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Original Research Article

Screening and assessment of polyneuropathy in adult patients and the effect of folic acid administration on the course of neuropathy

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ABSTRACT

Background: Multiple nerves damage (polyneuropathy) characterized by symmetrical sensory symptoms, such as numbness, paraesthesia, pain, andweakness predominantly in distal parts and pathophysiology depends on the underlying disease. Folic acid, (vitamin B9) deficiency causes many neurodegenerative and cerebrovascular diseases. Supplementation enhances neurodevelopment and provides neuroprotection in someneurological diseases by growth, differentiation and regeneration of the CNS.
Methods: Prospective open-label study included 60 patients visiting at tertiary care hospital of either sex with an age range between 18 to 70 years. We evaluated the role of folic acid in the course of neuropathy in all enrolled patients using various neuropathy scores like diabetic neuropathy symptom questionnaire, survey of autonomic symptoms questionnaire, neuropathy deficit (or disability) score, standardized nerve conduction studies and cardiac autonomic reflex test.
Results: NCV in the diabetic and alcoholic patients was statistically significant in almost all motor and sensory nerves in both upper and lower limb. In epileptic patients, was more significant in the lower limb in both motor and sensory nerves. In nutritional deficient patients was significant in only 2 nerves. In the diabetic patient, we also observed significance in DNS questionnaire (0.017).
Conclusions: Since folate is effective, cheap, treatment and, devoid of apparent toxicity for this obscure, chronic, neurological disorders would be agent justified. A significant improvement in the results was seen majorly in diabetic group, thus can be included for them.

Keywords: Polyneuropathy, Folic acid, NCV, Diabetes

INTRODUCTION

Polyneuropathy is a common neurological problem, defined as damage or disease affecting multiple peripheral nerves in roughly the same areasbilaterally.[1] Characterized by symmetrical sensory symptoms, such as numbness, paraesthesia, pain, and muscle weakness, which usually begins in the hands and feet and may progress to the arms and legs and sometimes to other parts of the body where it may affect the autonomic nervous system.[2] The overall worldwide prevalence of polyneuropathy in the general population seems around 1% and rises to up to 7% in the elderly. Prevalence seems to depend on socioeconomic status and the age distribution of the study population.[3] Polyneuropathies can impair sensory, motor, or autonomic function, either singly or in combination. The most common variety of polyneuropathy is distal symmetrical polyneuropathy.[1] Various causes of polyneuropathy are been identified

such as diabetes mellitus, alcohol, dietary deficiency, infective, immune-mediated, chronic inflammatory demyelinating polyneuropathy, chemotherapy induced, hereditary.[3] Screening and early identification of the neuropathic process offers a crucial opportunity for the physician as well as the patient to actively alter the course of the disease before the onset of significant morbidity. Folic acid (vitamin B9), a derivative of water-soluble vitamins, plays a key role in the growth, differentiation, and regeneration of the central nervous system. Folic acid shows great potential in repairing nervous system injury because of its neurotrophic effects.[4] Folic acid deficiency is related to increases in many neurodegenerative and cerebrovascular diseases. Besides, FA supplementation has been shown to enhance neurodevelopment and provide neuroprotection in some neurological diseases including stroke, Parkinson's disease, Alzheimer's disease, depression, psychosis, and spinal cord injury.[5,6] Neurologic manifestations of folate deficiency are variable and include spina bifida in the foetus, depression, dementia, optic neuropathy, myelopathy, and peripheral neuropathy.[7] In recent years progress has been made with various approaches involving autologous nerve grafts and nerve conduit combined with seed cells or neural growth factors; however, functional recovery remains unsatisfactory. For peripheral nerve reconstruction, neurotrophic factors released from the target organ and the proximal stump that forms after Wallerian degeneration play critical roles in building an effective microenvironment. Thus, it is reasonable to search for another substance to overcome these drawbacks.[4] The association between folate deficiency with diverse neurological lesions ranging from developmental abnormalities of the nervous system in newborns to senile dementia.[8] Recently the association between polyneuropathy and folic acid deficiency has been receiving increasing attention.[9,10] But most of the standard textbooks of medicine state that: "there are no specific neurological abnormalities due to folic acid deficiency".[11] In contrast, Balashova et al concluded that Folic acid shows great potential in repairing nervous system injury because of its neurotrophic effects.[12] Yilmaz et al demonstrated that folic acid can protect diabetic rats against diabetic peripheral neuropathy by reducing malondialdehyde levels and upregulating nerve growth factor (NGF) expression.[13] Also, folic acid supplementation does appear to have a positive effect on diabetic neuropathy according to a recent study.[14] Similarly, we planned to study the effect of folic acid on adults with different causes of polyneuropathy.

METHODS

This Prospective open-label study included 60 patients who visited Medicine OPD at SKNMC and GH, Narhe Pune, over 18 months (January 2019 to June 2020). Sample size calculated by using Open Epi statistical software with 95% confidence level, 80% power. Patients of either sex with an age range between 18 and 70 years; with a history of diabetes mellitus; or having nutritional deficiency; or on antiepileptic medication; or alcoholic were included in the study. Pregnant women, children <18 years and elderly >70 years, patients who were known cases of megaloblastic anaemia, guillain barre syndrome, myasthenia gravis, rheumatoid arthritis, Hansen's, CIDP, chemotherapy-induced, and any hereditary causes of neuropathy, Patients not willing to fill a consent form were excluded.

