By Hariharan Venkataraman
JSS Medical College, India

PERIPHERAL NEUROPATHY IN DIABETES MELLITUS

What is Diabetes Mellitus?

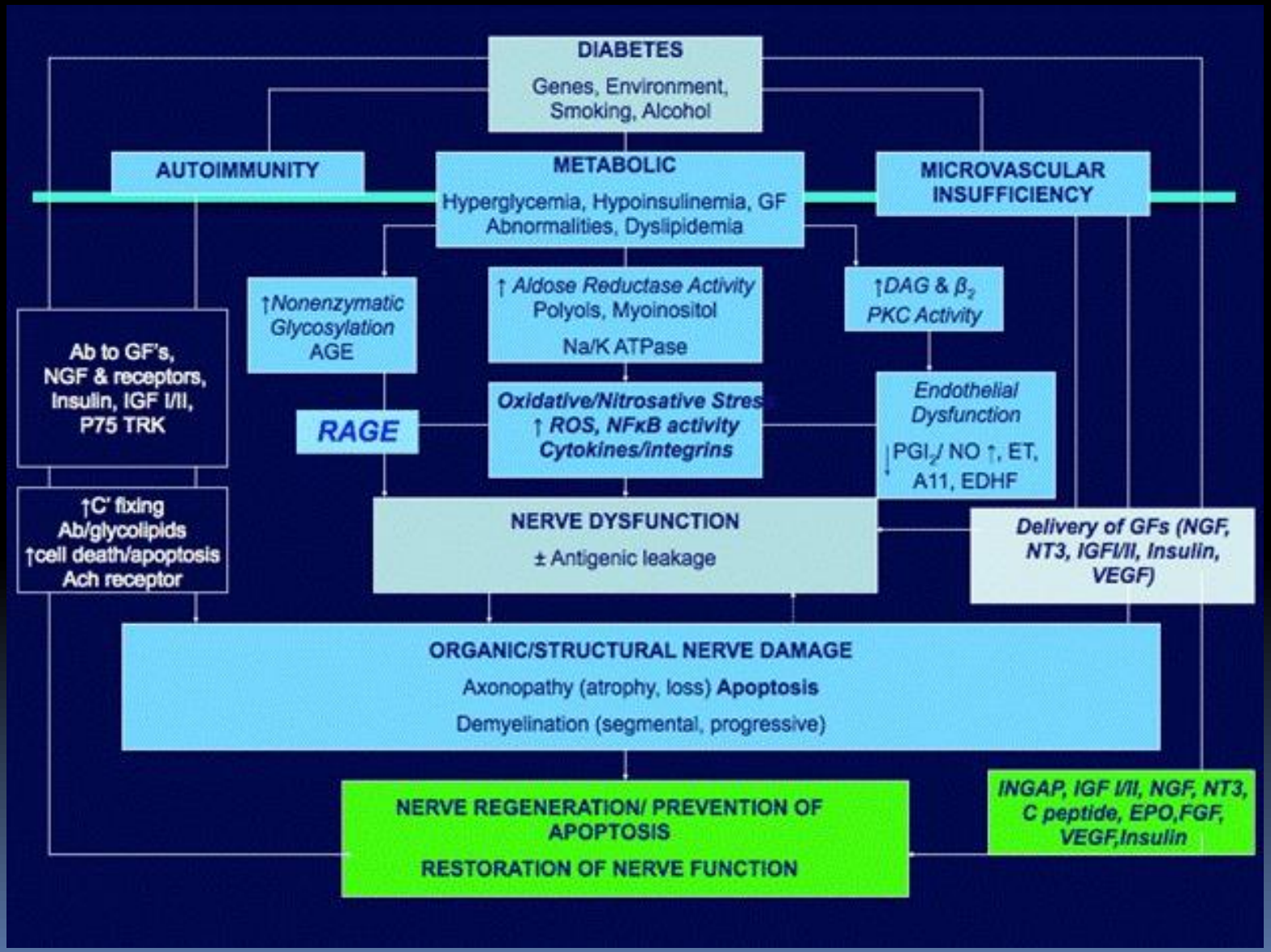
- Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia.
- It affects carbohydrate, protein and lipid metabolism.
- It is one of the leading causes of mortality and morbidity, and continues to have an increasing incidence worldwide.

