Original Article

Indian Journal of Pathology: Research and Practice

Pathophysiological Changes in Nerve Conduction Studies in Diabetic Peripheral Neuropathy: An Integrative Overview

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Abstract

Background: Nerve conduction studies (NCSs) involve the delivery of electric stimuli to peripheral nerves at accessible locations on the human body and the recording of electrophysiological responses. NCSs are considered as important evaluation tools for peripheral neuropathy (PN) and common disabling cause for PN is diabetic peripheral neuropathy (DPN). **Objective:** To perform an integrative overview on evidence for nerve conduction and its pathophysiological changes due to DPN in terms of assessment and treatment studies. **Methods:** A systematic review was performed using search terms 'diabetic neuropathy' and 'nerve conduction' in PubMed, CINAHL and Google scholar to identify relevant studies based upon their title, abstract and full-text and they were descriptively synthesized for their data and reported for measurement properties, comparison with other assessments and studying efficacy of interventions. **Results:** Of the total 45 included studies, 17 studies were on measurement properties (sensitivity/specificity=2, reliability=3, population comparison=3, prevalence=7, anthropometric factors=2); 12 studies compared NCSs with other assessment methods (clinical examination=2, clinical scales=4, current perception thresholds=1, electromyography=1, exercise-induced stress=1, ultrasonography=1, vibration perception thresholds=1, nerve morphology=1); and, 16 studies used NCSs as a therapeutic outcome measure for effects of interventions (4-methylcatechol=1, acetyl-l carnitine=1, adenosine=1, carbamazepine=1, pancreatic transplantation=1, alpha lipoic acid=2, fidarestat=2, gangliosides=1, insulin therapy=1, vitamins=1, ponalrestat=1, silymarin=1, sorbinil=1, zenarestat=1).**Conclusion:** NCSs remain to be established as a 'stand-alone' gold-standard objective and accurate assessment tool for diagnosis, therapeutic and prognostic decision-making for patients with DPN.

Keywords: Neurophysiology; Diabetic polyneuropathy; Electrodiagnosis; Electrophysiology; Physical examination.

Introduction

Anatomically and physiologically, peripheral nervous system represents a network of continuum from head to toe and right to left.[1] This inter-relationship between neuroanatomy and neurophysiology is responsible for structural and functional properties of peripheral nerves, in their response to tissue stress, injury and disease.[2]

Peripheral nerves have the ability to respond to injury and disease by plasticity and regeneration, whilst the former allows the nerve to adapt to existing structure-function balance and the latter allows it to recover from neuropathological processes.[3] The

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interactions between central and peripheral nervous systems influence structure-function balance from mind-brain-body continuum.[4]

The close inter-relationship between glycemia and peripheral nerve structure and function is understood from the integral role of insulin-like growth factors in growth and development of nerves in health and disease.[5] Mechanisms for peripheral nerve dysfunction in diabetes mellitus include but not limited to polyol flux, microangiopathy, oxidative stress, abnormal signaling from advanced glycation end products and growth factor deficiency.[6]

Neurological examination is undergoing a paradigm shift towards quantification and objectification[7] and the clinical tests and measures had been documented for their reliability and validity for assessing neurologic function.[8] Electrophysiological testing forms a comprehensive part of functional neurologic assessment in neurological examination[9] and is thus conventionally considered a gold standard in diagnosing peripheral neuropathies.[10]

Electrophysiological testing includes sensory and motor nerve conduction velocities, nerve and muscle action potentials, evoked potentials and electromyography.[11] Electro-physiological studies had revealed somatosensory conduction delay in both central and peripheral nervous system of diabetes patients which were measured by nerve conduction studies(NCS).[12]

NCSs involve the delivery of electric stimuli to peripheral nerves at accessible locations on the human body and the recording of electrophysiological responses.[13] NCSs had several components that might be analyzed and interpreted such as amplitude, duration, area, latency and conduction velocity.[14]

Competence in understanding the degree of axonal or myelin function or dysfunction in a nerve improve one's effectiveness not only in medical/surgical treatment but in prognostication of recovery of function in peripheral neuropathies.[15] NCSs thus provide essential diagnostic information in peripheral neuropathy on (1) the spatial pattern of neuropathy, (2) the pattern of abnormalities distinguishing between primarily axonal and demyelinating pathology, and (3) the severity of neuropathic damage.[16]