Procedure

Parameters: DNS (diabetic neuropathy symptom) questionnaire; all the selected subjects were given a DNS questionnaire form.[15] The form includes four questions related to polyneuropathy. A score of 1 or more points on the DNS score is considered significant when identifying neuropathy. The questions were answered either as YES (positive: 1 point) or NO (Negative: 0 points). The maximum score is 4 and the minimum score is 0. SAS (survey of autonomic symptoms) questionnaire: all the selected subjects were given a SAS (survey of autonomic symptoms) questionnaire form.[16] SAS questionnaire assesses both presence and severity of autonomic symptoms. 11 questions for females and 12 for males. The number of symptoms is reported 0-11 for females and 0-12 for males. The total symptom impact score was calculated by summating the rated severity of individual SAS scores. Results were compared.

Standardized nerve conduction studies

A nerve conduction velocity test was performed by technicians who will remain blinded to the status of the patient. Conduction velocity, latency, and distal amplitude values were taken as a parameter stating as normal or abnormal. Nerves of both upper limb and lower limb were tested.

Peripheral neuropathy testing

These tests were carried out by a second examiner who was blinded to the history, group of the patient, and results of the questionnaire assessment. Ankle reflex, Neuropathy Deficit (or disability) score (NDS): the score included vibration perception threshold, temperature perception on dorsum of the foot, pin prick test.[17,18] In all 3 tests, normal findings were considered 0 and abnormal as 1. With a total, NDS score of 10,0-2: clinical neuropathy is excluded,3-5: mild neuropathy,6-8: moderate neuropathy, >8: severe neuropathy

Cardiac autonomic reflex test and HRV (Heart Rate Variability)[19]

For assessment of autonomic functions, we used COMPASS 31 questionnaire at the central research lab. Screened patients were asked to fill this questionnaire. Details like BP, height, and weight were feed in the software. The CARTs testing procedures consist of resting heart rate, deep breathing test E:I ratio, 30:15

ratio, BP and heart rate response to orthostatic challenge, HRV (heart rate variability) test. Subjects showing any evidence of neuropathy based on the above tests will be given a tablet of folic acid 5mg BD daily for 3 months after which all the parameters along with sensory testing except the CART test were repeated to evaluate the course of neuropathy. The patient was asked to contact if there were any adverse effects experienced during the study. Informed consent was taken from all patients after discussing probable side effects as well as benefits of the drug.

Statistical analysis

Statistical analysis was done for values of each scale were compared between the groups using paired t test (Microsoft excel). A significance level of 0.05 was considered statistically significant.

RESULTS

Demographic profile

The mean age of the patients was 53.58± 9.2 years. Out of 60 patients enrolled there were 35 male patients and 25 female patients. Mean systolic blood pressure at baseline was 121.53±7.28 mmHg and diastolic 80.93±5.74 mmHg. A total of 15 patients gave a history of autonomic dysfunction. Number of patients in different groups in percent (number of cases) is shown in (Figure 1). 47% (28) were diabetic patient, 27% (16) were alcoholic patient, 13% (8) were antiepileptic and 13% (8) were patients with nutritional deficiency.

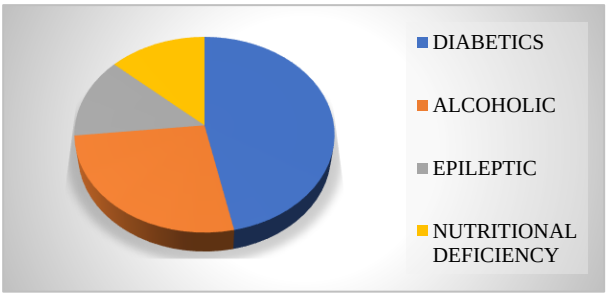

Figure 1: Patient distribution.

Diabetic group

In the diabetic group, a p value of scores DNS and TIS was 0.017 and 0.006 respectively, which is statistically significant (Table 1). NDS was statistically not significant in this group of patients. Ankle reflex was present in 22 patients and CART was positive in 20 patients.

Table 1: Nerve conduction velocity in diabetic patients (motor nerves).

Parameters		Pre-treatment	Post treatment	P value
		Mean±SD	Mean±SD	
RT median	Latency	3.73±0.49	3.69±0.47	0.236
	Amplitude	6.46±1.55	6.61±1.44	0.023*
	CV	53.57±4.43	53.85±4.36	0.003**
RT ulnar	Latency	3.81±0.63	3.78±0.59	0.150
	Amplitude	6.04±1.29	6.21±1.16	0.003**
	CV	54.11±4.26	53.95±4.62	0.670
LT median	Latency	3.72±0.43	3.63±0.38	0.018*
	Amplitude	5.94±1.19	6.18±1.17	0.0001***
	CV	53.25±4.26	53.43±4.18	0.002**
LT ulnar	Latency	3.84±0.75	3.75±0.70	0.021*
	Amplitude	5.92±1.07	5.98±1.09	0.012*
	CV	55.29±3.69	55.60±3.54	0.001**
RT peroneal	Latency	3.66±0.77	3.60±0.69	0.049*
	Amplitude	4.4±1.22	4.58±1.18	0.0002***
	CV	42.75±5.69	43.16±5.70	0.002**
RT tibial	Latency	3.85±0.62	3.74±0.54	0.030*
	Amplitude	6.33±1.18	6.46±1.21	0.0007***
	CV	42.48±5.16	42.79±5.20	0.002**
LT peroneal	Latency	3.82±0.68	3.70±0.61	0.082
	Amplitude	3.96±1.31	4.14±1.27	0.010*
	CV	43.05±4.78	43.01±4.35	0.929
LT tibial	Latency	3.835±0.58	3.82±0.57	0.120
	Amplitude	6.032±1.29	6.11±1.37	0.076
	CV	43.76±4.60	44.09±4.71	0.001**

