Diabetic Neuropathy

* affects 50-70% diabetics;

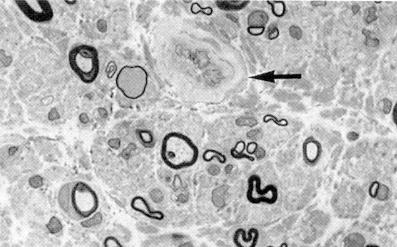
up to 100% have conduction abnormalities electrophysiologically;

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

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