Peripheral neuropathy is the most common microvascular complication of diabetes mellitus and the chronic disabling painful condition is termed as diabetic peripheral neuropathy (DPN). Although clinical tests for nerve function in diabetes are widely used, NCSs could detect subclinical nerve dysfunction which precedes the diagnosis of polyneuropathy.[17]

The objective of this study was to perform an integrative overview on evidence for nerve conduction and its pathophysiological changes due to DPN in terms of assessment and treatment studies.

Methodology

A systematic review was performed using search terms "(diabetes [Title] OR diabetic [Title]) AND (neuropathy [Title] OR neuropathic [Title]) AND (nerve[Title] AND conduction [Title])" in PubMed, CINAHL and Google scholar to identify relevant studies based upon their title, abstract and full-text and they were descriptively synthesized for their data and reported for measurement properties, comparison with other assessments and studying efficacy of interventions.

Results

Of the total 45 included studies, 17 studies were on measurement properties (sensitivity/specificity=2, reliability=3, population comparison=3, prevalence=7, anthropometric factors=2); 12 studies compared NCSs with other assessment methods (clinical examination=2, clinical scales=4, current perception thresholds=1, electromyography=1, exercise-induced stress=1, ultrasonography=1, vibration perception thresholds=1, nerve morphology=1); and, 16 studies used NCSs as

a therapeutic outcome measure for effects of interventions (4-methylcatechol=1, acetyl-l carnitine=1, adenosine=1, carbamazepine=1, pancreatic transplantation=1, alpha lipoic acid=2, fidarestat=2, gangliosides=1, insulin therapy=1, vitamins=1, ponalrestat=1, silymarin=1, sorbinil=1, zenarestat=1).

Measurement Properties

Anthropometric Factors

Gadia *et al* examined associations between height and quantitative sensory, nerve-conduction, and clinical indices of diabetic peripheral neuropathy in adult diabetic patients. The peroneal and posterior tibial motor nerve-conduction velocities were inversely related to height. Glycosylated hemoglobin was significantly related to peroneal and posterior tibial motor nerve-conduction velocities.[18]

Albers *et al* evaluated baseline nerve conduction measures from 429 patients and found that the men had lower amplitudes and conduction velocities and longer latencies than the women. The relationships between nerve conduction measures and age, sex, and anthropometric factors were similar for patients with type II, but not those with type I.[19]

Comparison between Populations

Ohgaki *et al* investigated the usefulness of a new parameter, the ratio of motor nerve conduction velocity to F-wave conduction velocity (M/F ratio), for the differential diagnosis of diabetic neuropathy by conducting Nerve conduction studies in 95 patients with diabetic neuropathy, 44 nondiabetic patients with peripheral neuropathy, and 24 normal control subjects. The MCV and SCV of diabetic patients were found to be slower and the M/F ratio was significantly lower than those of normal subjects.[20]

Caccia *et al* described a computer-assisted collision method to evaluate motor conduction velocity distribution of the ulnar and external peroneal nerves in normal subjects and in insulin-dependent and non-insulin-dependent diabetics. Distribution curves were sigmoidally (bimodally) shaped in normal and in insulin- and non-insulin-dependent subjects. In insulin-dependent patients, motor conduction velocity of the peroneal nerves was globally impaired, whereas of the ulnar nerves it was normal. In non-insulin-dependent patients, slower conduction velocity was involved in both nerves.[21]

Caccia *et al* explained the use of a new computer-assisted method to evaluate sensory conduction velocity distribution and dispersion of the digital nerve of the middle finger in normal subjects and in type I and type II diabetic subjects. Distribution curves were exponentially shaped in normal and in diabetic subjects. In insulin-dependent diabetics, only slower conduction velocity fibers were involved, whereas no significant difference was observed between the non-insulin-dependent diabetic group and the control group.[22]