*p<0.05,** p<0.01 , ***p≤0.0001, Statistically significant difference compared to baseline, †Intragroup comparisons for individual parameters carried out by paired t-test.

Table 2: Nerve conduction velocity in a diabetic patient (sensory nerves).

Parameters		Pre-treatment	Post treatment	P value
		Mean±SD	Mean±SD	
RT median	Latency	2.66±0.68	2.60±0.64	0.064
	Amplitude	10.88±1.25	11.08±1.17	0.005**
	CV	52.22±3.25	52.65±3.19	0.001**
RT ulnar	Latency	2.84±0.48	2.81±0.40	0.519
	Amplitude	11.11±1.02	11.28±0.89	0.114
	CV	53.26±5.36	53.60±5.34	0.0004***
LT median	Latency	2.93±0.43	2.82±0.38	0.008**
	Amplitude	11.26±1.35	11.36±1.30	0.007**
	CV	51.56±4.86	51.84±4.84	0.002**
LT ulnar	Latency	2.84±0.44	2.75±0.36	0.028*
	Amplitude	11.44±1.09	11.59±1.07	0.001**
	CV	52.43±5.07	52.81±5.05	0.0002***
RT peroneal	Latency	2.77±0.69	2.66±0.64	0.017*
	Amplitude	11.12±1.22	11.26±1.16	0.0003***
	CV	52.63±5.08	53.40±5.00	0.041*
RT sural	Latency	2.85±0.48	2.80±0.45	0.107
	Amplitude	10.94±1.35	11.10±1.37	0.005**
	CV	54.52±5.37	54.76±5.15	0.005**
LT peroneal	Latency	2.90±0.53	2.82±0.47	0.049*
	Amplitude	10.58±1.26	10.70±1.25	0.0002***
	CV	51.96±4.52	52.53±4.28	0.0003***
LT sural	Latency	2.77±0.62	2.67±0.55	0.014*
	Amplitude	10.74±1.61	10.94±1.53	0.002**
	CV	53.23±3.24	53.35±3.11	0.032*

*p<0.05,** p<0.01 , ***p≤0.0001, Statistically significant difference compared to baseline, †Intragroup comparisons for individual parameters carried out by paired t-test.

Nerve conduction velocity of motor nerves in diabetic patients: latency of left median (p=0.018), left ulnar (p=0.021), right peroneal (0.049) and right tibial (p=0.030) were statistically significant. Amplitude values of right median (p=0.023), right ulnar (p=0.003), left median (p=0.0001), left ulnar (p=0.012), right peroneal (p=0.0002) and right tibial (p=0.0007), left peroneal (p=0.010) were statistically significant. Conduction velocity values of right median (p=0.003), left median (p=0.0001), left ulnar (p=0.001), right peroneal (p=0.002) and right tibial (p=0.002), left tibial (p=0.001) were statistically significant.

Nerve conduction velocity of sensory nerves in diabetic patients: latency of left median (p=0.008), left ulnar (p=0.028), right peroneal (p=0.0 17), left peroneal (p=0.049) and left sural (p=0.014) were statistically significant**.** Amplitude values of right median (p=0.005), left median (p=0.007), left ulnar (p=0.001), right peroneal (p=0.0003), right sural (p=0.005), left peroneal (p=0.0002) and left sural (p=0.002) were statistically significant**.** Conduction velocity of right median (p=0.001), right ulnar (p=0.0004), left median (p=0.002), left ulnar (p=0.0002), right peroneal (p=0.041), right sural (p=0.005),left peroneal (p=0.003) left sural (p=0.032) were statistically significant**.** In alcoholic patients, neuropathy scores were not significant while ankle reflex was present in 16 patients and CART was positive in 2 patients (Table 2).

Nerve conduction velocity of motor nerves in alcoholic patients: Amplitude values in right median (p=0.005), right ulnar (p=0.028), left median (p=0.023), left ulnar (p=0.018), right tibial (p=0.030), left peroneal (p=0.022) were statistically significant. Nerve conduction velocity values in right median (p=0.003), right ulnar (p=0.0004), left ulnar (p=0.008), right tibial (p=0.020), left tibia (p=0.022) were statistically significant.

Nerve conduction velocity of sensory nerves in alcoholic patients: latency values in right ulnar (p=0.047), left peroneal (p=0.048) were statistically significant. Amplitude values in right median (p=0.001) right ulnar (p=0.048), left median (p=0.049), left ulnar (p=0.001), right peroneal (p=0.041) right sural (p=0.001), left peroneal (p=0.006) were statistically significant. Nerve conduction velocity values in right median (p=0.0003) right ulnar (p=0.047), left median (p=0.002), left ulnar (p=0.014), right peroneal (p=0.009), right sural (p=0.007), left peroneal (p=0.007) and left sural (p=0.014) were statistically significant.

