Tests of thin fiber function
- autonomic nervous system testing
- quantitative sensory thresholds
- intraepidermal nerve fiber density

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Clinical evaluation of ANS function

Orthostatic dysfunction
- mild if BP decrease >20 mmHg
- severe if BP decrease > 30 mmHg

Blood pressure
- Hypotonia
- Hypertonia
- Variation of blood pressure

Sweating and thermoregulation
- ability to cope with temperature changes reduced
- anhidrosis
- hyperhidrosis

Urinary tract dysfunction
- incontinence, urgency, atonic bladder

Gastrointestinal tract dysfunction
- Difficulties with swallowing
- Vomiting
- Diarrhea
- Paralytic ileus
- Constipation

Sexual function
- Impotence
- Retrograde ejaculation

Cardiac function
- Attacks of tachycardia
- Atrial fibrillation

Salivation
- Dry mouth
- Increased salivation

Pupillary dysfunction
- Unequal pupillary size

Peripheral blood circulation
- Variation of temperature in the hands and feet
- Cold distal parts of the extremities

Skin
- Trophic changes, dry and thin skin
- Seborrhea
CNS disorders with ANS dysfunction
- Parkinson's disease
- Spinal chord lesions
- Multiple-system atrophy (Shy-Drager)
- Wernicke's encephalopathy
- MS
- ALS
- Brain tumours

Spinal chord lesions
- Massively disordered ANS response to stimuli below the level of the lesion
- Altered supraspinal influences and activation of sympathetic efferent nerves below the lesion
- Often triggered by bowel and bladder distension
- Headache, hypertension, bradycardia and hyperhidrosis, piloerection

Chronic PNP with ANS dysfunction
- Diabetes
- Amyloidosis
- Chronic polyradiculitis
- Chronic parautonomic neuropathy
- Chronic paraneoplastic autonomic neuropathy
- Uremia
- Riley-Day syndrome
- B₁₂-vitamin deficiency

Acute PNPs with ANS dysfunction
- Guillain-Barré syndrome
- Botulinum intoxication
- Porphyria
- Acute parautonomic neuropathy
- Drug induced (vincristine, cis-platinium, perhexilene)
- Acute paraneoplastic autonomic neuropathy
- Toxic neuropathies (heavy metals, solvents)

Simple ANS tests
- Heart rate variability (HRV)
  - Vagal activity – low heart rate
  - Sympathetic stimulation – increased heart rate
HRV
- "Beat to beat" variation
- Short recordings (1-5min)
- Long recordings (24h ambulatory)

**HRV testing**
- 15 min of rest before study
- Quiet room
- Sinus rythm
  - Automatic and manual control of ectopic beats
  - If there is no sinus rythm, analysis cannot be made

**Short term recordings**
- Stationary conditions
  - Ectopic beats should be edited
- Responses to standardized tests
  - Tilt
  - Valsalva
  - Deep breathing 6/min

**Time and frequency domain**

**Time and frequency domain – diabetic patient**

**Frequency domain analysis**
- Fast Fourier Transformation (FFT spectra).
- Autoregressive model
**Frequency analysis**

- **High frequency HF (0.15-0.4 HZ)**
  - Parasympathetic activity
  - Breathing pattern
- **Low frequency LF (0.04-0.15 HZ)**
  - Sympathetic
- **Very low frequency VLF (< 0.04 HZ)**
  - ?
  - Only from 24 h recordings

**Provocation tests**

- **Sympathetic stimulation**
  - Mental stress
  - Hand grip
- **Vagal stimulation**
  - Deep breathing
  - Diving reflex
  - Oculo-cardial reflex

**Provocation tests**

- **Mixed sympathetic and parasympathetic**
  - Valsalva
  - Tilt
  - Stand up
  - Cold-pressor

**Sympathetic provocation**

- **Mental**
  - Arithmetic tasks, reaction time
  - HR, BP
- **Hand grip**
  - 30% of maximal strength 3 min.
  - BP, HR
  - Normal diastolic BP increase > 16 mmHg

**Vagal provocation**

- **Diving reflex**
  - Immersion of face in water
  - Ice pack over face and no breathing for 30 sec
  - HR decreases 70->45
- **Oculocardial reflex**
  - Weight over eyes (100mmHg for 10-30 sec)
  - Trigeminovagal reflex>Bradycardia

**Vagal provocation**

- **Deep breathing 6/min**
  - 5 sec inspiration and 5 sec expiration
- **Carotic massage**
**Sympathetic skin response SSR**

**SSR - Physiology**
- Electric response from the skin due to sympathetic nervous system
- Closely associated with sweating
  - Emotional sweating
  - Change in the potassium permeability of sweat glands
- Part of the orienting response

**SSR - Physiology**
- Sweat glands have only sympathetic cholinergic innervation
  - SSR can be abolished with atropine
  - Botulinum toxin can be used for hyperhidrosis
- Psychogenic sweating has considerable CNS representation
- The spontaneous fluctuations in the skin of the limbs is synchronous

**SSR - Recording environment**
- Quiet, warm and dimmed room
- Limb temperature 30 C
- 10 min rest before recording
- 30 sec rest between stimuli
- 3-5 repeated recordings

**SSR - Recording**
- Filter settings 0.2 Hz - 50 Hz
- Time window 5 - 10 sec
- Gain 100 - 500 μV/div
SSR - recording

- Ag/AgCl plate electrodes or disposable electrodes
- Good cleaning of the skin
  - Active electrode
    - palm of the hand
    - sole of the foot
  - Reference electrode
    - dorsum of the hand
    - Dorsum of the foot

