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Research Article

Electrophysiologic Features of Peripheral Neuropathy in Adults with an Isolated Elevated Plasma Level of Homocysteine

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Abstract

Introduction: An elevated level of plasma homocysteine (eHcy) is a recognized risk factor for many neurological conditions. Recent laboratory studies show a toxic effect of homocysteine causing neuropathy. Clinical observations disclosed that eHcy exacerbates prevalence and severity of peripheral neuropathy in diabetic patients. We have seen a group of neuropathy patients with an eHcy without any other identifiable etiology. We termed this entity as *isolated* eHcy-induced neuropathy (IHIN) and studied the electrophysiologic features of IHIN.

Methods: Conventional nerve conduction study and needle electromyography were performed in the upper and lower extremities of IHIN patients.

Results: Twenty-six arms and 26 legs of 28 cases of IHIN were studied. The electrophysiologic studies showed that 93% (26/28) of the IHIN patients had electrodiagnostic abnormalities including 75% (21/28) having mild sensorimotor neuropathy, 18% (5/28) with the electrophysiologic features of carpal tunnel syndrome; while only 7% (2/28) normal findings.

Conclusion: Our results suggested that IHIN is a large fiber neuropathy with electrophysiologic features of demyelination and axonal denervation.

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INTRODUCTION

Homocysteine is an intermediate metabolite of methinoine during methylation [1]. An elevated level of plasma homocysteine (eHcy) is a recognized risk factor for many neurological conditions including stroke, cognitive decline, and vascular dementia [1,2]. Recent clinical studies showed that eHcy increases the prevalence of peripheral neuropathy in diabetes and exacerbates the preexisting diabetic-neuropathy [3-5]. Lately, our clinical observation suggested that eHcy is an independent risk factor for the development of peripheral neuropathy [6]. Evidence from in vitro experiments and in vivo animal studies has suggested a toxic effect of homocysteine causing neuropathy [7,8]. Clinically, we have encountered a group of patients with symptoms and signs of peripheral neuropathy in whom an isolated eHcy was identified but with normal plasma levels of vitamin B12, folic acid, methylmanolic acid and without any other identifiable etiology. We named the entity as *isolated* eHcy-induced neuropathy (IHIN) and, therefore, performed neuroelectrodiagnostic studies to characterize the electrophysiologic features of IHIN.

METHODS

Neurophysiology laboratory databank and the charts of subjects with a clinical diagnosis of neuropathy seen in the neuromuscular clinic were retrospectively reviewed from 10/1/2004 to 9/30/2008. This study was approved by the Temple University Institutional Review Board. Data of clinical presentations, physical and neurological examinations, history of concomitant comorbidities including substance use; and laboratory findings including plasma levels of homocysteine, methylmalonic acid, vitamin B12, folic acid, mean corpuscular volume of red blood cells, glucose, creatinine, glycosylated hemoglobin, thyroid stimulating hormone, lipids and liver function panels; inflammatory and infectious studies including erythrocyte sedimentation rate, C-reactive protein, antinuclear antibody, *rapid plasma reagin*, Lyme titers, hepatitis profile, and h*uman immunodeficiency virus*; and neurophysiologic studies including the data of nerve conduction studies (NCS) and needle electromyography (EMG), were reviewed. The symptoms and signs of neuropathy included the presentations of numbness, tingling, and/or weakness in the distal limbs with a decreased

sensation in a glove-and/or stocking-like pattern and deceased tendon reflexes [6]. Subjects with neuropathy and an *isolated* eHcy who completed electrophysiologic studies were included. Subjects with an identifiable etiology, other than eHcy, for neuropathy such as vitamin B12 and/or folic acid deficiency, metabolic, toxic, endocrinologic, infectious, inflammatory, renal or liver diseases, or who did not undergo electrophysiologic studies, were excluded.

Neuroelectrophysiologic studies and data acquisition

Conventional NCS was performed including motor nerve study on median, ulnar, fibular and tibial motor nerves, and sensory nerve study on median, ulnar, radial and sural sensory nerves in one arm and/or one leg of the IHIN subjects using a Nicolette Biomedical EMG machine (Viking Select, version 10, Madison, WI). The skin temperature was monitored and maintained at 32°C or above for the upper and 30°C or above for the lower extremities. Data of NCS including distal latency, amplitude, duration and area of the action potentials, and conduction velocity of individual nerves were obtained. EMG using concentric electrodes was performed in one arm including deltoid, biceps, triceps, first dorsal interosseous, and abductor pollicis brevis muscles; and one leg including medial vastus, tibialis anterior, medial gastrocnemius, and pedis first dorsal interosseous muscles. Data of EMG including insertional, spontaneous, volitional activities, configuration of motor unit potentials, and recruitment pattern were collected.

RESULTS

A total of 28 IHIN-subjects who met the inclusion criteria were included (age: 66.3±9.4 year-old, mean±SD, Male/Female=12/16). Their plasma level of homocysteine was elevated (17.2±4.4 μmol/L, normal: ≤11.5) but with normal plasma levels of B12 (619.8±430.9 pg/mL; normal: 200-1100), folic acid (16.8±5.3 ng/mL; normal: >5.4), methylmanolic acid (183±88.9 nmoI/L; normal: 73-376), and a normal mean corpuscular volume (89.2±7.2 fl; normal: 80-100) of red blood cells.