Prevalence

Kiziltan *et al* analyzed the clinical and electrophysiological features in 318 patients with diabetic foot and found motor nerve conduction abnormalities and ulnar nerve involvement to be more frequent and severe in males. Among these 30 patients with severe demyelination, 6 male subjects had clinical features similar to that of chronic inflammatory demyelinating polyneuropathy.[23]

Sathiamoorthy *et al* performed electrophysiological evaluation of conduction in sensory fibres of right ulnar and median nerves in normal subjects and diabetics with and without neuropathy.[24] "The sensory conduction velocities of ulnar as well as median nerves are significantly depressed in both groups of diabetics, particularly in those with neuropathy. The diabetics with or without neuropathy require a higher strength of stimulus for conduction in both median and ulnar nerves as compared to the normal subjects. The amplitude of action potentials is also lowered in both ulnar and median nerves of the two groups of diabetics."

Kiziltan *et al* assessed if diabetic dermopathy (DD) was a sign for severe polyneuropathy (PNP) by investigating the clinical and electrophysiological characteristics of 166 diabetic men with different degrees of peripheral nerve involvement. Nerve conduction studies showed the mean compound muscle action potentials (CMAP) were smaller in the DD and DF patients than the PNP patients for peroneal, median and ulnar nerves. The mean nerve conduction velocities (NCV) of all nerves were slower in the DD and DF patients in compared to sole PNP patients. The mean distal latencies (DL) of the DD/DF patients were longer than the PNP group.[25]

Irkeç *et al* performed facial nerve conduction studies in 20 DPN patients and found prolonged facial nerve distal latency at least on one tested side in 70% of patients. Distal latency and amplitudes of muscle responses to facial nerve stimulation showed a statistically significant difference from controls.[26]

Bertora *et al* evaluated the presence of subclinical neuropathy in 138 diabetic patients by conduction velocity distribution (CVD) study of four motor nerves (external popliteal and ulnar nerves bilaterally) and two sensory nerves (median nerve bilaterally), and compared the obtained data standard electrophysiological parameters in the same nerve segments. Of the patients adequately evaluated by both techniques, 21 of 129 patients (16%) revealed altered CVD data unaccompanied by slowing of maximum nerve conduction velocity, and 37 patients of 101 (37%) showed similar findings for sensory nerves.[27]

Noël recorded median sensory nerve potentials in 59 DPN patients.

There were correspondingly low sensory nerve potentials with severity of median mononeuropathy, although no clinical signs were present.[28]

Lee *et al* investigated the changes of peripheral nerve conduction (median, ulnar, posterior tibial, peroneal, and sural) in 37 children with insulin-dependent diabetes mellitus (IDDM) and found 12 patients (32.4%) showed electrophysiological evidence of polyneuropathy in at least two different nerves including the sural nerve at the diagnosis of IDDM; 20 patients (54%) had multiple (e"2) abnormalities in parameters of NCS. Poor metabolic control, height, duration of diabetes, and older age of onset were related to the changes of parameters of NCS over 5 yr.[29]

Reliability

Bird *et al* evaluated the reproducibility of multiple electrophysiologic (nerve conduction studies, NCS) and quantitative sensory (QST) tests in 1100 patients and found that all NCS tests were highly reproducible. Repeating NCS and QST measures decreased sample sizes needed to show statistical significance.[30]

Chaudhry *et al* determined the inter- and intraexaminer reliability of nerve conduction measurements in six patients with diabetic peripheral neuropathy. Intraexaminer reliability was high for 11 of 12 measurements, and interexaminer reliability was high for eight of twelve.[31]

Tjon-A-Tsien *et al* studied the repeatability of compound muscle action potential (CMAP) and conduction parameters of conventional and large electrodes in 16 controls and 17 diabetic neuropathic patients, for right-sided median, peroneal, and tibial nerves. The use of large electrodes improved repeatability further: large electrodes resulted in substantially smaller coefficients of variation (CV) for duration, amplitude, area, and changes of amplitude and area over a length of nerve, which were reduced by 10%, 31%, 29%, 27%, and 16%, respectively.[31]

Sensitivity/Specificity

Uluc *et al* evaluated the medial plantar and dorsal sural NCS in a group of 30 diabetic patients with distal sensory neuropathy (DSN) and in 30 healthy controls.Among clinically defined 30 DSN patients, medial plantar NAP amplitude was abnormal in 18 (60%) and dorsal sural nerve amplitude was abnormal in 13