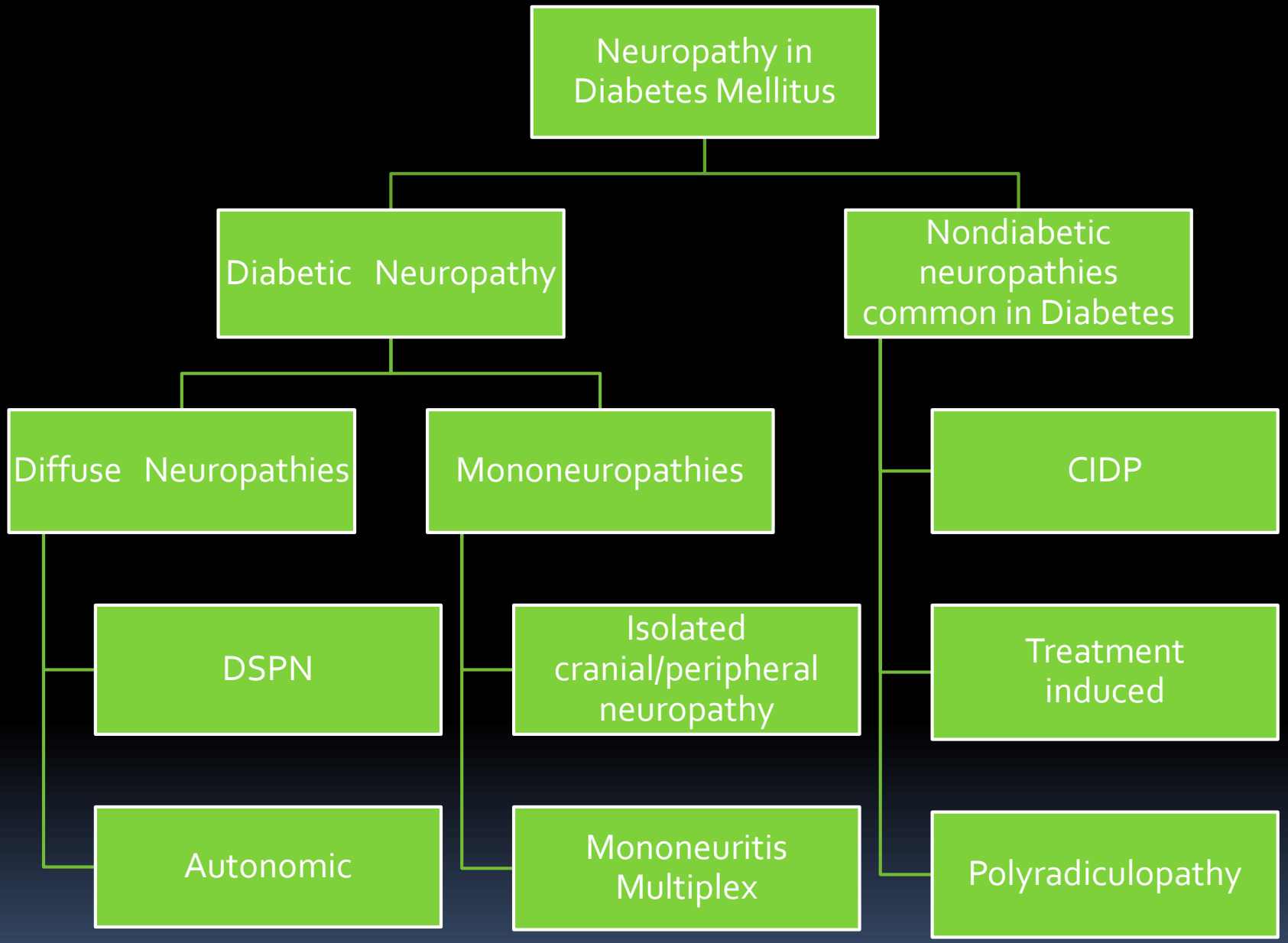
Types of Diabetes Mellitus

- Type 1
- Type 2
- Gestational Diabetes Mellitus
- Other types –

A. Genetic defects of beta cell development
B. Diseases of exocrine pancreas
C. Endocrinopathies
D. Drug induced
E. Wolfram's syndrome – DIDMOAD, Prader-Willi syndrome, Laurence-Moon-Biedl syndrome, Friedrich ataxia, etc.

How does Diabetes mellitus affects peripheral nerves?



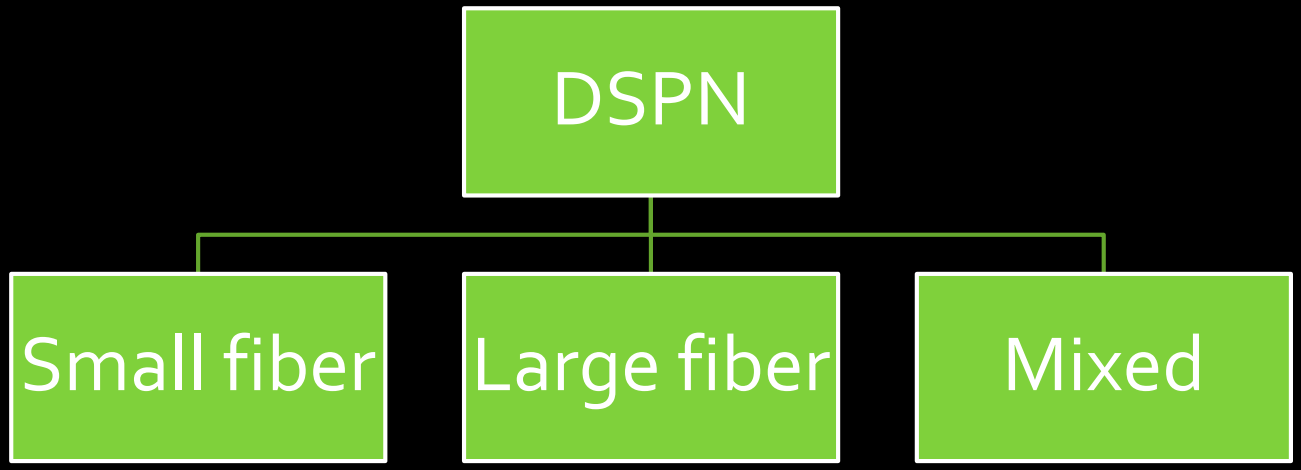


DSPN – Distal Symmetric Polyneuropathy

CIDP – Chronic Inflammatory Demyelinating Polyneuropathy

Length dependent axonal neuropathy

- Also called Distal Symmetric Polyneuropathy of Diabetes (DSPN)
- Most common, accounting for about 75% of cases of diabetic neuropathy
- Distally placed or longer neurons are first affected probably due to an increasing metabolic demand (Dying back phenomenon)
- Patients present with chronic sensory or sensorimotor neuropathy



- Small fiber - burning, lancinating or shooting in quality with unusual, tingling or crawling sensation referred to as formication. They are electrophysiologically silent.
- Large fiber - weakness, ataxia, loss of reflexes, loss of vibration sensation, loss of proprioception, and impaired nerve conduction.

Toronto classification of Distal Symmetric Polyneuropathy (DSPN)

Possible

The presence of symptoms (asleep numbness, prickling or stabbing, burning or aching pain in the toes, feet, or legs)

or

signs (signs–symmetric decrease of distal sensation or unequivocally decreased or absent ankle reflexes)

Probable

The presence of a combination of symptoms and signs of neuropathy including any 2 or more of the following: neuropathic symptoms, decreased distal sensation, or unequivocally decreased or absent ankle reflex

Confirmed

The presence of an abnormality of nerve conduction or validated measure of small fibre neuropathy, and a symptom or symptoms, or a sign or signs, of neuropathy

Subclinical

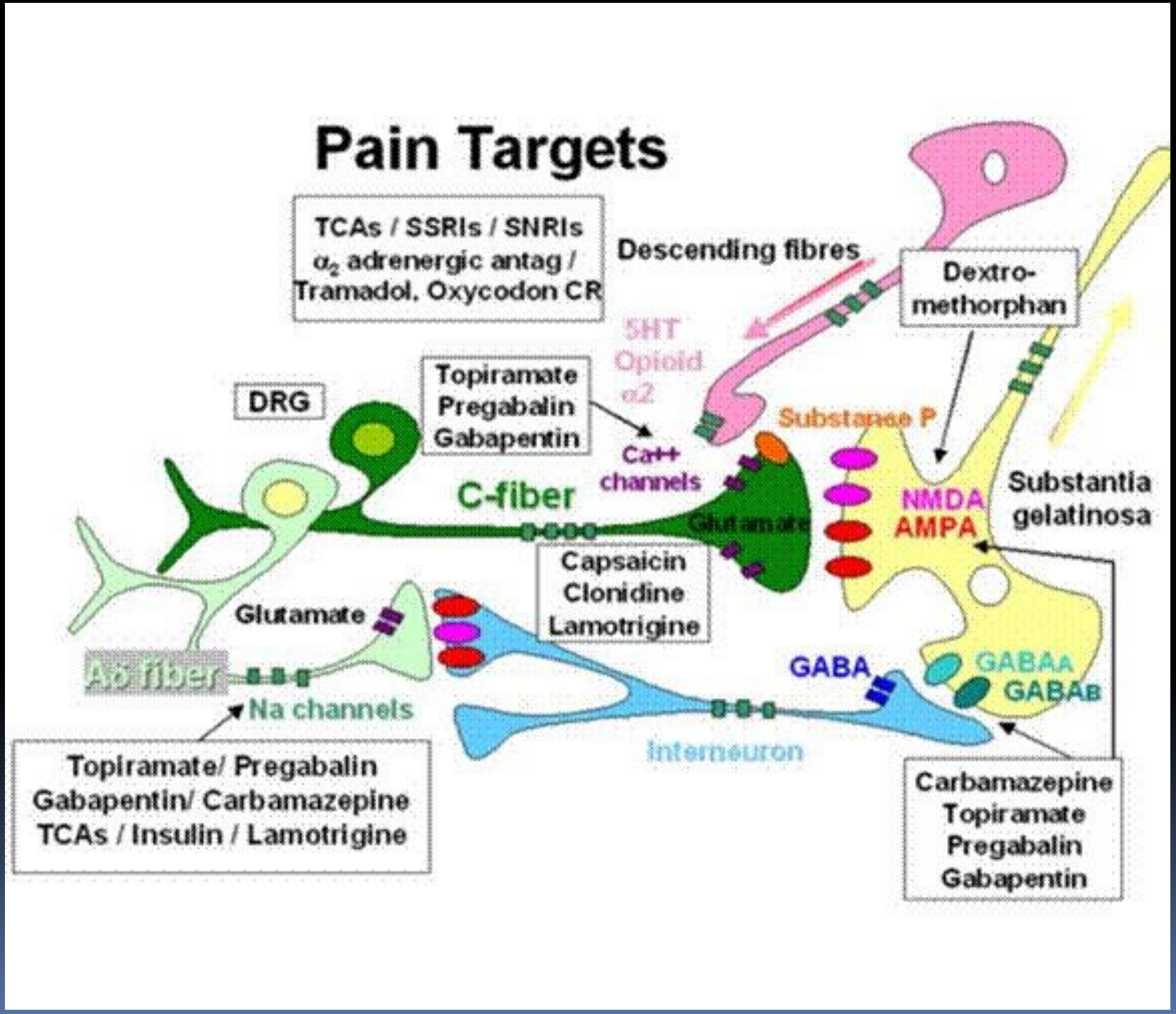
The presence of no signs or symptoms of neuropathy are confirmed with abnormal nerve conduction or a validated measure of small fibre neuropathy

