Diabetic Neuropathy - A Review On Conventional Generalisations

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Abstract: Diabetic neuropathy is common and key challenge to practising physician. Pain is ubiquitous acute neuropathathic patients and 50 percent of patients experience pain with the common chronic sensory motor neuropathy. The major step in treating DN is to stabilize glycaemic control. It is believed that hyperglycaemia and its concomitant biochemical characteristics can cause neuropathic pain directly. All treatment for diabetic neuropathy will work on symptoms preferably than the pathophysiologic abnormalities. First line agents are the tricyclic anti-depressants which should be taken at night. Common side effects are present. The use of antiarrhythmics, such as mexiletine, is not satisfactory. Therefore anticonvulsant drugs such as gabapentin is used as a major drug used in the management. Using a protein kinase C-β inhibitor various studies have been carried out. Phase-III, multicentre clinical trials are in progress.

Keywords: Neuropathy, mexiletine, gabapentin, protein kinase.

Introduction

Diabetic neuropathy is a frequent and prevalent snag of diabetes mellitus and is generally contemplate to duration and severity of hyperglycemia[1]. It is the main reason for 50-70 percent non-traumatic amputations and causes leg pain in patients. Diabetic neuropathy (painful) is miscellaneous disorder that encircle abnormalities which affect proximal and distal peripheral sensory and motor nerves along with autonomic nervous system[2,3]. Span of diabetes and glycaemic control are important speculating factor for the incidence of neuropathy. Thomas gave a classification based on anatomical characteristics[4].

Table -I Classification : Diabetic Neuropathy.

A	Generalized symmetrical polyneuropathies	B	Focal and Multifocal
1.	Chronic sensorimotor polyneuropathies	(i)	Mononeuropathies-cranial nerve and peripheral nerve
(i)	Sensory-thin fibres(C fibres)/thick fibres-Aα and Aβ fibres.	(ii)	Multiple mononeuropathy-mononeuritis multiplex
(ii)	Mixed nerves	(iii)	Focal limb/trunk involvement-thoracic, lumbosacral and cranial neuropathy.
2.	Acute sensory neuropathy	(iv)	Compression neuropathy: e.g., carpel tunnel syndrome
3.	Autonomic neuropathy-gastrointestinal tract, cardiovascular system and genitourinary system.	(v)	Inflammatory demyelinating neuropathy.

Pathogenesis

Currently there are four main hypothesis which provide pathogenesis of diabetic neuropathy:

(i) Activity of hexokinase pathway is increased.
(ii) Isoforms of protein kinase C (PkC) are activated.
(iii) Increased intracellular production of advanced glycation-end-products.
(iv) Flux of glucose and other sugars increases through polyol pathway.

These four mechanisms can be helpful in mitochondrial increased production of superoxide due to excessive glucose metabolism. This explains glucose aroused tissue damage and hyperglycaemic memory[5]. It has been found that by avoiding glucose into the hexosamine pathway hyperglycaemia can cause diabetic complication. Hyperglycaemia activates hexosamine pathway which results in various changes in gene expression as well as in protein function.

Second hypothesis states hyperglycaemia activated protein kinase C by forming diacylglycerol PkC changes the transcription of genes for contractile proteins, extracellular matrix proteins, type-IV collagen and fibronectin in endothelial cells and neurons.

AGEs change composition and structure of extracellular matrix. These cross link proteins, decrease synthesis of nitric oxide, accelerate atherosclerosis.

Aldoreductase enzyme can utilize carbonyl compounds as substrates and these are reduced by nicotinic acid adenine dinucleotide phosphate (NADP) to their specific sugar alcohols (polyols).

However, recent discovery showed that all the given mechanisms can cradle from hyperglycaemic process, which is excess of superoxide ion by the mitochondrial electron transport chain[6].

Diagnosis

Diagnosis is done by two approaches: (a) traditional (b) newer.

(a) Traditional approaches
(1) Clinical Examination:- it includes careful clinical evaluation of signs of sensory, motor and autonomic function deterioration. If asked patient describe numbness or feeling of dead feet. Pain fluctuates with the nature of diabetic neuropathy.

(2) Sensory function test:- Deep sensory examination is needed as routine clinical examination will detect abnormalities at advanced stage and selective involvement of fibre is not rare.
   (i) Light touch sensation:- This test is done by carrying sensation through large myelinated Aα and Aβ fibres. For light touch assessment nylon Semmes weinttin mono-filaments are used. Increasing series of filaments are tested and the threshold at which the one can feel when blocking is noted. If the patient can-not feel the 10gm filament, it indicates foot ulceration.
   (ii) Thermal thresholds:- In this cold and warm sensations can be tested respectively. The cold sensations can be tested by using small myelinated Aδ fibres where as warm can be tested by unmyelinated C fibres. Application of

high or low temperature leads to determination of pain threshold. However Pinchnometer or a set of weighted needles can be used to detect pain threshold.