Table 3: Nerve conduction velocity in alcoholic patient (motor nerves).

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
RT median	Latency	3.85±0.37	3.83±0.35	0.058
	Amplitude	5.91±1.04	6.17±1.07	0.005**
	CV	53.88±4.75	54.30±4.72	0.003**
RT ulnar	Latency	3.89±0.40	3.84±0.36	0.220
	Amplitude	6.06±1.54	6.30±1.38	0.028*
	CV	53.37±4.40	53.79±4.37	0.0004***
LT median	Latency	3.96±0.47	3.87±0.38	0.094
	Amplitude	5.73±1.53	5.96±1.47	0.023*
	CV	49.36±12.33	53.13±4.27	0.264
LT ulnar	Latency	3.71±0.69	3.62±0.60	0.060
	Amplitude	6.40±1.34	6.71±1.30	0.018*
	CV	53.19±4.54	53.64±4.38	0.008**
RT peroneal	Latency	3.85±0.60	3.79±0.51	0.354
	Amplitude	3.78±0.96	3.85±1.02	0.060
	CV	44.39±5.71	43.91±5.61	0.428
RT tibial	Latency	3.75±0.45	3.66±0.43	0.162
	Amplitude	6.04±1.52	6.19±1.48	0.03*
	CV	44.44±6.45	44.74±6.39	0.02*
LT peroneal	Latency	3.80±0.57	3.81±0.55	0.861
	Amplitude	4.26±0.95	4.34±0.92	0.022*
	CV	41.33±3.71	41.46±3.75	0.083
LT tibial	Latency	4.02±0.73	3.96±0.75	0.197
	Amplitude	5.68±0.94	5.84±0.85	0.052
	CV	41.17±3.76	41.44±3.84	0.022*

Table 4: Nerve conduction velocity in alcoholic (sensory nerves).

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
RT median	Latency	2.95±0.77	2.82±0.69	0.060
	Amplitude	10.66±1.58	10.98±1.54	0.001**
	CV	51.34±5.67	51.91±5.59	0.0003**
RT ulnar	Latency	2.83±0.74	2.73±0.63	0.047*
	Amplitude	11.23±0.92	11.30±0.92	0.048*
	CV	54.77±4.82	55.04±4.64	0.047*
LT median	Latency	2.84±0.57	2.71±0.46	0.064
	Amplitude	10.49±1.30	10.73±1.26	0.049*
	CV	56.04±4.91	56.35±4.96	0.002**
LT ulnar	Latency	2.85±0.46	2.81±0.43	0.153
	Amplitude	11.41±1.32	11.58±1.36	0.001**
	CV	52.16±5.87	52.42±5.97	0.014*
RT peroneal	Latency	2.82±0.42	2.74±0.41	0.068
	Amplitude	10.56±0.82	10.61±0.85	0.041*
	CV	52.02±4.49	52.40±4.39	0.009**
RT sural	Latency	3.10±0.44	3.00±0.41	0.059
	Amplitude	11.39±1.33	11.58±1.41	0.001**
	CV	53.92±4.95	54.20±5.02	0.007**
LT peroneal	Latency	3.05±0.63	2.89±0.58	0.048*
	Amplitude	11.51±1.51	11.64±1.54	0.006**
	CV	53.89±6.58	54.15±6.50	0.007**
LT sural	Latency	2.82±0.48	2.79±0.44	0.178

Continued.

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
	Amplitude	10.41±1.22	10.53±1.16	0.114
	CV	53.66±7.16	53.92±7.12	0.014*

Table 5: Nerve conduction velocity in epileptic group (motor nerves).

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
RT median	Latency	3.61±0.34	3.60±0.34	0.068
	Amplitude	6.45±0.98	6.51±0.93	0.180
	CV	52.31±4.75	52.39±4.70	0.251
RT ulnar	Latency	3.71±0.26	3.70±0.27	0.188
	Amplitude	6.55±0.79	6.56±0.78	0.351
	CV	52.60±2.24	52.52±2.14	0.848
LT median	Latency	3.40±0.82	3.43±0.84	0.491
	Amplitude	6.44±1.52	6.64±1.44	0.090
	CV	53.62±3.52	53.71±3.38	0.351
LT ulnar	Latency	3.62±0.64	3.61±0.64	0.106
	Amplitude	6.16±1.36	6.39±1.34	0.023*
	CV	56.35±5.07	56.48±4.98	0.124
RT peroneal	Latency	3.59±0.34	3.57±0.33	0.073
	Amplitude	4.31±1.19	4.53±1.23	0.021*
	CV	47.89±4.17	46.15±5.34	0.253
RT tibial	Latency	4.20±0.55	3.79±0.36	0.091
	Amplitude	6.89±0.78	7.03±0.96	0.083
	CV	44.96±4.89	44.96±4.96	0.977
LT peroneal	Latency	3.65±0.65	3.56±0.56	0.460
	Amplitude	3.58±0.70	3.85±0.91	0.147
	CV	42.59±2.14	42.98±2.33	0.023*
LT tibial	Latency	3.66±0.65	3.52±0.47	0.271
	Amplitude	6.35±1.70	6.49±1.57	0.304
	CV	43.28±4.09	43.58±4.05	0.038*

Table 6: Nerve conduction velocity in epileptic group (sensory nerves).