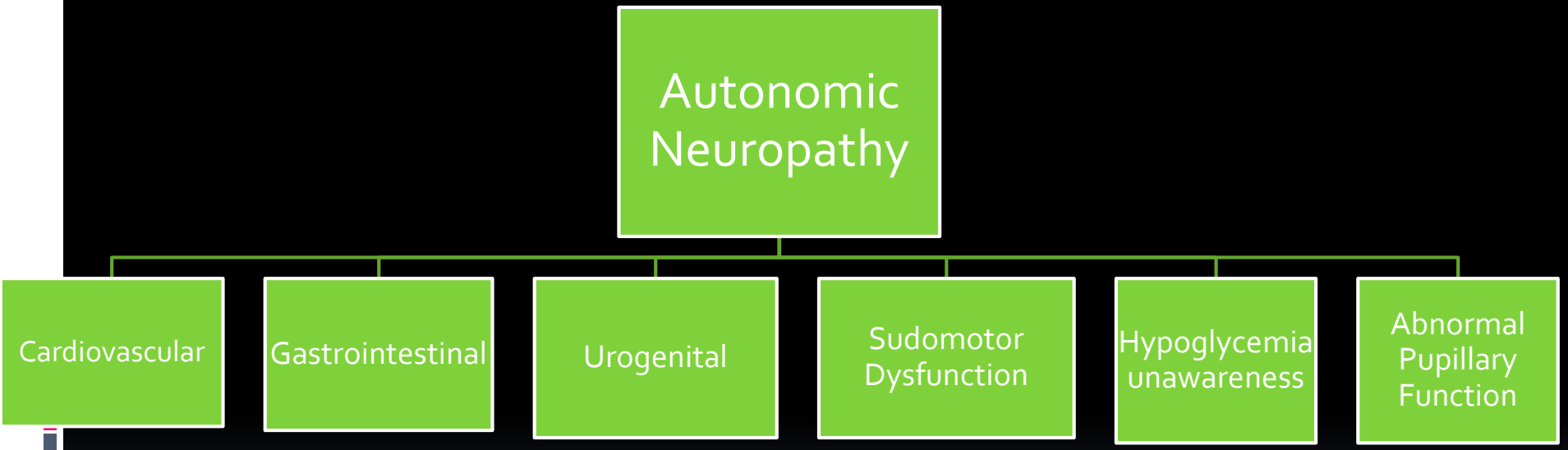
Tests for Small Fiber Neuropathy

- QST – Quantitative Sensory Testing
- Skin Biopsy – Look for altered IENFD (Morphological quantification of C fibers crossing basement membrane in epidermis)
- CCM – Corneal Confocal Microscopy
- CHEPS – Contact Heat Evoked Potentials

Treatment of DSPN

- Improvement of Glycemic control
- Tobacco cessation
- Increase in exercise
- Counseling about foot care
- Treatment of neuropathic pain


Pain Targets
TCAs / SSRIs / SNRIs
α_2 adrenergic antag /
Tramadol, Oxycodon CR
Descending fibres
Dextro-
methorphan
5HT
Opioid
α2
Topiramate
Pregabalin
Gabapentin
DRG
Substance P
Ca++
channels
C-fiber
Glutamate
NMDA
AMPA
Substantia
gelatinosa
Capsaicin
Clonidine
Lamotrigine
Glutamate
Aδ fiber
GABA
GABAA
GABAB
Na channels
Interneuron
Topiramate/ Pregabalin
Gabapentin/ Carbamazepine
TCAs / Insulin / Lamotrigine
Carbamazepine
Topiramate
Pregabalin
Gabapentin


Autonomic Neuropathy
Cardiovascular
Gastrointestinal
Urogenital
Sudomotor Dysfunction
Hypoglycemia unawareness
Abnormal Pupillary Function

CAN	Gastrointestinal	Urogenital	Sudomotor
Resting tachycardia Abnormal blood pressure regulation • Nondipping • Reverse dipping	Gastroparesis (Gastropathy) • Nausea • Bloating • Loss of appetite • Early satiety • Postprandial vomiting • Brittle diabetes	Bladder dysfunction • Frequency • Urgency • Nocturia • Hesitancy • Weak stream • Dribbling • Urinary incontinence • Urinary retention	Dry skin • Anhidrosis • Gustatory sweating
Orthostatic hypotension (all with standing) • Light-headedness • Weakness • Faintness • Visual impairment • Syncope	Esophageal dysfunction • Heartburn • Dysphagia for solids	Male sexual dysfunction • Erectile dysfunction • Decreased libido • Abnormal ejaculation	
Orthostatic tachycardia or bradycardia and chronotropic incompetence (all with standing) • Light-headedness • Weakness • Faintness • Dizziness • Visual impairment • Syncope	Diabetic diarrhea • Profuse and watery diarrhea • Fecal incontinence • May alternate with constipation	Female sexual dysfunction • Decreased sexual desire • Increased pain during intercourse • Decreased sexual arousal • Inadequate lubrication	
Exercise intolerance	Constipation • May alternate with explosive diarrhea		