(iii) Vibration perception threshold (VPT):-128Hz tuning fork is used to access VPT. Vibration perception can only be checked on the tip of great toe or over lateral malleolus. Instruments used are biosthesiometer, vibrometer. Biosthesiometer is commonly used, foot ulceration risk increases if VPT surpass 25 volts.

(iv) Autonomic function test:- Cardiovascular test evaluate autonomic neuropathy. Table II gives tests of cardiac autonomic functions[7].

Table-II :- Tests of cardiac autonomic function.

Test(parasympathetic)	Normal	Borderline	Abnormal
Valsalva	≥ 1.21	1.11-1.20	≤ 1.10
Deep breathing	≥ 15beat/min	11-14 beat/min	≤10 beats/min
Standing (30:15 ratio R-R)	≥ 1.04	1.01-1.03	≤ 1.00
Sympathetic			
Standing (decreased systolic)	≤ 10mm Hg	11-29mm Hg	≥ 30mm Hg
Exercise(increased diastolic)	≥ 16mm Hg	11-15mm Hg	≤ 10mm Hg

(v) Electrophysiology:- Electrophysiological method has been used to identify and follow the progression of diabetic neuropathy[8]. Too less demyelination in the premature stages conduction velocity independently proved a awful measure to detect diabetic neuropathy[9].

(b) New prespectives towards the diagnosis of DN

(i) Quantitative Sensory Testing (QST):- it enables premature diagnosis and precise evaluation of DN. In QST to rule and supply specific stimuli at desirable ferocity to test sensory testing instruments are used. QST can be measured by:-

(a) A simple screening device used to identify foot ulceration in diabetic patient. The instrument is Tactile Circumferential Discriminator.
(b) Computer facilitated sensory estimation.
(c) Physitemp NTE-2a thermal tester which is also used to check warm and cold thresholds.

Irregularities in QST indicate axonal pathology or changes in sensory transduction. Recent development showed the divergence in distal peptide neurotransmitter levels may occur in peripheral nerve fibres of patients prior axonal loss is dectectable[10]. A finding proved that QST of vibratory threshold distinguish subclinical neuropathy in type-I diabetics.

There are only two problems in QST:

- This is a semi objective measure.
- Unusual conclusions from QST can result from altered spinal cord anatomy.

Hence QST however is sensitive for peripheral neuropathy but it is not specific for this condition[11].

(ii) Skin punch biopsy and immunohistochemical staining:-

Under aseptic conditions and lidocaine anaesthesia biopsy specimens (3-4mm in dia.) is obtained, and fixed in formalin, cut into 50mm frozen sections and processed for immunohistochemistry[11]. Lindberger has reported the decreased levels of both substance P and CGRP (calcitonin gene related peptide) in skin biopsies of diabetic patients. Levy proved that there is a big loss in number and area innervated by CGRP positive nerve fibres in normal subjects when compared to patient with DN[12].

The collaboration of skin punch biopsy and immunostaining with particular antibodies shows minimum pain. The classical skin punch biopsy is very useful in diabetes because classic insult in diabetic somatic neuropathy is dying back of axons. Examination of various biopsies can better evaluate distal to proximal gradient of axonal pathology. Currently only few centres have experience with this procedure, so data available are less.

Management therapy of Diabetic Neuropathy

The diabetes control and complication trial has shown that with improved blood glucose control in diabetic patients, the risk of DN and autonomic neuropathy can be decreased. Prevention is better then cure so its good to control the blood glucose levels.

Specific treatment:-

Many therapeutic agents are used for the treatment of painful symptoms of DN.

The potency of various SSRIs, opioids, N-methyl-D-aspartate (NMDA) receptor antagonists, anticonvulsants and TCAs has been illustrated in various arbitrary controlled trials. There are several newer and evident therapeutic drugs for the management of painful DN. It involves α_2-δ ligand pregabalin, ruboxistaurin the protein kinase C inhibitor which is currently in Phase-III trials.

Serotonin/norepinephrine inhibitor duloxetine and NMDA receptor antagonist Perzinfotel which is under Phase-II clinical trials. Aldose reductase inhibitors, gangliosides, gamma linolenic acid, nerve growth factor, pancreatic transplant are also being tested.

Directions for Pharmacotherapy

- Start with lowest effective dose and increase the dosage gradually.
- No equivalence with regard to dose serum level and pain relief.
- Individual variation exists for all drugs.
- Due to improper dose titration or early polytherapy leads to no response.
- Aim of the therapy is to increase functional activity.
- Treatment duration can be a variant in the therapy.
- Medication can be tapered off after 6 months of pain relief.

Selective Serotonin Reuptake Inhibitors

SSRIs treatment for DN is mostly discouraging. These agents work by inhibiting presynaptic reuptake of serotonin only. They do not inhibit norepinephrine. In small controlled studies some evidence support the use of citalopram and paroxetine in dosage of up to 40mg/day.

Duloxetine

It is a non-selective reuptake inhibitor of both serotonin and norepinephrine. Two blind folded studies (placebo control) have shown its potency in the treatment of depression and neuropathic pain[13].