(40%) of the patients bilaterally. Evaluation of both of these nerves increased the sensitivity up to 70% in the detection of neuropathy.[33]

Papanas *et al* evaluated the sensitivity and specificity of a new indicator test (Neuropad) for the diagnosis of peripheral neuropathy in 120 type 2 diabetes patients as compared with clinical examination and nerve conduction study (NCS) performed on radial, ulnar, sural, and common and deep peroneal nerves. The sensitivity of NCS for clinical neuropathy was 94%, and its specificity was 62.1%.[34]

Comparison with Other Assessment Methods

V/s Clinical Examination

Palmer *et al* studied 56 type II diabetic males of whom 19 were diagnosed as having secondary impotence (SI); and found correlation between slow (less than 42 M/sec) motor nerve conduction velocity (MNCV) and SI, amounting to 58 per cent of the 19 cases.[35]

Braddom *et al* studied the electrophysiologic and clinical characteristics in 56 patients and the study findings indicated a close correlation of clinical and electrophysiologic findings. The study concluded that diabetic peripheral neuropathy was present if two of the following three determinations were abnormal: median motor or sensory latency, ulnar sensory latency and sural latency.[36]

V/s Clinical Scales

Feki and Lefaucheur designed a software tool to convert electrophysiological data into one single index of polyneuropathy (IPN) which was calibrated to grade the severity of a polyneuropathy from 0.00 to 1.00. The author calculated NDS, NSS and IPN In a series of 38 diabetic patients, and found correlations between these variables, NDS and IPN exhibiting the more significant association.[37]

Dyck and O'Brien suggested that in controlled clinical trials, a mean change of 2 points on the neurologic disability score is clinically detectable and meaningful which corresponds to a change of motor nerve conduction velocity of the average ulnar median and peroneal nerves of 2.9 m/s and peroneal nerve of 2.2 m/s. The corresponding changes of amplitude were 1.2 and 0.7 mV, respectively.[38]

An *et al* evaluated the correlation between DNS score and medial plantar NCS in 50 diabetic patients (35 asymptomatic and 15 symptomatic) and 19 healthy subjects.. The amplitudes of sural and medial plantar NAP were found to correlate with DNS score.[39]

Asad *et al* compared the nerve conduction studies in 30 clinically undetectable and 30 detectable sensorimotor polyneuropathy which was done according to Diabetic Neuropathy Symptom Score and Diabetic Neuropathy Examination scores. The amplitudes, velocities, latencies, outcome and grading of neuropathy in nerve conduction studies when compared with neurological detection scores showed a significant relation in each group regarding evaluation.[40]

V/s Current Perception Thresholds

Rendell *et al* tested sensory and motor NCVs and CPTs at 5, 250, and 2000 Hz of the upper and lower extremities in 71 individuals with diabetic neuropathy of varying degrees of severity. The strongest of the correlations were found between the physical scores and motor NCVs of the median nerve and the tibial nerve. Normal NCVs were present in the face of very significant historical and physical abnormality.[41]

V/s Electromyography

Vinik *et al* studied 17 DPN patients by performing NCS using the NC-stat nerve conduction testing system (NEUROMetrix, Inc., Waltham, MA) and compared the results with neurologist-supervised electromyographic study, as a reference method. There was high positive correlation observed between the NC-stat system and the reference measurements for DML and F-wave latency for the median and ulnar nerves.[42]

V/s Exercise-Induced Stress

Tesfaye *et al* recorded sural sensory conduction velocity (x3) in 12 non-neuropathic diabetic subjects, 15 diabetic subjects with established neuropathy and 16 age-matched normal control subjects, before and after exercise to 80% age/sex predicted maximum heart rate. Sural sensory conduction velocity increased by 5.07 m/s after exercise in normal subjects and 3.99 m/s in non-neuropathic diabetic subjects but only 0.99 m/s in neuropathic subjects.[43]