Cardiovascular Autonomic Neuropathy

Treatment –

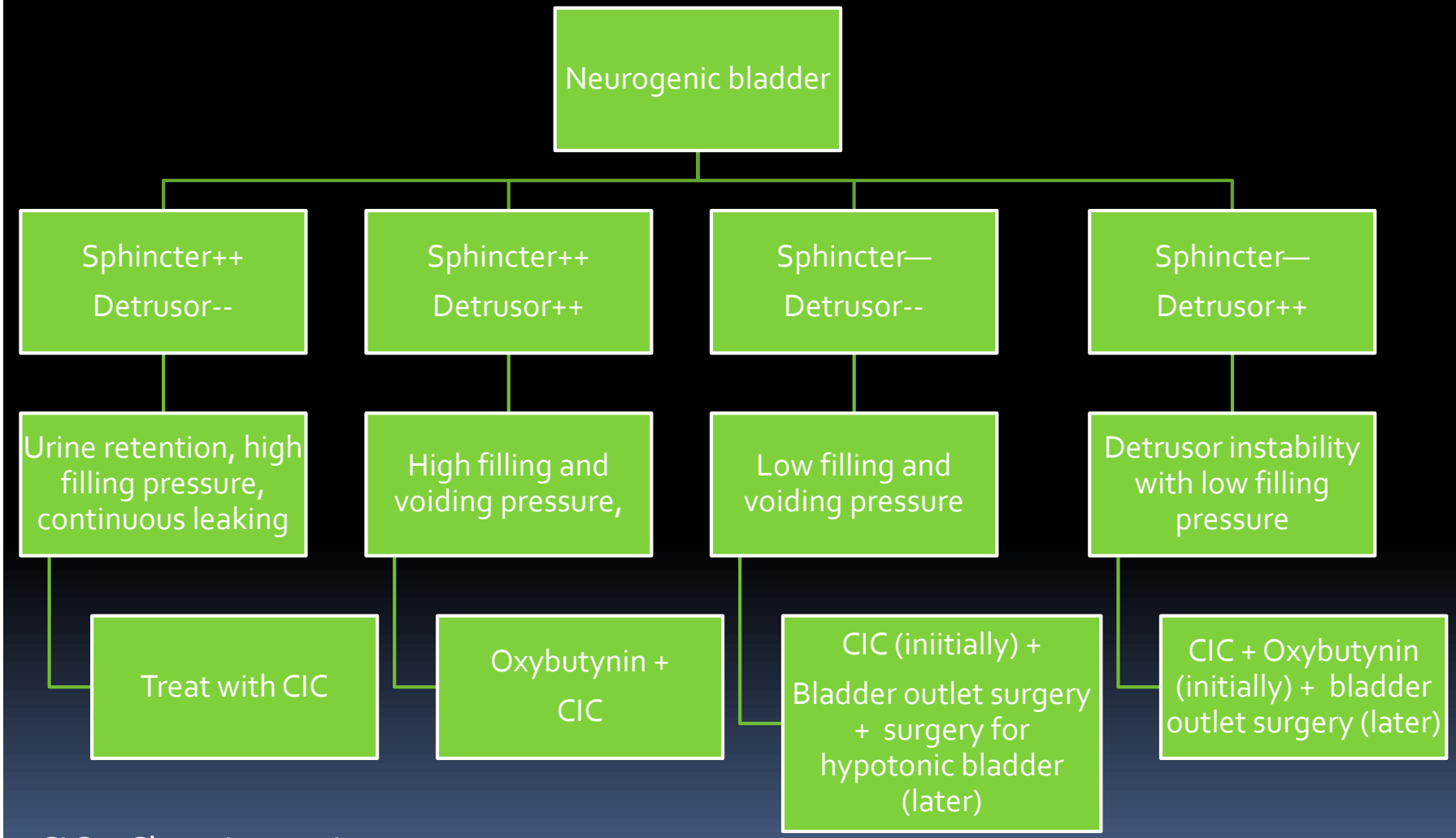
- Physical activity should be promoted to avoid deconditioning
- Midodrine used Orthostatic hypotension
- Low dose Fludrocortisone can be beneficial, but runs the risk of supine hypertension.
- Droxidopa – recently approved drug

Gastrointestinal Autonomic neuropathy

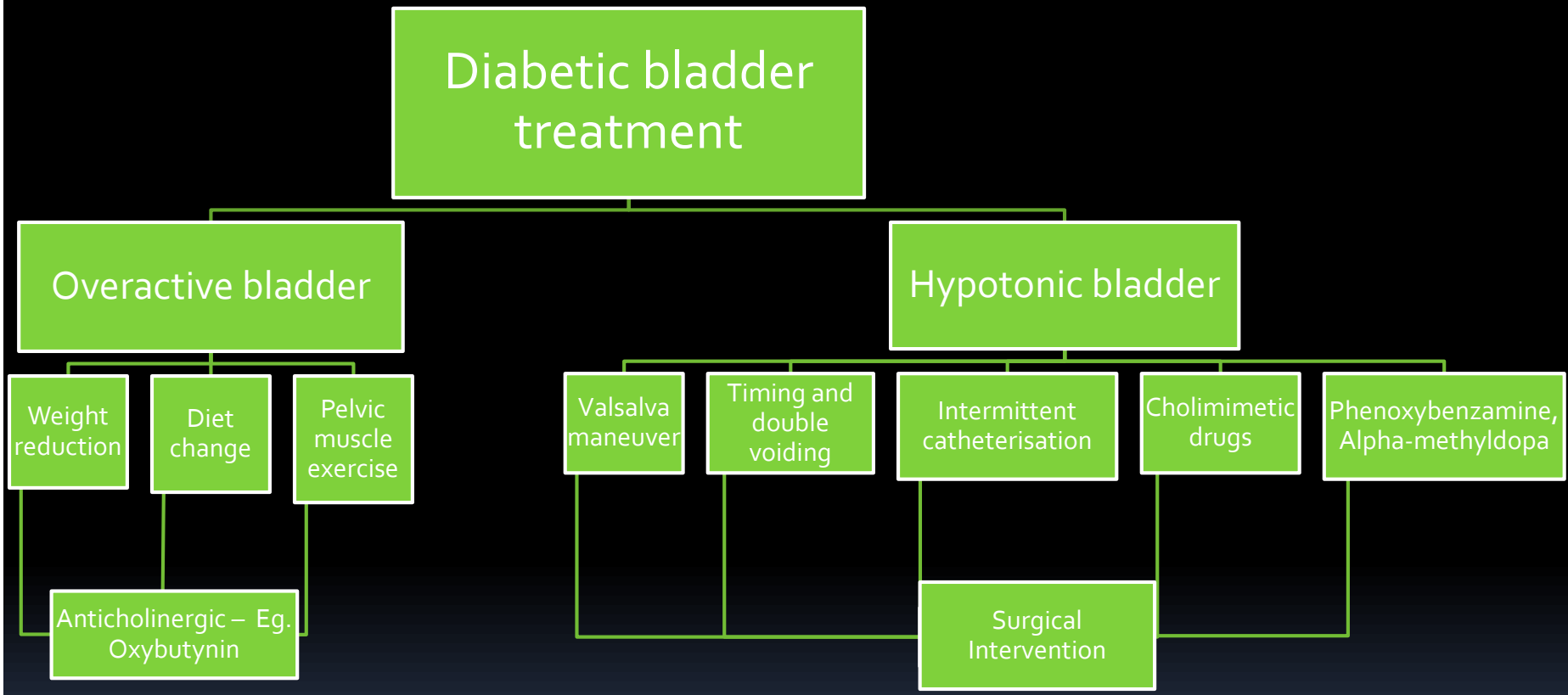
Treatment –

- Drugs causing alterations in bowel movements have to be withdrawn (opioids, anticholinergics, TCAs, GLP-1 receptor agonists and DPP-4 inhibitors)
- Dietary changes – Small quantity, frequent meals, low fat diet, avoid lying down for 2 hours after meals
- Metoclopramide is approved for gastroparesis, for 5 days, used only if other measures aren't effective.
- Surgical options – Jejunostomy tube, Gastric electric stimulation