Effective dose: 60-120mg/day, effect may be seen by 1-2 weeks.

Side effects: GI distress, dry mouth, headache.

Tricyclic Antidepressants

TCAs are the first line drugs for the pain relief in DN and it is supported by several controlled studies[14,15]. The use is restricted due to frequency and severity of side-effects. These drugs act on CNS inhibiting the reuptake of both norepinephrine and serotonin at the synapses involved in pain inhibition.

Amitriptyline is the most commonly used drug started at low dose of 10-20mg every night and is increased gradually until the pain is relieved. However, its role is contraindicated in patients with heart failure, heart block, orthostatic hypotension, urinary tract obstruction and myocardial infarction. Pain relief is achieved at a dose of 150mg/day for 3-6weeks[16].

Anticonvulsants

If the treatment with amitriptyline is not successful anticonvulsants are used. Frequently used drugs are carbamazepine, clonazepam, phenytoin and gabapentin. Gabapentin is now widely used for DN. Side-effects are less than TCAs. Side-effects include dizziness, headache, pedal oedema, weight gain. In clinical trials average dose for pain relief was approximately 1.8gm/day. A CNS active compound and analogue of neurotransmitter aminobutyric acid drug named **Pregabalin** has been recently introduced. Introductory verification purpose that this drug can be useful along with anticonvulsant which are helpful in neuropathic pain[13].

Sympatholytic Agents

Clonidine can be given to the patients by (oral/transdermal/intrathecal route). It is a peripheral α-2 receptor agonist with CNS activity.it is used in managing complex regional pain syndromes.

Local Anaesthetics and Anti-arrhythmics

Lidocaine is most common drug used in this category. It results in sodium channel blockage and supress both peripheral and nociceptor sensitization and ultimately CNS hyperexcitability. Oral analogue of lidocaine Mexiletine is reported to be beneficial in recent studies[17]. It is not widely used because side-effects and need of regular Electrocardiogram monitoring with its use.

Opioids

Opioids are not used in the management of DN pain but in recent trials two agents suggest potency. Tramadol which is opioid like centrally acting narcotic analgesic, confirmed to be efficacious in a controlled trial[18,19]. Recently two studies confirmed the potency of controlled release Oxycodone[20]. Both drugs cab be used as add on therapies for the patients failing to respond to non-opioid medication.

e.g. Tramadol (100-400mg/day)

Oxycodone (30-40mg/day)

Side-effects of both drugs include nausea, constipation and addiction is also problematic[19].

Topical Agents

Capsaicin is trans-8 methyl-N vanilly-6-nonemide which is found in red pepper, decreases tissue of substance P. its topical application reduces chemically induced pain[21]. The mechanism of substance P depletion is secondary to the release of substance P from nerve terminals, decreased axonal transport of substance P to replenish it in the nerve terminals and inhibition of its synthesis [22].

Topical nitrate

Recent studies suggest that diminished NO synthesis plays a vital role in the pathogenesis of DN. In experimental models it has been shown that impaired neuronal NO generation induces hyoeralgesia[23]. If it will be confirmed in further studies, it can give promising results for neuropathic symptoms.

New Promising Therapies

One treatment which can relive neuropathy is now in clinical trials. However, one has proved beneficial i.e. *α-lipoic acid*:

Recent trials have been conducted with DN patients who received 600mg α-lipoic acid. The treatment reduces pain, poresthesias and numbness when administered parenterally

Protein kinase C inhibition:

Increased protein kinase C activity plays an important role in diabetic microvascular complication. Studies have been conducted using a protein kinase C-β inhibition[25]. Phase-III multicentre clinical trials are in progress[26].

Miscellaneous Agents

- Levodopa
- Methylcobalamin
- Nerve Growth Factor
- A-lipoic acid (600-1200mg/day IV)
- Bupropion (150-300mg/day)

Neurotrophic factors (agents used for nerve regeneration)

Neurotrophic factor is a naturally occurring protein which is released by target tissue in responsive neurons and binds to specific receptors. A large number of neurotrophic factors are there but the most promising are from the neurotrophin gene family- nerve growth factor, insulin like growth factor, brain derived neurotrophic factor and glial cell derived neurotrophic factors[27].

Table-III : Neurotrophic factors

Neurotrophins	Haematopoietic cytokines	Insulin like growth factors	Heparin-binding family	Epidermal growth factor	TGF-β family	Tyrosine kinase-associated cytokines
Nerve growth factor	Oncogene M	Insulin	Basic-FGF	EGF	TGF-β_1	Platelet derived growth factors
NT-3	IL-1,3	IGF-I	Int-2onc	Transforming growth factor TGF-α	TGF-β_2	Colony stimulating factor-1
NT-4/5	IL- 6,7	IGF-II	Hst/k-FGF onc		TGF-β_3	Stem cell factor
NT-6	IL- 9,11		FGF-4,5,6		Neurturin	
	Granulocyte colony-stimulating factors		Keratinocyte growth factor		Activin A	
					BMP_s	

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