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
RT median	Latency	2.54±0.63	2.54±0.63	0.104
	Amplitude	11.71±1.35	11.83±1.40	0.026*
	CV	54.50±6.39	54.79±6.58	0.145
RT ulnar	Latency	2.75±0.64	2.72±0.49	0.719
	Amplitude	10.51±0.81	10.64±0.87	0.060
	CV	50.94±3.92	51.55±3.89	0.015*
LT median	Latency	2.85±0.52	2.83±0.53	0.022*
	Amplitude	10.26±1.25	10.40±1.33	0.073
	CV	53.68±3.17	54.08±3.16	0.007**
LT ulnar	Latency	2.63±0.67	2.60±0.69	0.189
	Amplitude	10.91±1.38	11.10±1.48	0.018*
	CV	54.40±5.78	54.52±5.85	0.351
RT peroneal	Latency	2.64±0.58	2.57±0.55	0.580
	Amplitude	10.50±0.88	10.65±0.81	0.119
	CV	54.68±4.02	54.91±4.07	0.095
RT sural	Latency	2.96±0.82	2.90±0.83	0.310
	Amplitude	11.21±0.94	11.29±1.05	0.413

Continued.

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
	CV	55.95±5.54	56.40±5.50	0.020*
LT peroneal	Latency	2.40±0.48	2.34±0.43	0.264
	Amplitude	11.23±2.01	11.44±1.90	0.015*
	CV	50.21±4.51	50.60±4.61	0.019*
LT sural	Latency	2.50±0.53	2.47±0.49	0.117
	Amplitude	10.45±1.55	10.70±1.59	0.052
	CV	54.65±4.39	54.50±4.30	0.351

Table 7: Nerve conduction velocity in nutrient deficient group (motor nerves).

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
RT median	Latency	3.32±0.74	3.30±0.74	0.040*
	Amplitude	5.86±1.31	6.15±1.17	0.132
	CV	52.14±3.79	52.36±3.76	0.070
RT ulnar	Latency	4.33±0.72	4.10±0.64	0.052
	Amplitude	6.23±0.98	6.34±1.00	0.051
	CV	54.59±3.29	54.75±3.44	0.090
LT median	Latency	4.04±0.75	4.02±0.62	0.864
	Amplitude	5.71±1.39	5.99±1.13	0.085
	CV	52.78±5.54	53.41±5.36	0.009**
LT ulnar	Latency	3.87±0.34	3.72±0.40	0.255
	Amplitude	6.13±1.19	6.28±1.09	0.134
	CV	50.86±3.65	51.33±3.58	0.060
RT peroneal	Latency	3.67±0.40	3.71±0.35	0.400
	Amplitude	4.26±1.13	4.36±1.18	0.121
	CV	38.52±4.48	38.98±4.29	0.033*
RT tibial	Latency	3.88±0.56	3.83±0.56	0.280
	Amplitude	6.44±1.31	6.63±1.32	0.022*
	CV	46.72±5.17	46.90±5.22	0.180
LT peroneal	Latency	3.79±0.50	3.72±0.47	0.342
	Amplitude	4.48±1.00	4.74±0.80	0.108
	CV	40.32±6.20	40.15±6.13	0.351
LT tibial	Latency	3.72±0.32	3.71±0.32	0.087
	Amplitude	5.80±0.74	5.99±0.73	0.022*
	CV	43.67±2.01	43.90±2.10	0.095

Table 8: Nerve conduction velocity in nutrient deficient group (sensory nerves).

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
RT median	Latency	2.90±0.44	2.79±0.28	0.109
	Amplitude	11.04±1.31	11.20±1.43	0.055
	CV	51.60±7.07	51.86±7.18	0.114
RT ulnar	Latency	2.84±0.66	2.75±0.61	0.241
	Amplitude	11.64±1.78	11.76±1.77	0.106
	CV	54.45±4.12	54.69±3.86	0.172
LT median	Latency	2.92±0.64	2.82±0.63	0.175
	Amplitude	11.18±1.71	11.26±1.73	0.041*
	CV	50.24±2.95	50.86±3.00	0.031*
LT ulnar	Latency	2.76±0.39	2.60±0.35	0.130
	Amplitude	11.09±1.06	11.16±1.12	0.111
	CV	51.91±3.04	52.14±3.11	0.101

Continued.

Parameters		Pre-treatment Mean±SD	Post treatment Mean±SD	P value
RT peroneal	Latency	3.01±0.72	3.05±0.64	0.807
	Amplitude	11.35±0.52	11.44±0.64	0.133
	CV	52.65±4.35	53.16±4.28	0.017*
RT sural	Latency	2.81±0.71	2.80±0.70	0.094
	Amplitude	11.10±1.47	11.28±1.58	0.041*
	CV	55.88±2.81	56.13±2.93	0.083
LT peroneal	Latency	3.23±0.54	3.07±0.55	0.077
	Amplitude	11.63±1.57	11.84±1.61	0.031*
	CV	51.42±3.09	51.94±2.78	0.083
LT sural	Latency	2.84±0.62	2.90±0.54	0.520
	Amplitude	10.88±1.71	10.94±1.68	0.565
	CV	53.90±6.35	54.33±6.31	0.066