V/s Ultrasonography

Severinsen and Andersen evaluated the relationship between nerve conduction studies (motor nerve conduction studies of the peroneal and tibial nerves) and the size of small foot muscles in 17 DPN patients. Close relations were found between extensor digitorumbrevis muscle size and the amplitude of the CMAP of the peroneal and of the tibial nerve. Further there were close relations between the muscle size and the NCV of the peroneal and of the tibial nerve.[44]

V/s Vibration Perception Thresholds

Klima *et al* compared the two parameters of nerve conduction studies (nerve conduction velocities and amplitudes of the evoked sensory and motor responses) with quantitative vibration perception thresholds (VPT) in patients with peripheral neuropathy (diabetes mellitus and/or end-stage renal disease). VPTs were found to be correlated with nerve conduction velocities in all upper and lower extremity sensory and motor nerves tested, and with the amplitudes of the evoked motor responses in three motor nerves: median and ulnar (motor components) and tibial.[45]

V/s Nerve Morphology

Behse *et al* reported association of morphological findings in sural nerves with nerve conduction in 12 patients with diabetic neuropathy, five with mainly sensory involvement, four with severe, symmetrical sensory-motor polyneuropathy, and three with multiple mononeuropathy. The relationship indicated slowing less than 20 to 30% was due to causes other than fibre loss.[46]

Effects of Interventions

4-Methylcatechol

Hanaoka *et al* examined the effects of 4-methylcatechol (4-MC), a nonamine catechol compound, on the neuropathic process of streptozotocin (STZ)-induced diabetic rats. 4-MC treatment was found to elevate the NGF content and prevent the reduction in MNCV.[47]

Acetyl-L-Carnitine (ALC)-Cyclooxygenase (COX) Inhibition

Pop-Busui *et al* explored the relationships between COX-mediated and acetyl-L-carnitine (ALC)-sensitive defects that contribute to functional, metabolic, and vascular abnormalities of experimental DN and their study findings implied: 1) a tonic role of the COX-1 pathway in the regulation of nerve osmolytes and Na,K-ATPase activity and the maintenance of nerve blood flow (NBF) in non-diabetic (ND) animals and 2) activation of the COX-2 pathway as an important mediator of NBF and motor nerve conduction velocity (MNCV) deficits in experimental DN.[48]

Adenosine and Adenosine A2A Receptor Agonist

Kumar *et al* examined the effects of chronic administration of adenosine and CGS 21680 hydrochloride (adenosine A(2A) receptor agonist) on motor nerve conduction velocity (MNCV), nerve blood flow (NBF) and histology of sciatic nerve in animal model of diabetic neuropathy. Adenosine significantly improved sciatic MNCV and NBF in diabetic rats.[49]

Carbamazepine

Chakrabarti and Samantaray[50] treated 54 patients with carbamazepine for a period of one year and found that 49 patients had symptomatic relief of all sensory manifestations

but NCV remained essentially unchanged.

Combined Pancreatic and Renal Transplantation (CPRT)

Solders *et al* performed CPRT surgey on 18 T1DM patients versus 18 control diabetic patients with only a kidney grafts. After initial improvement of nerve conduction in both groups, probably caused by the elimination of uremia, further improvement was seen only in the euglycemic pancreas-graft recipients.[51]

DL-Alpha-Lipoic Acid

Stevens *et al* reported effects of administration of the antioxidant DL-alpha-lipoic acid (LA) to streptozotocin-injected diabetic rats. LA improved digital sensory but not sciatic-tibial motor NCV, corrected endoneurial nutritive but not composite NBF, increased the mitochondrial oxidative state without correcting nerve energy depletion, and enhanced the accumulation of polyol pathway intermediates without worsening myo-inositol or taurine depletion.[52]

Nagamatsu *et al* evaluated the efficacy of LA supplementation in improving nerve blood flow (NBF), electrophysiology, and indexes of oxidative stress in peripheral nerves affected by SDN and found that the conduction velocity of the digital nerve was reduced in SDN and was significantly improved by LA.[53]