Urogenital Autonomic Neuropathy



CIC – Clean Intermittent Catheterization


Diabetic bladder treatment
Overactive bladder
Hypotonic bladder
Weight reduction
Diet change
Pelvic muscle exercise
Valsalva maneuver
Timing and double voiding
Intermittent catheterisation
Cholimimetic drugs
Phenoxybenzamine, Alpha-methyldopa
Anticholinergic – Eg. Oxybutynin
Surgical Intervention

- **Erectile dysfunction** – It could be due to autonomic neuropathy, but is usually multifactorial. The vascular risk factors and hypogonadism should be evaluated.
- First line of treatment is Phosphodiesterase-5 inhibitors
- Other treatments include transurethral prostaglandins, intra-cavernosal injections,
- vacuum devices, and penile prosthesis in more advanced cases.

- **Female sexual dysfunction -** DM could influence female sexual function via both psychological (e.g. depression, anxiety) and physiological (neuropathy, vaginal dryness, etc.) factors
- Treatment - lifestyle changes, optimal diabetic control, psychotherapy
- Hormonal replacement in post menopausal women
- PDE5 inhibitors might theoretically improve vaginal lubrication and vulvar engorgement but there no studies that proven its benefit.

Sudomotor dysfunction

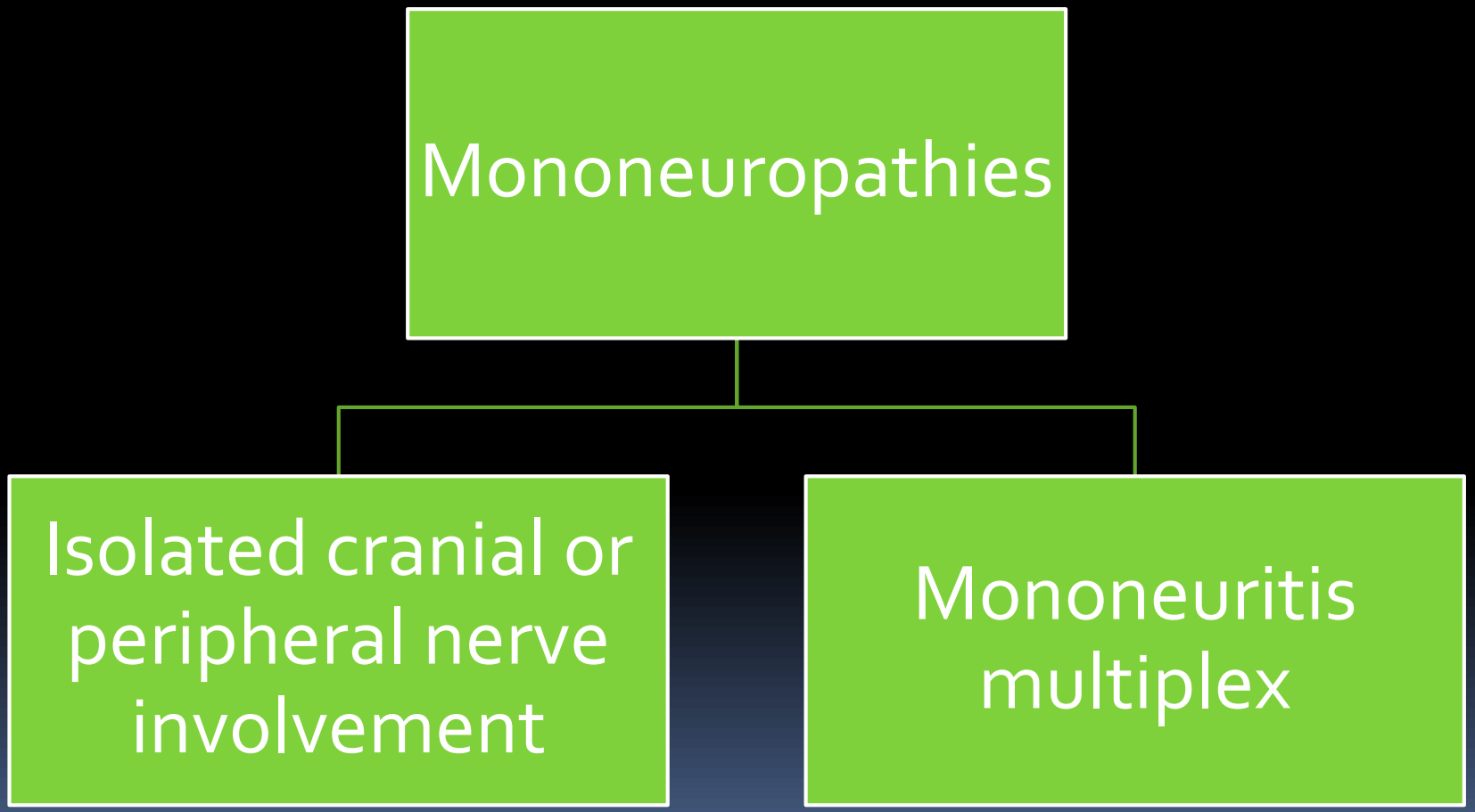
- The pattern of sudomotor dysfunction matches the distribution of the sensory neuropathy, typically presenting in a stocking-and-glove distribution
- Compensatory Hyperhidrosis in proximal areas
- Clinical testing for sudomotor dysfunction - including the quantitative sudomotor axon reflex test (QSART), thermoregulatory sweat testing
- Glycopyrrolate is used in gustatory sweating

Hypoglycemia unawareness

- Normally, hypoglycemia will lead to activation of counterregulatory mechanisms to increase the glucose levels, one of which is sympathetic activation.
- Sympathetic activation leads to symptoms like tremors, palpitations, sweating, etc.
- In autonomic neuropathy, sympathatic activation will be impaired. Thus the patient will be unaware of his/her hypoglycemia.