NCS and EMG were performed on one arm in 2 patients, one leg in another 2, and both one arm and one leg in 24 patients. A total of 26 arms and 26 legs were evaluated in 28 patients. The numbers of abnormal recordings in motor NCS with a prolonged distal latency (p-DL) /decreased amplitude (d-Amp) /slowed conduction velocity (s-CV) of the compound muscle action potentials were 21 (p-DL) /4 (d-Amp) /8 (s-CV) in median; 5 (p-DL) /0 (d-Amp) /7 (s-CV) in ulnar; 3 (p-DL) /10 (d-Amp) /5 (s-CV) in fibular; and 4 (p-DL) /9 (d-Amp) /5 (s-CV) in tibial motor nerves; respectively. The numbers of abnormal sensory NCS were 12 (d-Amp) /20 (s-CV) in median; 9 (d-Amp) /14 (s-CV) in ulnar; 4 (d-Amp) /3 (s-CV) in radial; and 13 (d-Amp) /10 (s-CV) in sural sensory nerves; respectively (Table 1 and supplementary table I and II). EMG showed abnormal findings (61%; n=17/28) including chronic neurogenic changes (36%; 10/28) such as polyphasias with enlarged motor unit potentials; distal active denervation (7%; 2/28) such as fibrillation or positive sharp potentials; both chronic neurogenic changes and distal active denervation (18%, 5/28) ; and normal EMG findings (39%; 11/28) (Table 2, and supplementary table 3). The electrophysiologic studies combining NCS and ENG showed that 93% (26/28) IHIN patients had electrodiagnostic abnormalities including 75% (21/28) with mild sensorimotor neuropathy, 18% (5/28) with the electrodiagnostic features of carpal tunnel syndrome; while only 7% (2/28) had normal findings (Table 3 and Supplementary Table III). These results suggested that the electrophysiologic features of IHIN are a mixed type of large fiber neuropathies with mild demyelination and axonal degeneration.

DISCUSSION

eHcy can be caused by deficiency of either B12 or folic acid alone, or in combination, or genetic variation. The electrophysiologic features of B12 deficiency related neuropathy have been reported as axonal degenerating and/or demyelinating [9-12]. To our knowledge, there is no published report on the electrophysiologic findings in IHIN. The current study provided the electrophysiologic evidence that IHIN is involving a large fiber neuropathy with a mixture of mild demyelination and

Table 1: Abnormal findings of nerve conduction studies.

Nerve	Prolonged DL	Decreased AMP	Slowed CV
Motor			
Median	81% (21/26)	15% (4/26)	31% (8/26)
Ulnar	19 (5/26)	0 (0/26)	27 (7/26)
Fibular	12 (3/26)	39 (10/26)	19 (5/26)
Tibial	15 (4/26)	35 (9/26)	19 (5/26)
Sensory			
Median		46% (12/26)	77% (20/26)
Ulnar		35 (9/26)	54 (14/26)
Radial		15 (4/26)	12 (3/26)
Sural		50 (13/26)	39 (10/26)

DL: distal latency.
AMP: amplitude.
CV: conduction velocity.
*: for detail, please see the supplementary tables.

Table 2: Electromyographic findings.

Findings*	%	(n/total)
Abnormal	61	(17/28)
CNC:	36	(10/28)
DAN	7	(2/28)
DAN + CNC	18	(5/28)
Normal	39	(11/28)

CNC: chronic neurologic changes.
DAN: distal active degeneration.
*: for detail, please see the supplementary tables.

Table 3: Electrodiagnostic findings.

Findings*	**%**	**(n/total)**
Abnormal	93	(26/28)
SM-NP	75	(21/28)
CTS	18	(5/28)
Normal	7	(2/28)

SM-NP: sensorimotor neuropathy
CTS: carpal tunnel syndrome.
*: for detail, please see the supplementary tables.

axonal degeneration features, similar to those of B12 deficiency-induced neuropathy, though the possibility of whether the small fiber involvement needs further investigation.

Our findings also support the notion that, in addition to the deficiency of B12 and/or folic acid, eHcy may be a potential risk factor for the development of neuropathy [6]. eHcy results from many pathophysiologic conditions including aging [13,14], obesity [15,16], diabetes mellitus [17-19], renal function impairment [19], medications and/or toxic substances such as levodopa [20-22], anti-gastric acid agents [23,24], anti-epileptics [25,26], tobacco [27-29] and alcohol [30-32] and genetic predispositions such as C677T polymorphism of MTHFR [33,34]. Homocysteine, especially eHcy, can be toxic because of its excitatory properties which markedly enhance the vulnerability of neuronal cells to excitotoxic- and oxidative-stress-induced injury [35-38], and cause neuropathy [6-8]. Previous clinical studies showed that eHcy exacerbates prevalence and severity of diabetic-neuropathy [3-5].

eHcy is a treatable medical condition. A regimen of combined vitamin B12, folate, and B6 reduces eHcy [39-41] although the efficacy on IHIN remains to be elucidated [2]. Nevertheless early establishment of the diagnosis and prompt initiation of treatment may be critical in facilitating recovery at the early stage and preventing, or delaying, the occurrence of a late, possibly irreversible, neuropathologic course of the secondary axonal denervation observed electrophysiologically in IHIN patients.

CONCLUSION

Our study showed electrophysiologic evidence that IHIN is a large fiber sensorimotor neuropathy with mixed neurophysiologic features of mild demyelination and axonal degeneration. Additional study in a large number of IHIN is needed to validate the findings and further study on the small fibers is warranted. Early diagnosis may be crucial in effective management of IHIN patients.

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