Outline

- Narcolepsy:
  - Historical Background
  - Clinical Symptoms
  - Clinical Course (and DD)
  - Pathophysiology
  - Diagnostic criteria and procedures
  - Treatment
- New Highlights
- Daytime sleepiness and narcolepsy like symptoms in PD
- How to handle a complaint of daytime sleepiness in a PD patient
- Treatment alternatives

Historical Aspects of Narcolepsy

- Westphal 1877: First description
- Gelineau 1880: First use of the designation: narcolepsy
- Term derived from ancient Greek
- 1930 and following years:
  - First successful treatment reports with amphetamines and ephedrin

Narcolepsy: frequency in the population

- Approx 1 in 2000 affected in the general population
  - USA: 57 / 100000  Silber et al. Sleep 2002;25:197-202
  - Europa: 47 / 100000  Ohayon et al. Neurology 2002;58:1826-33
  - Hong Kong: 34 / 100000  Wing et al. Ann Neurol 2002;51:578-84
- However only 10-20 % of the affected have been diagnosed
### Narcolepsy: Clinical Symptoms

#### Classical „Narcoleptic Tetrade“

- Excessive Daytime Sleepiness
- Cataplexy
- Hypnagogic hallucinations
- Sleep Paralysis

Further possible symptoms

- Disturbed nighttime sleep / insomnia
- „Automatic actions“
- Other parasomnias

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#### Excessive Daytime Sleepiness:

- Intolerance for monotonous situations
- Sleepiness may vary over the day
- Naps are refreshing
- CAVEAT: non specific

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#### Cataplexy

Criteria first defined by Y Honda in the 60ies and 70ies

A: Sudden bilateral weakness of the skeletal muscles
B: Triggered/provoked by sudden strong emotion
C: No impairment of consciousness or memory
D: Duration less than minutes
E: Good response to Clomipramin oder Imipramin
Hypnagogic/Hypnopompic Halluzinations

- "Halluzinatorische Erlebnisse" vor dem Einschlafen
- Meist visuell, aber auch taktile und auditiv
- Häufig assoziiert mit Angstgefühlen
- Kann zu Angst vor dem Schlafengehen führen

Narcolepsy: Clinical Symptoms

Sleep Paralysis

- Upon Awakening or when falling asleep
- Complete inability to move or talk
- Perpetuation of environment
- Duration: Seconds-Minutes
- Ends spontaneously or can be interrupted by external stimulation
- At first manifestation often associated with massive fear

Disturbed night time sleep (insomnia)

- Disorder of Sleep Maintenance
Narcolepsy: Clinical Course

- Disease Onset often in pubertal age or young adulthood
- However, onset also possible during infancy or in later adult life
- Often sudden onset and subjectively associated with triggering situation
  - z.B. Stress, Infekte, Operation, Impfung
Narcolepsy: Clinical Course

- Daytime sleepiness often precedes cataplexy
- Classical symptom tetrad less frequent
- Lifelong disease, but no influence of age at disease onset on severity and course

Narcolepsy: Differential Diagnosis

Daytime sleepiness: Other disorders to be considered
- Other Hypersomnias
  - Idiopathic Hypersomnia
  - Kleine Levin Syndrome
  - Menstruation Related Hypersomnia (KLS in ICD3)
  - Substance induced hypersomnias
- Insufficient Sleep Syndrome
- Multiple other neurological disorders
- Sleep Related Breathing disorders
- Periodic Limb Movement Disorder (?)
- Psychiatric disorders
- Circadian disorders

Differential diagnosis

Cataplexy
- "weak with laughter"
- Syncope, drop attacks
- Atonic seizures
- Neuromuscular disorders
- Psychiatric disorders
- Paralysis related to abnormal potassium

Sleep paralysis
- Isolated sleep paralysis
- Paralysis related to abnormal potassium

Hypnagogic hallucinations
- Nightmares, RBD, NR parasomnia
Genetics and Pathophysiology

Hypocretin/Orexin

- Hypocretin/Orexin Cells in DL Hypothalamus
- Hypocretin role in S/W function
- Narcolepsy 85-95% decrease of Hcrt cells

Thannickal et al. Neuron 2000;27:469-474

Role of Hypocretin in Humans

Nach Meyer G, Potthacker T. Thieme 2007
Genetics

- Assosiation of narcolepsy with HLA system reported in 1983

- Humanes Leukozyte Antigen System on Chromosom6 6
  - HLA DRB1*1501
  - HLA DQB1*0602
  - HLA DQA1*0102 prädisponierend

- Complex HLA DR and DQ interactions (Mignot 2001)
  - Tafti et al. DQB1 locus alone explains most of the risk and protection in narcolepsy with cataplexy in Europe.
  - HLA-DPB1 and HLA Class I Confer Risk of and Protection from Narcolepsy.

Narcolepsy is strongly associated with a genetic variant in the T-cell receptor alpha locus

- Genome-wide association study in Caucasians with replication in 3 ethnic groups
- 1st documented genetic involvement of the T-cell receptor alpha locus in any disease
- T-cell receptor alpha locus encodes the major receptor for HLA-peptide presentation
- HLA-TCR interactions could contribute to organ-specific autoimmune-targeting
- Narcolepsy as model for > 100 other HLA-associated disorders?
Narcolepsy is associated with flu vaccination, but also with H1Ni influenza

AS03 Adjuvanted AH1N1 Vaccine Associated with an Abrupt Increase in the Incidence of Childhood Narcolepsy in Finland.