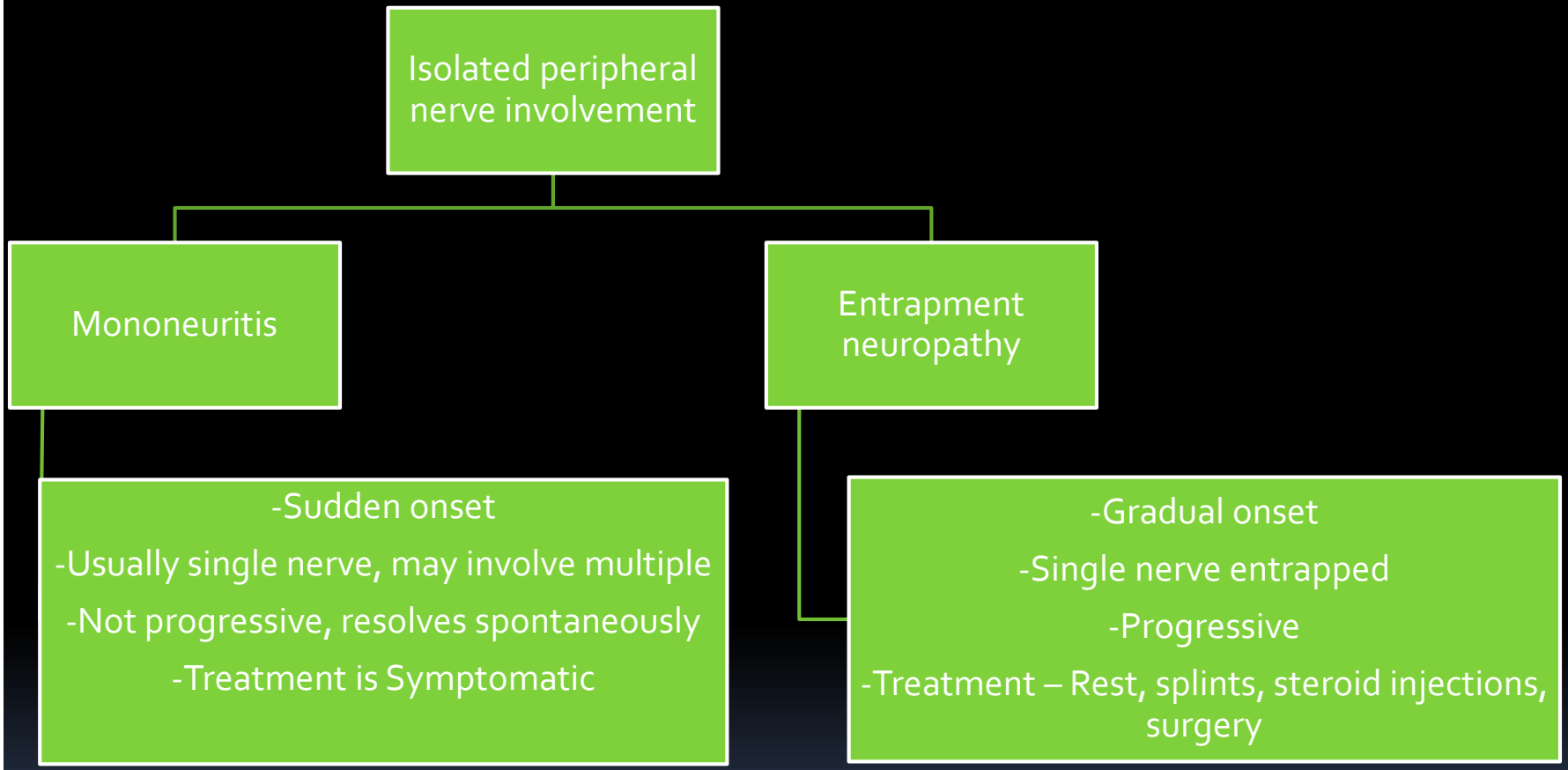
Pupillary impairment

- Pupillary abnormalities from autonomic neuropathy are common in diabetes
- The deficiency in the sympathetic innervation to the dilator pupillae - difficulty in night vision in diabetic patients
- Impairment of the parasympathetic control of the sphincter pupillae - diminished reflex response to light.
- Diabetic patients with mild autonomic dysfunction have smaller pupil diameters than healthy controls, suggestive of early involvement of autonomic nerves


Mononeuropathies
Isolated cranial or peripheral nerve involvement
Mononeuritis multiplex

Isolated cranial nerve involvement

- They present acutely and are rare
- It primarily involves cranial nerves III, IV, VI, and VII
- Requires correction of glycemic status and usually resolves spontaneously over several months
- Pathogenesis - hyperglycemia-induced damage to nerve cells and neuronal ischemic change
- The classic pupillary sparing in third nerve palsy is because the artery supplying cranial nerve III is located centrally


Isolated peripheral nerve involvement
Mononeuritis
Entrapment neuropathy
-Sudden onset
-Usually single nerve, may involve multiple
-Not progressive, resolves spontaneously
-Treatment is Symptomatic
-Gradual onset
-Single nerve entrapped
-Progressive
-Treatment – Rest, splints, steroid injections, surgery

Nerves	Location of the most common entrapments	Distribution of sensory impairment	Distribution of motor impairment	Signs	Diagnosis by NCV	Differential diagnosis
Median nerve	Wrist (CTS)	Palmar aspects of I–III, 0.5 IV fingers, medial aspect of the palm, and intact thenar eminence	Weakness and atrophy of abductor policis brevis	Tinel's sign, Phalen's maneuver, carpal compression test, and weakness of thumb opposition	Wrist/palm stimulation	C8 radiculopathy, proximal compressions of median nerve
Ulnar nerve	Elbow (cubital tunnel syndrome)	Palmar aspects of V, 0.5 IV fingers, medio-dorsal aspect of the hand, and hypothenar eminence	Weakness and atrophy of adductor digiti minimi, hypothenar, and intrinsic muscle of the hand	Tapping or pressure over the ulnar nerve at the medial epicondyle reproduces sensory symptoms, Froment's sign	Below/above elbow stimulation	C8-T1 radiculopathy, brachial plexoapthy (medial cord), and ulnar nerve entrapment at the wrist
Radial nerve	Elbow (radial groove)	Dorsal aspect of the forearm, hand, and fingers I–III and 0.5 IV	Drop wrist: weakness of the extensors of the hand and fingers, intact function of the forearm extensors	Aching and soreness in the elbow region, weakness of supination and extension of index finger and hand	NCV–electromyography activity*	Wartenberg's syndrome, tennis elbow, radiculopathy C7, brachial plexopathy (posterior cord)
Peroneal nerve	Fibula head	Lateral aspect of the leg and dorsum of the foot	Drop foot: weakness of the extensors of foot and toes	Tapping or pressure below the fibula head provokes sensory symptoms	Above/below fibula stimulation	Compression at the knee level, radiculopathy L5
Tibial nerve	Ankle-tarsal tunnel	Plantar: medial and lateral surfaces	Atrophy of the intrinsic muscles of the foot	Tinel's sign, tapping in the nerve distribution	Sensory medial and lateral plantar nerves	Radiculopathy S1, polyneuropathy (DSPN), and Morton's neuroma
Lateral cutaneous nerve of the thigh	Ilioinguinal ligament (meralgia paresthetica)	Lateral aspect of the thigh	None	Extremely sensitive skin in corresponding dermatome	Above/below ilioinguinal ligament stimulation	Femoral neuropathy, radiculopathy L2–3, and lumbar plexopathy

*Radial nerve entrapment requires conduction velocity done over muscles of forearm because, unlike the ulnary median nerves, the radial nerve does not innervate muscles in the hand.