Epileptic group

In epileptic patients, scores were not significant while ankle reflex was present in 8 patients and CART was positive in 3 patients. Nerve conduction velocity of motor nerves in epileptic patients: amplitude values in left ulnar (p=0.023), right peroneal (p=0.021) were statistically significant. Nerve conduction velocity values in the left peroneal (p=0.023) and left tibial (p=0.038) were statistically significant. Nerve conduction velocity of sensory nerves in epileptic patients: latency values in left median (p=0.022) were statistically significant. Amplitude values in right median (p=0.026), left ulnar (p=0.018), left peroneal (p=0.015) were statistically significant. Conduction velocity values in right ulnar (p=0.015), left median (p=0.007) right sural (p=0.020) left peroneal (p=0.019) were statistically significant.

Nutritional deficient group

Values are expressed as mean±SD* p<0.05, **p<0.01, ***p≤0.0001, statistically significant difference compared to baseline, †intragroup comparisons for individual parameters carried out by paired t-test. In nutritional deficient patients, neuropathy scores in nutritional deficient patients were not significant. Ankle reflex was present in 8 patients and CART was positive in 2 patients.

Nerve conduction velocity of motor nerves in nutritional deficient patients: latency values in right median (p=0.040) were statistically significant. Amplitude values in right tibial (p=0.022), left tibial (p=0.095) were statistically significant. Nerve conduction velocity values in left median (p=0.009), right peroneal (p=0.033) were statistically significant. Nerve conduction velocity of sensory nerves in nutritional deficient patients: amplitude values in left median (p=0.041) right sural (p=0.041) left peroneal (p=0.031) were statistically significant. Nerve conduction velocity values in left median (p=0.031) right peroneal (p=0.017) were statistically significant.

DISCUSSION

Polyneuropathy is a common disorder and presents as a diagnostic and therapeutic challenge to physicians and neurologists even today. The role of folic acid in the treatment of peripheral neuropathies is not been well documented yet, but the availability and affordability of folic acid make this drug a frequent choice for treating peripheral neuropathy. In the present study, we evaluated the role of folic acid in the course of neuropathy in all enrolled patients using various neuropathy scores like diabetic neuropathy symptom questionnaire, survey of autonomic symptoms questionnaire, neuropathy deficit (or disability) score, and peripheral neuropathy tests using standardized nerve conduction studies and cardiac autonomic reflex test along with heart rate variability. A significant improvement was seen in the course of neuropathy with 5 mg twice a day folic acid supplementation for 3 months.

Over the last decade, studies were suggesting a positive effect of folate supplementation on the improvement of neuropathy. Iskandar et al in their study suggested that the effects of folic acid supplementation are not confined to the embryonic period but also can influence repair mechanisms in the adult CNS. They also stated that there is a significant increase in the regeneration of axons into peripheral nerve grafts after damage to the spinal cord or optic nerves and a substantial improvement in functional recovery from spinal cord injury.[20] Balashova et al identified the mechanism underlying folate action in axon regeneration depends on FOLR1 and is correlated with changes in DNA methylation.[12] In our study, we conducted subjective as well as objective tests. Only in the diabetic patient, we observed significance in DNS (0.017) and TIS (0.006). We also conducted nerve conduction velocity in our study patients and the results were statistically significant in almost all motor and sensory nerves in both upper and lower limb. A similar study was conducted in diabetic patients with NCV of the only lower limb, Mottaghi et al in their study showed that administration of 1 mg folic acid per day for 16 weeks in

diabetic polyneuropathy (DPN) patients significantly increased serum folic acid levels. The study also showed that folic acid increased sural amplitude in sensory nerves, amplitude and velocity of motor nerves, and decreased peroneal and tibial onset latency of motor nerves.[14] Some other diabetic neuropathy studies like Yilmaz et al in their study showed the beneficial effects of Folic acid in the prevention of DPN through improving the expression of NGF (nerve growth factor) and lowering MDA levels, and so suggested that Folic acid supplementation can be considered as an adjunctive therapy in diabetes patients to improve symptoms of neuropathy. They also suggested folic acid may be considered as an effective antioxidant in patients; this can be a result of decreased production of free radicals and folic acid treatment may also decrease the epineural fibrosis and increase the NGF immunoexpression.[13] One animal study carried out in diabetic rats was able to verify the possibility of FA as a neuroprotector. Oxidative stress has been shown to be a critical factor in the development of DPN. Hyperglycemia and the resulting superoxides may have a role in increasing oxidative stress. It was reported that FA supplementation ameliorates inflammation, oxidative damage, and insulin resistance in diabetes mellitus.[21] So the improvement in the expression of the nerve growth factor decreased free radicals, and lipid peroxidation causing improvement in inflammation, oxidative damage, also improved resistance to insulin in diabetic patients could be some of the reasons for positive results in this study. As per our knowledge, there were a limited number of direct head-to-head comparison studies reported.

According to the literature chronic alcohol intake impairs folate status by inhibiting the absorption of folate from the intestine, reducing its hepatic stores, and increasing its urinary excretion. The main causes of chronic-alcoholism-associated neuropathy are the direct toxicity of ethanol or its metabolites.