SSR - stimulation

- Electric shock
  - stimulus duration 0,5 ms
  - stimulus intensity 10 - 20 mA
  - Should be unpleasant
- Sudden sound
- Touch
- Immersion of face or hand into cold water
- Deep inhalation

Normal finding – electric shock

Normal finding – inhalation

Normal finding – loud sound

SSR – reference values

<table>
<thead>
<tr>
<th></th>
<th>normal</th>
<th>abnormal</th>
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<tbody>
<tr>
<td>latency hand foot</td>
<td>1,5 sec</td>
<td>&gt; 2,0 sec</td>
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<tr>
<td>ampl hand foot</td>
<td>500 uV</td>
<td>100 uV</td>
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</table>
SSR – reference values
- Large interindividual variability
- Large intraindividual variability to different stimuli
- Always obtainable in subjects < 60 years
- Only missing response abnormal with certainty
- Repeated prolonged latency (unusual)
- Reduced amplitude
- Marked side difference

SSR – left sided plexopathy

SSR – Clinical utility
- Evaluation of autonomic nervous system function in polyneuropathies
  - Diabetic PNP
  - Alcohol related PNP
  - Uremic PNP
  - Polyradiculitis

SSR – clinical utility
- Spinal chord lesions
- Erectile dysfunction
- Horner’s sdr (recording over the forehead)
- MS
- Parkinson’s disease

Sensory thresholds

Quantitative sensory thresholds (QST)
- Sensory pathways from receptors and nerve terminals to cortex
- Possible to quantify the degree of a sensory deficit
- Provide information of Aβ, Aδ and C axon function
QST — why?
- Quick
  - method of limits
  - ascending series
- Non-invasive
- Hypo-phenomena
- Hyper-phenomena may be quantified
  - Hyperalgesia
  - Hyperesthesia

QST — disadvantages
- Dependent on patient co-operation
- Quiet environment - no distractions
- Do not define the level of disturbance
  - Abnormalities caused peripheral and central disorders

Equipment

QST in clinical practice
- Inter-session variability range from 50% to 200%
- Inter-examiner differences may be significant

Sensory thresholds
- Vibratory (VDT)
- Thermal
  - Cold (CDT) thin myelinated axons
  - Warm (WDT) unmyelinated axons
  - Heath-pain (PDT)
  - Detection thresholds
- Method of limits
  - repeated 5 times
  - ascending series with linear ramps
  - at random intervals

Sensory thresholds
- Polyneuropathy
- Focal nerve lesions
- Neuropathic pain
Sensory abnormalities
- Hypoestesia = Reduced sensation
- Hyperestesia = Increased sensation
- Hypoalgesia = Reduced pain sensation
- Hyperalgesia = Increased pain sensation
- Allodynia = Normally painless sensation painful
- Dysesthesia = Altered sensation
- Paresthesia = Numbness, tingling
- Hyperpathia = Painful stimulus causes an increased level and duration of pain
- Pallanestesia = Loss vibration sensation

QST - Comparison of algorithms
- Method of limits
  - Reaction time, cognitive capacity and motor performance included
  - Higher than real thresholds
- Forced choice
  - Accurate
  - Time consuming
  - Non-compliance (boredom, fatigue)

QST in clinical practice
- Inter-session variability
  - 50% to 200%
- Clinical trials
  - Inter-examiner differences
- Pain threshold measurements
  - ML is recommended

Proctocol QST
- Vibratory (VDT)
- Thermal
  - Cold (CDT)
  - Warm (WDT)
- Heat-pain (PDT)
- Method of limits, 5 repeated ascending series with linear ramps

Punch biopsy of skin
Method

- 3 mm punch biopsy from skin
  - Distal leg: 10 cm above lateral malleolus
  - Proximal thigh: 20 mm below iliac spine
- 50 μm sections
- Stained with pan axonal marker
  - PGP 9.5 (protein gene product)
- Axon density calculated

Rules for counting axons

Control subject

Diabetic thin fiber neuropathy
Focal neuropathy

Practice Parameters: Evaluation of clinical symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review)

Abstract:
Clinical symmetric polyneuropathy (CSP) is the most common variety of neuropathy. Until a few decades ago, there was little understanding of the pathophysiology of CSP, and only recently has a variety of diagnostic and therapeutic options been developed. The aims of this paper are to review the evidence for the use of autonomic testing, nerve biopsy, and skin biopsy in the diagnosis and management of CSP.

Methods:
A literature review of the English-language medical literature was performed using Medline, EMBASE, and the Cochrane Library, with additional searches of abstracts from the American Academy of Neurology, American Association of Nerve Injury, and European Federation of Neurological Society meetings. The search was limited to articles published from 1966 to 2007.

Results and Recommendations:
1. Autonomic testing may be useful in the evaluation of the autonomic dysfunction in some cases of CSP, but further studies are needed to determine its role in the diagnosis and management of CSP.
2. Nerve biopsy may be useful in the diagnosis and management of CSP, but further studies are needed to determine its role in the diagnosis and management of CSP.
3. Skin biopsy may be useful in the diagnosis and management of CSP, but further studies are needed to determine its role in the diagnosis and management of CSP.

The End

Skin biopsy in the management of peripheral neuropathy

Skin biopsy has been widely used in recent years to aid the diagnosis of autonomic nerve lesions, including diabetic autonomic neuropathy and small fiber neuropathy. Historically, skin biopsy has been performed in different clinical settings and has been used to evaluate autonomic nerve function, and in recent years, it has been used to evaluate nerve fiber density and nerve fiber size. However, it is still not clear whether skin biopsy is a reliable tool for the diagnosis of peripheral neuropathy.

Review

The End