Mononeuritis multiplex

- It is an acute/subacute onset painful, asymmetrical, asynchronous sensory and motor peripheral neuropathy involving isolated damage to at least 2 separate nerve areas
- Causes apart from Diabetes include collagen vascular diseases, Amyloidosis and paraneoplastic syndromes
- Treatment includes glycemic control and is usually self limiting and resolves spontaneously

Bruns-Garland syndrome

- Diabetic lumbosacral radiculoplexus neuropathy - 1% of DM patients.

- Presents in the elderly (median age 65 years). It is an episodic, monophasic disease that is clinically active for a relatively short period (few months - 2 years)

- Acute/subacute onset; asymmetrical, focalized, unilateral, and proximal lower extremity distribution early in the disease.

- Presentations - severe neuropathic pain, with predominant motor-strength weakness, proximal muscle atrophy, and frequently associated weight loss

- Some patients develop thoracic radiculopathy or, even less commonly, a cervical polyradiculoneuropathy.

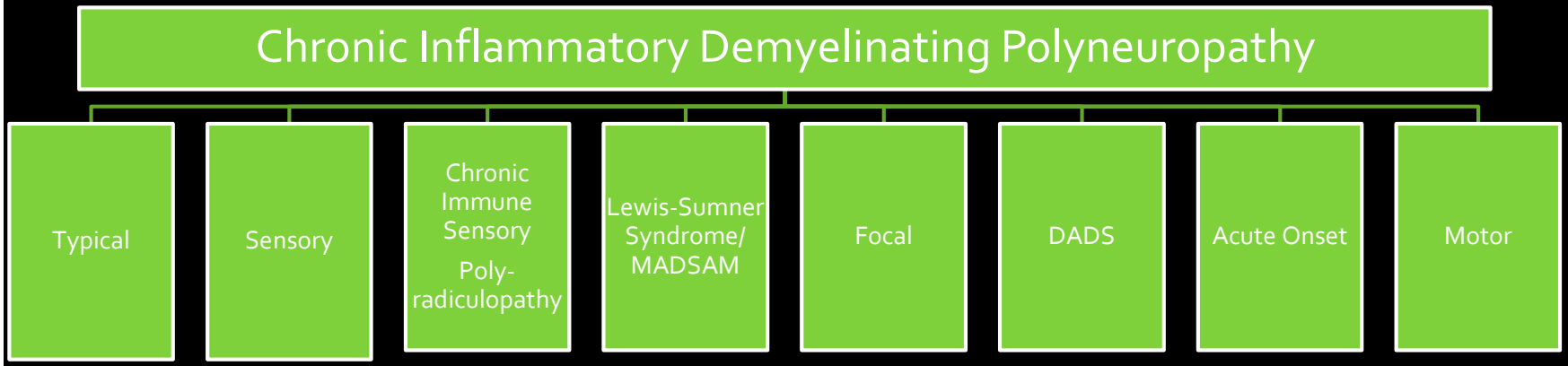
- Hypothesis - immune-mediated, inflammatory state, resulting in vasculitis with ischemic nerve injury
- Associated with less prolonged exposure to hyperglycemia, better glycemic control
- Abnormal sphingolipid metabolism - critical regulatory role in immunity and inflammation
- Pathophysiologic similarities between this disease and LRPN (idiopathic lumbosacral radiculoplexus neuropathy).
- Nerve biopsy - degenerative changes secondary to microvasculitis with accompanying ischemia and inflammation
- CSF usually shows increased protein with normal proteins
- Neurophysiology studies - multifocal process involving the lumbosacral plexus, nerve roots, and the peripheral nerves

- This disease follows a limited disease course
- Symptomatic improvement with the use of immunosuppressant agents: steroids, immunoglobulin, and plasma exchange, but clear evidence is still necessary due to conflicting outcomes
- Pain management with NSAIDs is an option, and opioids can be used for severe cases. Amitriptyline, SSRIs and anticonvulsant agents (gabapentin) are also used.

Treatment induced Neuropathy

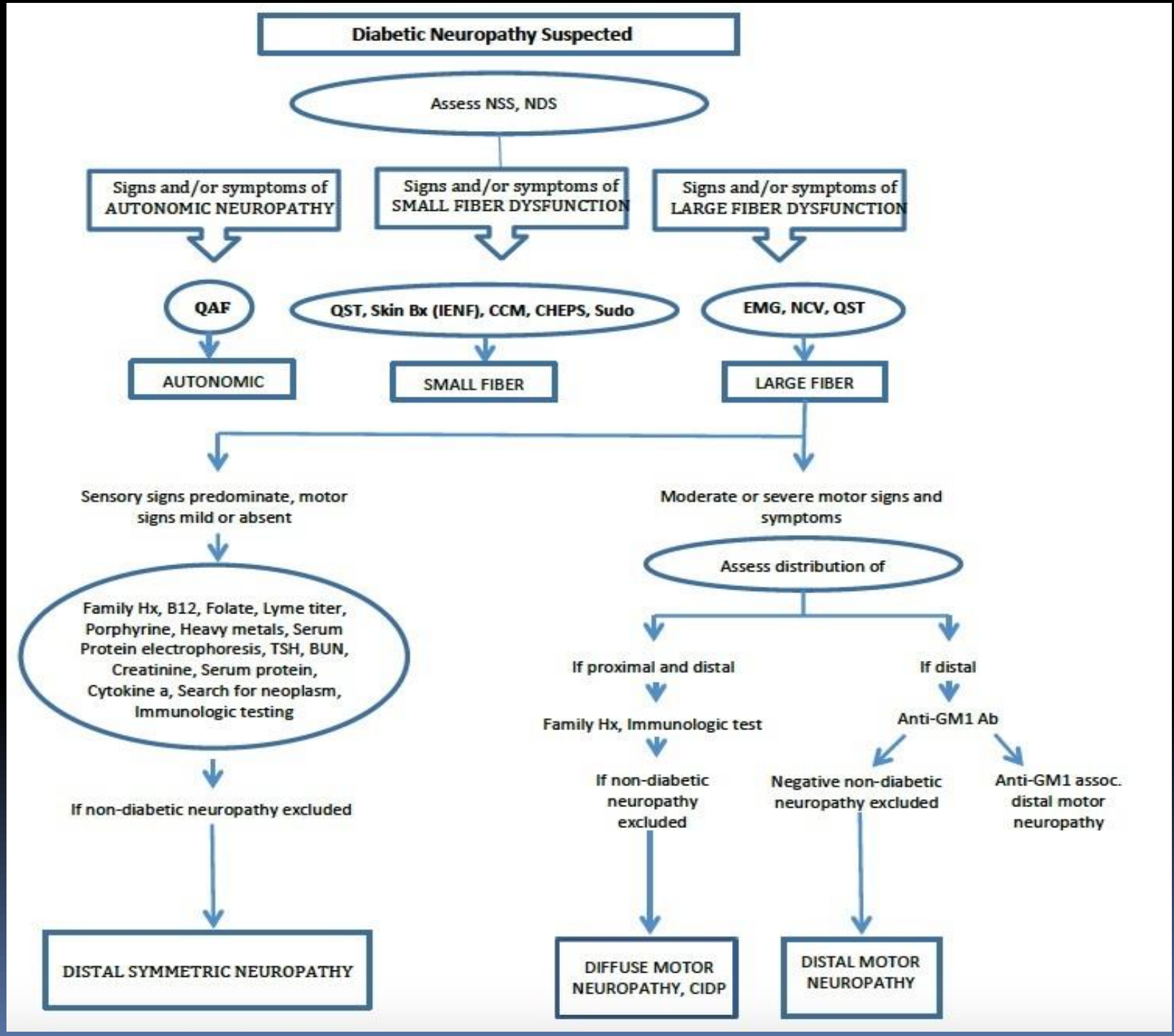
- Previously known as insulin neuritis, or acute painful neuropathy
- It develops suddenly following rapid improvement in glycemic control in the setting of chronic hyperglycemia
- It is characterized by the acute onset of neuropathic pain in a length-dependent or generalized distribution, often with accompanying autonomic symptoms
- In addition to the development of neuropathy, individuals who develop treatment-induced neuropathy of diabetes also frequently have renal and retinal involvement simultaneously, suggesting this is a diffuse microvascular process