In the present study, the nerve conduction test results were significant in both upper and lower limbs. Koike et al in a case report of a 33 years old woman with chronic alcoholism who presented with the acutely progressive glove- and stocking-type sensorimotor polyneuropathy and Nerve conduction studies indicated axonal neuropathy. Sural nerve biopsy findings supported this finding as the teased-fibre preparations revealed a high frequency of axonal degeneration (51%), with no evidence of segmental demyelination, was started with daily intravenous supplementation of 15 mg folic acid, and the patient gradually recovered from weakness in the extremities.[22]

In another experimental study, Ojeda et al demonstrated, that dietary folic acid supplementation is an economical and efficient therapy against oxidative damage in lipids caused due to binge drinking in rats.[23] Figueroa et al described a 75% prevalence of electro physiologically-diagnosed neuropathy in 19/29 epilepsy patients on long term although unspecified antiepileptic drugs. All 19 had low serum and cerebrospinal fluid folate levels, and Folate therapy (3-5 mg intramuscular 3 times daily for 1 month) reversed abnormalities in motor and sensory nerve distal latencies although there were no effects on nerve conduction or sensory amplitude.[24] Comparing this with the present study the amplitude values were significant in upper limb and conduction velocity was more significant in the lower limb in both motor and sensory nerves. Horowitz et al studied 52 patients with epilepsy, amongst whom 20 had neuropathy both clinically and electro physiologically. Comparison of the neuropathic vs. non-neuropathic group within that cohort failed to show a difference in serum folate levels, with 50% of patients presenting deficiency in both. Supplementation for 3 months, on a double-blind basis, did not result in an improvement of those with neuropathy.

The probable mechanism for improvement among the patients can be explained by the process of DNA formation. For DNA formation, FA is necessary where it serves as a carrier of hydroxymethyl and formyl groups. Methylterahydrofolate transforms homocysteine to methionine as a derivative of this group, which preserves the concentration of blood homocysteine at a satisfactory level. However, AEDs have been shown to inhibit homocysteine to methionine conversion. FA supplementation replenishes folate levels which expedite re-methylation of homocysteine into methionine and hence DNA methylation.[25]

Interestingly conduction velocity in nutritional deficient patients was significant in only 2 nerves i.e. left median, right peroneal in both motor and sensory nerves, which was analogous to Botez et al who described the clinical and electrophysiologic features of 5 patients also having malabsorption. The neuropathy was an axonal form of the sensorimotor type that was predominant in the lower extremities and is substantially improved after the folic acid supplementation.[26]

A partly supporting study examined the clinicopathologic features of 18 consecutive patients with neuropathy caused by folate deficiency, folic acid supplementation was done and an improvement in functional status, was reported only in 5 patients within 3 months, thus H. Koike et al concluded that early diagnosis and intervention are important to prevent irreversible neurologic deficits caused by folate deficiency.[27] In one study serum, folate levels were measured in patients with various neurological diseases in Japan. 36 patients showed decreased serum folate levels among 343. Folate administration (15mg/d) to folate-deficient patients improved neurological symptoms in 24 of 36 cases after 2 months.[28]

Regarding the prognosis of neurologic complications caused by folate deficiency, the response to supplementation with folic acid has been considered to be

favourable if the treatment is initiated in the early disease phase.[29] Although there has been no reported toxicity to folic acid, whether, in our study of the literature, it is reassuring that the pro-regenerative effect of folic acid does not require supramaximal doses.[30]

Polyneuropathy often affects the entire autonomic nervous system in this regard we also conducted cardiac autonomic reflex testing in all the patient while enrolment, 27 patients were tested positive indicating the presence of cardiac autonomic neuropathy (CAN). For peripheral nerve reconstruction, neurotrophic factors released from the target organ and the proximal stump that forms after Wallerian degeneration play critical roles in building an effective microenvironment.[4] Folic acid shows great potential in repairing nervous system injury because of its neurotrophic effects.[12] Our analysis may be limited by potential selection bias in this hospital-based study. Also, we did not evaluate the serum folate levels. It is plausible that poor diet and malabsorption may be contributing factors instead of AED exposure per se. It remains to be seen whether folate deficiency is solely responsible for the peripheral neuropathy.

CONCLUSION

It can be concluded that since folate is effective, cheap, treatment and, devoid of apparent toxicity for this obscure, chronic, neurological disorders would be agent justified. A significant improvement in the results was seen majorly in diabetic group, thus can be included for them. Duration of study is 3 months so symptomatic improvement may sometimes cannot be seen but early improvement can be diagnosed by these scores and test. This is the advantage of technology.