Fidarestat-Mitogen-Activated Protein Kinase P38

Price *et al* examined the role of p38 mitogen-activated protein (MAP) kinase in transducing high glucose into deficits in nerve conduction velocity (NCV) that are characteristic of diabetic neuropathy. Dorsal root ganglia (DRG) from diabetic animals showed marked activation of p38 at 12 weeks of diabetes. Treatment of diabetic animals with a specific inhibitor of p38 (SB 239063), fidarestat, or insulin also prevented reductions in both motor and sensory NCV.[54]

Middlemas *et al* determined the association between phosphorylation of c-Jun N-terminal kinase (JNK) and one of its transcription factors, c-Jun, in sensory neurones innervating the lower limb, and also examined the effect of aldose reductase inhibition on JNK and c-Jun phosphorylation. Phosphorylation was found to be prevented in all cells by fidarestat, which normalisedpolyol pathway metabolites as well as motor nerve and sensory nerve conduction velocity for sciatic nerve.[55]

Gangliosides

Spüler *et al* studied the motor nerve as well as the maximal proximal and distal nerve conduction velocity in 55 DPN rats. Injections of gangliosides (Cronassial) significantly counteracted the slowing of nerve conduction in comparison to that observed in the diabetic placebo group during the development of the neuropathy.[56]

Insulin Therapy

Service *et al* compared conventional insulin therapy (CIT) and continuous subcutaneous insulin infusion (CSII) in 12 C-peptide deficient Type 1 (insulin-dependent) diabetic patients with abnormal peripheral nerve function and found improved glycaemia and improved HbA1, nerve conduction and vibratory sensation threshold in patients treated with CSII than those who received CIT, at 8-months follow-up.[57]

Neurotropic Vitamins

Tong studied 33 diabetics with polyneuropathies using Neurobion administration and found increases in the nerve conduction velocity, which had decreased prior to the beginning of treatment, coinciding closely with clinical examinations.[58]

Ponalrestat

Calcutt *et al* measured motor nerve conduction velocity (MNCV), Na(+)-K(+)-ATPase activity, polyol-pathway metabolites,

and myo-inositol in sciatic nerves from control mice, galactose-fed (20% wt/wt diet) mice, and galactose-fed mice given the aldose reductase inhibitor ponalrestat (300-mg/kg diet). Treatment of a separate galactose-fed group with sorbinil also attenuated the MNCV deficit and prevented the increased Na(+)-K(+)-ATPase activity associated with galactosemia.[59]

Silymarin

Baluchnejadmojarad *et al* studied the effects of chronic silymarin (SM) treatment on hyperalgesia, sciatic motor nerve conduction velocity (MNCV) and oxidative stress in streptozotocin (STZ)-diabetic neuropathic rats which were divided into control, diabetic, SM-treated control and diabetic, and sodium salisylate (SS)-treated control and diabetic. SM treatment significantly ameliorated the alteration in MNCV, hyperalgesia, MDA level and antioxidant enzyme SOD in diabetic rats.[60]

Sorbinil

Sima *et al* obtained sural nerve biopsies from 16 neuropathic diabetic patients participating in a clinical trial of the aldose reductase inhibitor sorbinil. The improvement in sural nerve conduction velocity in sorbinil-treated patients correlated with the product of the quantitative improvements in axo-glial dysjunction and axonal atrophy.[61]

Zenarestat

Greene *et al* determined the efficacy of aldose reductase inhibitor (ARI) zenarestat on nerve conduction velocity (NCV) and nerve morphology in diabetic peripheral polyneuropathy (DPN) and observed dose-dependent increments in sural nerve zenarestat level and sorbitol suppression were accompanied by significant improvement in NCV.[62]

Discussion

This study was aimed at providing an integrative literature update on the role of nerve conduction studies in DPN and the present evidence reiterates the leading role of NCS as a gold standard diagnostic tool and a valuable prognostic tool for evaluating effects of interventions.