- Management of treatment-induced neuropathy - managing symptomatic pain while encouraging glucose stabilization at the current hemoglobin A1c level until symptoms begin to improve
- It can be prevented by making sure that their HbA1c is not rapidly reduced and is more gradual
- Reversibility exists in some patients, but the neuropathy does not entirely resolve



DADS – Distal Acquired Symmetric Neuropathy
MADSAM - Multifocal acquired demyelinating sensory and motor neuropathy

- Prevalence of CIDP in patients with diabetes was 9 times higher than in the general population
- CIDP is a heterogeneous immune-mediated condition of the peripheral nervous system that may present in a progressive or relapsing-remitting fashion. CIDP typically presents with the symmetric onset of proximal and distal sensory and motor symptoms
- CIDP is a clinical diagnosis based on the presence of proximal and distal weakness with areflexia, and it is a widely overdiagnosed condition
- Treatment includes corticosteroids and IVIg/Plasmapheresis


Diabetic Neuropathy Suspected
Assess NSS, NDS
Signs and/or symptoms of AUTONOMIC NEUROPATHY
Signs and/or symptoms of SMALL FIBER DYSFUNCTION
Signs and/or symptoms of LARGE FIBER DYSFUNCTION
QAF
QST, Skin Bx (IENF), CCM, CHEPS, Sudo
EMG, NCV, QST
AUTONOMIC
SMALL FIBER
LARGE FIBER
Sensory signs predominate, motor signs mild or absent
Moderate or severe motor signs and symptoms
Assess distribution of
Family Hx, B12, Folate, Lyme titer, Porphyrine, Heavy metals, Serum Protein electrophoresis, TSH, BUN, Creatinine, Serum protein, Cytokine a, Search for neoplasm, Immunologic testing
If proximal and distal
If distal
Family Hx, Immunologic test
Anti-GM1 Ab
If non-diabetic neuropathy excluded
If non-diabetic neuropathy excluded
Negative non-diabetic neuropathy excluded
Anti-GM1 assoc. distal motor neuropathy
DISTAL SYMMETRIC NEUROPATHY
DIFFUSE MOTOR NEUROPATHY, CIDP
DISTAL MOTOR NEUROPATHY

References

1. Harrison Principles of Internal Medicine 20th Edition

2. Dr. Christopher Gibbons; CONTINUUM (MINNEAP MINN) 2020;26(5, PERIPHERAL NERVE AND MOTOR NEURON DISORDERS): 1161–1183.

3. Longitudinal Assessment of Small Fiber Neuropathy - Evidence of a Non–Length-Dependent Distal Axonopathy. Khoshnoodi MA; Truelove S; Burakgazi A et al *JAMA Neurol.* 2016;73(6):684-690. doi:10.1001/jamaneurol.2016.0057

4. Diabetic Neuropathy: A Position Statement by the American Diabetes Association - Rodica Pop-Busui, Andrew J.M. Boulton, Eva L. Feldman, Vera Bril, Roy Freeman, Rayaz A., Malik Jay M. Sosenko and Dan Ziegler

5. Elyasi F, Kashi Z, Tasfieh B, Bahar A, Khademloo M. Sexual dysfunction in women with type 2 diabetes mellitus. Iran J Med Sci. 2015 May;40(3):206-13. PMID: 25999619; PMCID: PMC4430881.

6. Sudhakar P. Recognizing pupillary dysfunction in diabetic autonomic neuropathy Indian Journal of Ophthalmology: August 2019 - Volume 67 - Issue 8 - p 1320-1321

7. Golbidi S, Laher I. Bladder dysfunction in diabetes mellitus. Front Pharmacol. 2010 Nov 16;1:136. doi: 10.3389/fphar.2010.00136. PMID: 21833175; PMCID: PMC3153010.

8. Verpoorten C, Buyse GM. The neurogenic bladder: medical treatment. Pediatr Nephrol. 2008 May;23(5):717-25. doi: 10.1007/s00467-007-0691-z. Epub 2007 Dec 19. PMID: 18095004; PMCID: PMC2275777.

9. Maiorino MI, Bellastella G, Esposito K. Diabetes and sexual dysfunction: current perspectives. Diabetes Metab Syndr Obes. 2014 Mar 6;7:95-105. doi: 10.2147/DMSO.S36455. PMID: 24623985; PMCID: PMC3949699.

10. Focal Entrapment Neuropathies in Diabetes. Aaron Vinik, MD, Anahit Mehrabyan, Lawrence Colen, Andrew Boulton. Diabetes Care 2004 Jul; 27(7): 1783-1788

11. Kelkar P, Parry GJ. Mononeuritis multiplex in diabetes mellitus: evidence for underlying immune pathogenesis. *Journal of Neurology, Neurosurgery & Psychiatry* 2003;**74:**803-806.

12. Mathey EK, Park SB, Hughes RAC, *et al*. Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype. *Journal of Neurology, Neurosurgery & Psychiatry* 2015;**86:**973-985.

13. Ng PS, Dyck PJ, Laughlin RS, Thapa P, Pinto MV, Dyck PJB. Lumbosacral radiculoplexus neuropathy: Incidence and the association with diabetes mellitus. Neurology. 2019 Mar 12;92(11):e1188-e1194. doi: 10.1212/WNL.0000000000007020. Epub 2019 Feb 13. PMID: 30760636; PMCID: PMC6511105.

14. **Diabetic Amyotrophy.** Levi A. Diaz; Vikas Gupta. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-