Diabetic Neuropathy

* affects 50-70% diabetics;

up to 100% have conduction abnormalities electrophysiologically;

symptomatic neuropathy affects 5-10%.

Diabetes is most frequent cause of peripheral neuropathy worldwide!

* usually ***symmetrical***, but may be *focal* (more common in older type 2 patients).
* often involves *autonomic nervous system*.
* pathogenetic factors (poorly understood):
	1. **Hyperglycemia** → accumulation of sorbitol in Schwann cells → segmental demyelination and axonal degeneration → ***chronic***, more insidious neuropathies.
	2. **Ischemia** → ***acute***, often self-limiting neuropathies.
* *monocytic infiltration* in autonomic ganglia and *complement-fixing antibodies* to sympathetic ganglia suggest **autoimmune mechanisms**.

Predominant pathologic finding is ***axonal*** neuropathy with some segmental *demyelination*.

Diabetic neuropathy with marked loss of myelinated fibers, thinly myelinated fiber, and thickening of endoneurial vessel wall *(arrow).*


| CLASSIFICATION OF DIABETIC NEUROPATHY |
| --- |
| **POLYNEUROPATHIES** | **MONONEUROPATHIES** |
| I. Distal symmetrical | I. Isolated nerve lesions |
|  1. Chronic sensorimotor |  1. Peripheral |
|  2. Acute sensory / painful |  2. Cranial |
| II. Proximal motor | II. Radiculopathy |
| III. Autonomic |  |

N.B. **diabetes** can cause any type / category of neuropathy!!!

Classification according time course

A. **Transient**:

* 1. Acute sensory / painful neuropathies
	2. Mononeuropathies
	3. Radiculopathies

B. **Progressing steadily** - sensorimotor polyneuropathies ± autonomic symptoms.

POLYNEUROPATHIES

Pain is frequent feature of diabetic neuropathies!

##### I. DISTAL sensory / SENSORIMOTOR polyNEUROPATHY

- the most common diabetic neuropathy!

Klinika - **sensorinės skaidulos** nukenčia labiau negu motorinės;

* + - ***small nerve fibers*** (myelinated and unmyelinated) are affected first, beginning in feet.
		- symmetrical numbness and tingling in feet & hands (worsen at night); less often, debilitating, severe, deep-seated neuropathic pain and hyperesthesias (walking often is distressing - "it feels like I'm walking on coals").
		- eventually all sensation types suffer.
* minor wasting of intrinsic muscles of hands and feet.
* develops slowly (related to duration of diabetes); progresses relentlessly (never remits or recovers).
* kartais manifestuoja tik komplikacijomis (e.g. foot ulceration).
* clinical picture is not distinguishable from other forms of distal neuropathy (e.g. alcohol, heavy metal, uremia, amyloidosis) - **diagnosis is by exclusion**.
* risk of ulcer & amputation can be gauged by 10-g Semmes-Weinstein monofilaments.
* FDA approved – duloxetine.

##### II. ACUTE SENSORY / painful NEUROPATHY

- acute symptomatically distressing (but usually self-limiting):

* + 1. continuous disablingburning **pain** in stocking distribution (feet & legs), worsening at night.
		2. **hyperesthesias** (even contact with bedclothes brings on distressing pain)
* provokuojantys faktoriai - diabetic ketoacidosis, weight loss, depression.
* biopsy - loss of small sensory fibers.
* pain may last for months; recovery is usually complete within year (does not necessarily progress to conventional sensory polyneuropathy!).

##### III. PROXIMAL MOTOR NEUROPATHY (s. diabetic amyotrophy, diabetic lumbosacral plexopathy, femoral neuropathy)

1. ***Pain*** (džn. in femoral nerve distribution).
2. Severe asymmetric muscle ***weakness***, absent knee jerks.
3. ***Wasting*** of **major proximal muscle groups of pelvis** (iliopsoas, quadriceps, adductors).
* anksčiau buvo gavojama, kad tai *diabetinė miopatija*.

N.B. vienintelė “raumeninė” diabeto komplikacija yra išeminis raumens infarktas (džn. šlaunies; dgn. – CT / MRI).

* onset is usually acute.
* males > females (esp. elderly type 2 patients).
* often occurs in setting of recent severe (> 10%) loss of body weight.
* biopsy - *ischemic changes* (vascular cause?) in lumbosacral plexus.
* good prognosis - most resolve spontaneously within 12-36 months.

##### IV. AUTONOMIC NEUROPATHY - wide range of problems with poor prognosis.

* occurs nearly always in association with distal sensorimotor neuropathy!
* loss of small myelinated and unmyelinated nerve fibers.
* recovery is unusual.
* may play role in pathogenesis of other chronic diabetes complications (through disturbed regulation of local blood flow).