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REFERENCES

1. England JD, Asbury AK. Peripheral neuropathy. Lancet Lond Engl. 2004;363(9427):2151-61.
2. Teunissen LL, Eurelings M, Notermans NC, Hop JW, van Gijn J. Quality of life in patients with axonal polyneuropathy. J Neurol. 2000;247(3):195-9.
3. Hanewinckel R, van Oijen M, Ikram MA, van Doorn PA. The epidemiology and risk factors of chronic polyneuropathy. Eur J Epidemiol. 2016;31(1):5-20.
4. Kang W-B, Chen Y-J, Lu D-Y, Yan J-Z. Folic acid contributes to peripheral nerve injury repair by promoting Schwann cell proliferation, migration, and secretion of nerve growth factor. Neural Regen Res. 2019;14(1):132-9.
5. Ma W, Xiang L, Yu H-L, Yuan L-H, Guo A-M, Xiao Y-X, et al. Neuroprotection of soyabean isoflavone co-administration with folic acid against beta-amyloid 1-40-induced neurotoxicity in rats. Br J Nutr. 2009;102(4):502-5.
6. Manschot SM, Biessels GJ, Rutten GEHM, Kessels RPC, Kessels RCP, Gispen WH, et al. Peripheral and central neurologic complications in type 2 diabetes mellitus: no association in individual patients. J Neurol Sci. 2008;264(1-2):157-62.
7. Koike H, Takahashi M, Ohyama K, Hashimoto R, Kawagashira Y, Iijima M, et al. Clinicopathologic features of folate-deficiency neuropathy. Neurology. 2015;84(10):1026-33.
8. Strachan RW, Henderson JG. Dementia and folate deficiency. Q J Med. 1967;36(142):189-204.
9. Botez MI, Fontaine F, Botez T, Bachevalier J. Folate-responsive neurological and mental disorders: report of 16 cases. Neuropsychological correlates of computerized transaxial tomography and radionuclide cisternography in folic acid deficiencies. Eur Neurol. 1977;16(1-6):230-46.
10. Reynolds EH, Rothfeld P, Pincus JH. Neurological disease associated with folate deficiency. Br Med J. 1973;2(5863):398–400.
11. Longo DL, editor. Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill; 2012.
12. Balashova OA, Visina O, Borodinsky LN. Folate action in nervous system development and disease. Dev Neurobiol. 2018;78(4):391-402.
13. Yilmaz M, Aktug H, Oltulu F, Erbas O. Neuroprotective effects of folic acid on experimental diabetic peripheral neuropathy. Toxicol Ind Health. 2016;32(5):832-40.
14. Mottaghi T, Khorvash F, Maracy M, Bellissimo N, Askari G. Effect of folic acid supplementation on nerve conduction velocity in diabetic polyneuropathy patients. Neurol Res. 2019;41(4):364-8.
15. Meijer JWG, Smit AJ, Sonderen EV, Groothoff JW, Eisma WH, Links TP. polyneuropathy in diabetes: the Diabetic Neuropathy Symptom score. Br Med J. 2002;6:52-9.
16. Zilliox L, Peltier AC, Wren PA, Anderson A, Smith AG, Singleton JR, et al. Assessing autonomic dysfunction in early diabetic neuropathy. Neurology. 2011;76(12):1099-105.
17. Young MJ, Boulton AJ, MacLeod AF, Williams DR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia. 1993;36(2):150-4.
18. Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med J Br Diabet Assoc. 2002;19(5): 377-84.
19. Yajnik CS, Kantikar V, Pande A, Deslypere J-P, Dupin J, Calvet J-H, et al. Screening of cardiovascular autonomic neuropathy in patients with diabetes using non-invasive quick and simple assessment of sudomotor function. Diabetes Metab. 2013;39(2):126-31.

20. Iskandar BJ, Nelson A, Resnick D, Skene JHP, Gao P, Johnson C, et al. Folic acid supplementation enhances repair of the adult central nervous system. Ann Neurol. 2004;56(2):221-7.
21. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107(9):1058-70.
22. Koike H, Hama T, Kawagashira Y, Hashimoto R, Tomita M, Iijima M, et al. The significance of folate deficiency in alcoholic and nutritional neuropathies: Analysis of a case. Nutrition. 2012;28(7-8):821-4.
23. Ojeda ML, Rua RM, Nogales F, Díaz-Castro J, Murillo ML, Carreras O. The benefits of administering folic acid in order to combat the oxidative damage caused by binge drinking in adolescent rats. Alcohol Alcohol. 2016;51(3):235-41.
24. Martinez Figueroa A, Johnson RH, Lambie DG, Shakir RA. The role of folate deficiency in the development of peripheral neuropathy caused by anticonvulsants. J Neurol Sci. 1980;48(3):315-23.
25. Bhosale UA, Yegnanarayan R, Agrawal A, Patil A. Efficacy study of folic acid supplementation on homocysteine levels in adolescent epileptics taking antiepileptic drugs: a single blind randomized controlled clinical trial. Ann Neurosci. 2019;26(3-4):50-4.
26. Botez MI, Peyronnard JM, Bachevalier J, Charron L. Polyneuropathy and folate deficiency. Arch Neurol. 1978;35(9):581-4.
27. Koike H, Takahashi M, Ohyama K, Hashimoto R, Kawagashira Y, Iijima M, et al. Clinicopathologic features of folate-deficiency neuropathy. Neurology. 2015;84(10):1026-33.
28. Yukawa M, Naka H, Murata Y, Katayama S, Kohriyama T, Mimori Y, et al. Folic acid-responsive neurological diseases in Japan. J Nutr Sci Vitaminol (Tokyo). 2001;47(3):181-7.
29. Green R, Miller JW. Folate deficiency beyond megaloblastic anemia: hyperhomocysteinemia and other manifestations of dysfunctional folate status. SeminHematol. 1999;36(1):47-64.
30. Iskandar BJ, Nelson A, Resnick D, Skene JHP, Gao P, Johnson C, et al. Folic acid supplementation enhances repair of the adult central nervous system. Ann Neurol. 2004;56(2):221-7.

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