid method, Values of 500 mmol in absence of UTI or severe hypertension were considered to have nephropathy. Renal insufficiency was defined as a serum creatinine of 133 moI/L[19].

Observations

Observations are tabulated below-

Table 1
Age Vs peripheral neuropathy in NIDDM

Age (years)	Cases	P. Neuropathy	%
25	10	02	20
26-35	52	25	47.7
36-45	204	83	40.6
46-55	310	159	51.2
56-60	128	112	87.5
61 and above	134	128	95.5
Total	838	509	

Above table shows highly significant increase ($p<0.001$) in frequency of distal polyneuropathy with advancing age.

Table 2
Peripheral Neuropathy and B.M.I.

B.M.I.	NIDDM	P. Neuropathy	%
19	250	100	66.6
19-23	294	200	68.02
above 23	294	209	71.06

This table reveals that B.M.I, has no bearing on the incidence of peripheral neuropathy.

Table 3
Peripheral neuropathy and duration of diabetes

Duration	Cases	P. Neuropathy	%
0-5 yrs	612	403	66.17
6-10 yrs	70	50	71.42
11-15 yrs	52	30	57.69
16-20 yrs	24	20	83.33
above 20 yrs	10	6	60

The table shows that duration has no linear correlation though highest incidence was encountered in disease of 16-20 yrs. duration. However, this rising trend of incidence was not maintained in disease of more than two decades.

Table 4
Peripheral Neuropathy Vs **Caloric intake**

Calories	NIDDM	P. Neuropathy	%
1500	298	285	90.63
1501-2000	500	204	40.80
2000-2500	38	20	52.63
2500 and above	2	0	—

It is revealed from the above table that low caloric intake has significant bearing ($p<0.05$) in the frequency of poly neuropathy.

Table 5
Peripheral Neuropathy Vs Fasting Blood Sugar level

Fasting blood sugar	No. cases	NIDDM with P. Neuropathy	%
120 mg%	312	169	45.16
120-140	168	100	59.52
141-160	76	70	92.10
161-180	60	60	100
181-200	64	60	93.75
Above 200 mg%	158	150	94.93

Table 5 shows that fasting blood sugar has no linear relationship with incidence of peripheral neuropathy.

Table 6
Peripheral Neuropathy with post-prandial Blood Sugar

Blood Sugar (pp)	NIDDM	NIDDM P. Neuropathy	%
150 mg%	86	20	23.25
151-200	230	80	34.78
201-240	194	100	51.54
241-280	108	104	96.29
281-320	92	85	92.39
231 and above	128	120	93.75

It is evident from above table that post-prandial hyperglycemia too does not have linear relationship with peripheral neuropathy.

Table 7
Peripheral Neuropathy Vs **Serum Cholesterol**

Serum Cholesterol	NIDDM	P. Neuropathy	%
150-200 mg%	176	109	61.93
201-250,,	316	208	65.32
251-300,,	260	130	50.00
301-350,,	58	52	89.65
350 and above ,,	28	10	37.51

Thus no cosistent correlation was observed between serum cholesterol and peripheral neuropathy.

Table 8
Peripheral Neuropathy and Serum Triglyceride level:

Serum Triglyceride	NIDDM	P. Neuropathy	%
100 mg%	318	109	34.27
101-150	402	300	74.62
151-200	92	81	88.04
201-250	18	15	83.33
251-300	3	3	100
301 and above	1	1	100

Table 8 shows close and significant correlation between serum triglycerides and peripheral neuropathy.

Table 9
Peripheral Neuropathy and HDL Cholesterol

HDL mg%	NIDDM	P. Neuropathy	%
36-45	318	139	43.71
46-55	402	310	77.11
56-64	102	56	54.60
65 and above	12	4	33.33

Table 9 shows that values of HDL Cholesterol have significant correlation with frequency of peripheral neuropathy. It is inversely proportional to the incidence of peripheral neuropathy. Probably lower HDL values enhance the micro—angiopathy and thereby lead to increase in incidence of peripheral neuropathy.

Table 10
Peripheral Neuropathy with L.V.D. in 838 cases

Peripheral Neuropathy	Cases (509)	%
P.V.D.	Cases 178	% 34.97
C.V.A.	Cases 158	% 31.04
I.H.D.	Cases 154	% 30.25

This table does not show any definite correlation. P.V.D., C.V.A., I.H.D. appear to be problems associated with peripheral neuropathy.