Waxman reviewed the pathophysiologic and clinicopathologic aspects of diabetic nerve disease and explained, "Abnormal modes of impulse conduction in diseased nerves include decreased conduction velocity, temporal dispersion of impulses, frequency-related and total conduction block, abnormal cross-talk, and impulse reflection. Because structural and electrophysiologic variables (such as fiber geometry, ionic channel density, and properties of the extracellular milieu) vary with diameter, it is suggested that pathophysiologic mechanisms also should vary with diameter. Topographic patterns of clinical deficit, and their pathologic basis, are reviewed; it is suggested that lesions distributed at random along the length of the entire fiber may result in dysfunction that exhibits distinct proximal-distal gradients."[63]

The value of NCSs in detecting diabetic polyneuropathy is important, considering the fact that they were used to derive the diagnostic criteria from the Rochester Diabetic Neuropathy Study by Dyck *et al* which included: "fibular motor nerve conduction velocity (MNCV; 26.3%); sural sensory nerve conduction velocity (SNAP; 25.4%); tibial MNCV (24.8%); ulnar MNCV (21.3%); fibular F-wave latency (16.9%); and ulnar F-wave latency (16.0%)."[64]

It is essential to recognize the facts, fallacies and fancies,[65] and, principles and pitfalls of NCS[66] so that their findings could be interpreted to provide unique quantitative information about neurological function in patients with a variety of neuromuscular

disorders.[67]

Indications for nerve conduction studies are many, including evaluation of the nature of the pathophysiology, quantification of the severity of involvement, detection of the level of a neurologic deficit, and determining prognosis,[68] which should be kept in mind when selecting patients for testing.

Repeated measurements of NCS were prone to huge variability which was influenced by tester, testing method, test tool, testing instrument and testing environment,[69] and the methodological statistics in reporting scientific findings[70] and thus it is imperative to maintain these confounding factors fairly under control when using NCSs for people with DPN.

Also is well known the different methodologies of performing NCSs, such as evaluating orthodromic and antidromic latencies in sensory nerve action potentials;[71] and various other variables as listed by Wilbourn[72] as: "(a) bipolar vs. monopolar recording; (b) antidromic vs. orthodromic technique; (c) needle vs. surface stimulating electrode(s); (d) needle vs. surface recording electrodes; (e) fixed vs. variable distances between cathode and active recording electrode; (f) measuring latencies to onset vs. to peak; and (g) measuring amplitudes baseline to peak vs. peak to peak." Equally so with motor nerve conduction studies in terms of electrode placement, stimulus intensity, algorithms for measurement of parameters, causes of variability, reference values, and reporting.[73]

An abnormal NCS finding was associated commonly with neurological referral diagnosis, history of paraesthesias and of weakness and sensory loss on examination, and a negative effect of history of pain.[74] Also, other uncontrollable confounders were the anatomic variations of the peripheral nerve in its branches or its course.[75] Nerve conduction tests provide the most specific, objective, sensitive, and repeatable procedures to detect, characterize and assess the severity of DPN, although these may be the least meaningful.[76]

Newer diagnostic tests are available for DPN which were classified into those mainly assessing large-fiber function (tactile circumferential discriminator, steel ball-bearing, and automated nerve conduction study) and those mainly assessing small-fiber function (NeuroQuick and Neuropad),[77] all of which indicate validation by comparison with NCSs. Also is essential to compare NCSs with cluster of symptoms and signs in their diagnostic ability to detect diabetic sensorimotor polyneuropathy.[78]

Few limitations of this study include a lack of meta-analysis and use of a non-validated search strategy including only studies which listed the search terms in their title. The former was inevitable due to the heterogeneity between the studies and the latter was acceptable to focus on the assumption relating significant terms to be mentioned in study titles.

Clinical trials on DPN should follow the suggestions provided by Olney:[79] "the attributes of nerve conduction studies that are likely to be most useful are summated or averaged sensory nerve action potential amplitudes and averaged motor nerve conduction velocities. Summated or averaged compound muscle action potential amplitude and mean F-wave latencies are also highly informative."

Future assessment studies should provide population-specific and disease-specific reference values[80] and also compare and correlate NCS findings with clinical examination,[81] clinical scales,[82] neurodynamic examination,[83] neuropathic pain and quality of life[84] in people with DPN, and treatment studies should study the effects of medical,[85] surgical,[86] physiotherapeutic [87] neurodynamic[88] and acupuncture[89] treatments on NCSs.

Conclusion

NCSs remain to be established as a 'stand-alone' gold-standard objective and accurate assessment tool for diagnosis, therapeutic and

prognostic decision-making for patients with DPN.

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