1. **Cardiovascular system** - impaired ***sympathetic vasoconstrictor response*** and ***cardiac reflexes*** (cardiac denervation):

*Increases mortality* - essential to screen for autonomic involvement in diabetics!

1. **orthostatic hypotension!!!**
2. tachycardia, defective heart rate and BP response to stress / exercise.
3. silent myocardial ischemia or infarction.
4. QT prolongation (risk of sudden death↑)
* adrenergic symptoms↓ in hypoglycemia (damage to sympathetic innervation of adrenal gland → lack of epinephrine release) → hypoglycemia unawareness.
* geriausias diagnostinis testas - *reduced RR interval changes* (in ECG) during Valsalva maneuver or standing or deep breathing; other tests show postganglionic autonomic failure (low supine plasma NE levels, decreased BP response to tyramine, enhanced pressor response to phenylephrine).

see Veg1 p.

2. **Sudomotor dysfunction**: distal anhidrosis + compensatory truncal and facial sweating, heat intolerance, ± gustatory sweating.

* may facilitate foot infections by creating skin breaks.
* *heat stroke / hyperthermia* are the most serious risks.

3. **GI system**

1. **constipation** – most common.
2. **diarrhea** (impaired sympathetic inhibition, bacterial overgrowth due to hypomotility, pancreatic insufficiency, celiac sprue). H: clonidine
3. **gastroparesis** - early satiety, nausea and vomiting.
4. **fecal incontinence**

N.B. *unpredictable food absorption* may adversely affect glycemic control and exacerbate hypoglycemia.

4. **GU system**

1. **bladder dysfunction** - infrequent urination, incomplete bladder emptying, dribbling, overflow incontinence (*bladder residual volumes may exceed 150 mL* → urinary tract infection).
2. **impaired sexual function** (impotence, retrograde ejaculation).

MONONEUROPATHIES

- sudden asymmetric isolated lesions affecting:

1. **cranial nerves** (džn. III, IV, VI)

Stereotyped disorder is *diabetic third nerve palsy* with spared pupil.

1. **peripheral nerves** (džn. median, radial, lateral popliteal).

*Truncal (thoracoabdominal) painful neuropathy* - involves intercostal or lumbar nerves unilaterally.

1. **spinal roots** – asymmetric painful radiculopathies.
* cause is unknown, but sudden onset suggests *vascular component*.
* usually localized to common sites of nerve entrapment or external compression (pressure palsies superimposed on generalized neuropathy).
* symptomatically distressing, but all tend to ***completely spontaneously*** ***resolve with time***.

TREATMENT

Aldose reductase inhibitors!

* **glycemic control** is most effective before clinical symptoms have developed.

rapid normalization of blood glucose may cause acute severe painful tingling of extremities!

* once diagnosis of diabetic polyneuropathy is established, ***no specific treatment*** for neuropathy is currently available!

Prevention of cycle: painless injury → ulceration → cellulitis → osteomyelitis → amputation

see *diabetic foot* in 2750 p.

1. **pain control** is the highest priority:
	1. standard analgesic therapies
	2. pregabalin (Lyrica®)\* see S20 p.
	3. anticonvulsants (e.g. gabapentin)
	4. tricyclic antidepressants (e.g. amitriptyline , desipramine), duloxetine\*
	5. i/v lidocaine when pain is extremely severe.
	6. opiates are usually contraindicated.

\*FDA approved for this indication

* COMBO-DN - the largest trial ever has shown that initial treatment with duloxetine provides better analgesia than pregabalin in treatment-resistant patients.
1. for **orthostatic hypotension** - stocking supports, 9α-fluorohydrocortisone, pindolol (β-blocker with partial agonist properties), clonidine.
2. for **gastroparesis** – metoclopramide, cisapride, erythromycin.
* avoid high-fiber diets.
1. for **diarrhea** - broad-spectrum antibiotics, clonidine, diphenoxylate, loperamide.
2. for **bladder dysfunction** – bethanechol.
3. for **impotence** - sildenafil citrate (efektyvu 50% diabetikų), vacuum erection aids, intracorporeal papaverine or phentolamine injections, penile prosthetic implants.

*Bibliography*: see also p. PN1

Cecil Textbook of Medicine, 2000

Merck Manual 1999

NMS Medicine, Pediatrics, Surgery, Emergency Medicine, Pathological Anatomy, Physiology, Pharmacology

Robbins Pathologic Basis of Disease, 1999

Lippincott Pharmacology Review, 2000