Table 11
Peripheral Neuropathy Vs S.V.D. in 838 cases

Peripheral Neuropathy	Cases (509)	%64
Retinopathy	Cases 124	% 24.36
Neuropathy	Cases 320	% 62.85

$Z = 14.35$, $P<0.001$.

Table 11 shows that microangiopathy (Retino + Nephropathy) was encoun tered in 444 out of 838 diabetics and distal polyneuropathy was observed in 64% of the patients ($p < 0.001$).

Table 12
Symptomatology of Distal Polyneuropathy in 509 cases

Symptoms	Literature %	Present series %
Subjective disturbances	86.2	82
Pain	*76.1*	70.3
Paraesthesia	47.7	60
Cramps	37.7	10
Sensation of weakness and haviness in lower extremities	18.5	2
Objective disturbances	85	78
Sensory disorders	83.8	62
Tactile hypoaesthesia	35.4	18
Diminished sense of vibration	80	76
Impaired musculo-articular sense	- 9.2	1.8
Impaired discriminative sensation	35	1.2
Motor Disorders		
Atrophy of muscles of extremities	16.1	2
Fasciculations	00	00
Paresis	00	00
Diminished Reflexes	85.3	97
Biceps	11.5	10
Triceps	10	6
Redial	10	6
Knee Jerk	50.8	48
Ankle jerk	98	95
Irophic Disorders	51.6	21.2
Ulcer	0.8	1.2
Osteoarthopathy	1.8	6.2

Above table shows that distal polyneuropathy frequently presents as pain syndromes and paraesthesiae. Vibration sense was more diminished in lower extremities than in the upper limbs. Motor disorders were found in only 2% cases. In 95% of patients with distal polyneuropathy the tendon reflexes were diminished. Abnormal ankle jerk was encountered most frequently, and diminution was often asymmetric. Symmetric polyneuropathy was encountered in 488 out of 509.

Table 13
Asymmetric Polyneuropathy Total cases: 21 (4.0%)

Asymmetric Polyneuropathy	Cases	%
Total	21	4.01
Acute/Sub-acute motor	2	0.4
Cranial mono-neuropathy	7	1.1
Truncal neuropathy	12	2.1
Entrapment neuropathy	Nil	0

Above table reveals that Asymmetric polyneuropathy is less common among the Diabetics.

Table 14
Features of Autonomic Neuropathy

SYMPTOMS	%
Diabetic impotence	60.00
Cardiac neuropathy	19.1
Neurogenic bladder	11.0
Sweating disturbance	9.00
Neuropathic ulcer	0.6
Nocturnal diarrhea	0.3

Impotence is probably the most frequent manifestation" of Autonomic Neuropathy.

Table 15
Correlation of peripheral neuropathy with Management

Group	Cases	Peripheral Neuropathy	%
1. Diet	296	180	60.8
2. OHA+Diet	480	350	72.9
3. Insulin	40	04	10
4. OH A + Insulin	22	20	90

*Includes cases of IGT &NIDDM with mild hyperglycaemia. It appears from the above table that the incidence of peripheral neuropathy is lowest in insulin treated group as compared to those on oral hypoglycaemic agents/or combinations. Oral hypoglycaemic agents might probably contribute to peripheral neuropathy.

Table 16
Correlation of peripheral neuropathy with Glycaemic control

HbA1C%	NIDDM cases	Peripheral Neuropathy	%
Less than 8%	202	109	53.9
8% and above	638	400	62.89
Z = 2.55, ($p<0.01$)			

Table 16 shows that in uncontrolled diabetes frequency of polyneuropathy is higher which is statistically significant ($p<0.01$). It seems to be an important exacerbating factor of subclinical polyneuropathy.

Discussion

Analysis of our meterial reveals a highly significant increase in frequency of distal polyneuropathy with increase in patient age (Table-11) ($p<0.01$). This

is coroborated with earlier finding[18]. The factor of age in the development of distal polyneuropathy could be due to:

i. Increase in duration of diabetes as the age advanced.
ii. Higher incidence of concommittant atherosclerosis leading to distal polyneuropathy[18].
iii. Lowering of the resistance of the peripheral nerve. Whittingham et al (1971) have postulated that diabetics may acquire senile neuropathy at middle age[16].

We observed that incidence of polyneuropathy in obese diabetics is about the same as in normal weight. (Table-2) This is corroborated with the finding of Richardson (1953)[18]. Higher incidence of peripheral neuropathy in diabetes of long duration might be due to degree and severity of diabetes and its decompensation leading to development of angiopathy in the middle age patient Table 3 shows the linear correlation though highest incidence was encountered in disease of 16-20 years, this rising trend of incidence was not maintained in disease of more than two decades.

We found that low caloric intake (Table 4) correlates favourably with the frequency of polyneuropathy. Other workers[6],[10],[18] beliave that long term hyper-glycaemia is a direct or indirect cause of peripheral neuropathy. We found that the incidence of distal polyneuropathy shows no linear correlation with fasting or post-prandial hyperglycaemia (Table 5 & 6). Moreover distal polyneuropathy was also encountered in IGT group. This too shows that glycaemia is probably not intimately related to polyneuropathy.

It has been shown[14,15] that in diabetes content of cholestrol, phospholipid in peripheral nerve was reduced, Adams (1954)[13] found that activity of acetic-thiokinase in peripheral nerve of alloxen-diabetic animals was sharply reduced. Others[18] considered it as a manifestation of the syndrome of abnormal fat metabolism which may lead to earlier development of atherosclerosis in vessels of the extremities. However (Table 7) shows no consistent correlation, though (Table 8) shows highly significant correlation with serum triglycerides. Table 9 shows that HDL cholesterol is inverely proportional to the incidence of polyneuropathy. Probably lower HDL values enhance the micro-angiopathy and thereby lead to increase incidence of peripheral neuropathy.

The significance of LVD has been emphasised[13]. Analysis of our data reveals that LVD in form of PVD, CVA & IHD are the concomitant problems

rather than complications. (Table 10). Some workers[7,18] hold that micro-angiopathy, affection of vasa nervorum were identical to those in the small vessels of the kidney, retina and nerve, and developed in a parallel as component of diffuse diabetic micro-angiopathy. Duration of diabetes and low HDL values probably also contribute to the development of angiopathy. Nephro and Retinopathy (Table 11) was encountered in 444 cases out of 838 patients.

Vibration sense was more diminished in lower extremities than in upper limbs. Disparity between manifestations in upper and lower limb could be explained on anatomical basis. The cranial mono-neuropathy involving 7th and 3rd cranial nerves) may be due to compression of nerve in a bony canal[12,15].

It is known that prolonged administration of large doses of sulphanilamide may produce polyneuritis. Distal polyneuropathy in diabetes due to sulphony-lurea therapy has been suggested[2,16,18]. Our observations contained in (Table 15) corroborates these reports.

Several theories have been postulated for pathogenesis of polyneuropathy viz[4]:

1. Accumulation of sugar, alcohol, leading to swelling & tissue damage.
2. Deficiency of intracellular myoinositol leading to impairment of membrane phospholipid function.
3. Deficiency of myelin synthesis due to hypoinsulinemia, leading to the segmental myelin loss.
4. Glycosylation of neural membrane proteins with impairment of neural function.
5. Accelerated death and turnover of Schwann cell either secondary to cell injury from any of the above or directly due to diabetes independent of metabolic abnormality leading to thickening & accumulation of abnormal basal lamina & impaired nerve function.
6. Immunoreactive mechanism with lipoid acting as hapten and glucolipid as antigen.

B.M.E. (1961)[18] Tabir's cyclopedia (1984), Weber (1985) have defined complication as "Any pathological process that occurs in attendance but not compulsory to main disease, and the causes for the development of which are not connected with the cause of principal disease". The contrary to the consensus regarding polyneuropathy as a complication of diabetes, we believe that it is an accompaniment.

Conclusion

1. Mode of therapy and glycemic control can only lessen the severity.
2. Metabolic decompansation of diabetes has a deterimental effect.
3. No single mechanism appears to explain polyneuropathy, a combination of factors appears to be responsible.
4. Diabetic polyneuropathy be regarded as a component of and not a complication of diabetes

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