Hanna Nohynek, Jukka Jokinen, Markku Pantti, Olli Vannio, Turku Kajava, Jorina Sundholm, Saara-Lena Hirvonen, Christo Hubak, Ukko Jalkinnen, Peter Chen, Olli Saarenpää - Hekkä, Terhi Kip

PLoS ONE 3 March 2012 (7),3 e33536

Is Narcolepsy an autoimmune disease?

- Narcolepsy is caused by loss of hypocretin-producing neurons
- The Stanford Team had reported to have found the first evidence of autoimmunity: a special group of CD 4+ T cells, which target hypocretin and were found only in narcolepsy patients.

White and Gray Matter Abnormalities in Narcolepsy with Cataplexy

- Aim: DTI including measurements of mean diffusivity (MD), a parameter of tissue integrity, fractional anisotropy (FA), a parameter of neuronal fiber integrity, and VBM, a measure of gray and white matter volume, to detect brain tissue changes in narcolepsy-cataplexy.
- Subjects: Patients with narcolepsy-cataplexy (n = 16) and age-matched healthy control subjects (n = 12)
- Results: Significant MD increases and concomitant FA decreases in the fronto-orbital cortex and the anterior cingulate in NC. Additional MD increases without FA changes in the VTA, dorsal raphe nuclei, and hypothalamus. FA signal decreases in the white matter tracts of the inferior frontal and inferior temporal cortices of NC. Brain volume loss in focal areas of the inferior and superior temporal cortices and the cingulate.
- Conclusions: Areas of increased diffusivity in the hypothalamus appear consistent with hypocretinergic cell loss. Signal abnormalities in the VTA and dorsal raphe nuclei correspond to major synaptic targets of hypocretin neurons. These tissue alterations identified in the frontal cortices and cingulate are crucial in the maintenance of attention and reward-dependent decision making.
Diagnosis criteria and procedure for narcolepsy

- **History**
- **Polysomnography and MSLT**
- **Role of HLA-Typing**
- **Role of lumbar puncture with measurement of Hypocretin/Orexin**

Narcolepsy Type 1

Alternate Names: Hypocretin deficiency syndrome, narcolepsy-cataplexy, narcolepsy with cataplexy.

Diagnostic Criteria

- **Criteria A and B must be met**
  - **A.** The patient has daily periods of irresistible need to sleep or daytime lapses into sleep occurring for at least three months.
  - **B.** The presence of one or both of the following:
    1. Cataplexy (as defined under Essential Features) and a mean sleep latency of ≤ 8 minutes and two or more sleep onset REM periods (SOREMPs) on an MSLT performed according to standard techniques. A SOREM P (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
    2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤ 110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay.

Notes

1. In young children, narcolepsy may sometimes present as excessively long sleep or as resumption of previously discontinued daytime napping.
2. If narcolepsy type I is strongly suspected clinically but the MSLT criteria of B1 are not met, a possible strategy is to repeat the MSLT.

American Academy of Sleep Medicine, International Classification of Sleep Disorders, 3rd ed., 2014

Narcolepsy Type 2

Alternate Names: Narcolepsy without cataplexy.

Diagnostic Criteria

- **Criteria A-E must be met**
  - **A.** The patient has daily periods of irresistible need to sleep or daytime lapses into sleep occurring for at least three months.
  - **B.** A mean sleep latency of ≤ 8 minutes and two or more sleep onset REM periods (SOREMPs) are found on a MSLT performed according to standard techniques. A SOREM P (within 15 minutes of sleep onset) on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.
  - **C.** Cataplexy is absent.
  - **D.** Either CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either > 110 pg/mL or > 1/3 of mean values obtained in normal subjects with the same standardized assay.
  - **E.** The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

Notes

1. If cataplexy develops later, then the disorder should be reclassified as narcolepsy type I.

American Academy of Sleep Medicine, International Classification of Sleep Disorders, 3rd ed., 2014
Polysomnography in Narcolepsy

Multiple sleep latency test MSLT

Еinschlaflatenz < 8 Min. ≥ 2 SOREMs

HLA Typing

HLA DQB1*0602

- 93% Narcolepsy with cataplexy
- 56% Narkolepsie without cataplexy

Mignot E. et al. Arch Neurol 2002; 59:1553-1562

- 18-32% in normal population
Do we need CSF hypocretin/orexin

- Sensitivity and specificity in narcolepsy with typical cataplexy 87%, 99%
- Typical cataplexy was a better predictor for reduced hypocretin than MSLT
- EFNS Guidelines: diagnostic biomarker for NC

Narcolepsy Treatment

Nondrug treatment

- Sleep Hygiene
- Avoid night and shift work
- Planned daytime naps
Treatment targets

- Daytime sleepiness
- Cataplexy
- Sleep Paralysis
- Hypnagogic Hallucinations
- Sleep fragmentation

Treatment

- **Daytime sleepiness** -

  FIRST LINE

  - Modafinil
    100 - 400 mg
  - Sodium oxybate
    4.5 - 9 g

  SECOND LINE

  - Methylphenidate (off label in some countries) zugelassen
    10 - 60 mg

  EFNS Guidelines 2006

- **Cataplexy** -

  FIRST LINE

  - Sodium oxybate
    4.5 - 9 g
  - Clomipramin
    10 – 75 mg
  - other antidepressants off label

  EFNS Guidelines 2006
Treatment
- Sleep fragmentation / Insomnia -

- Sodium oxybate
  4.5 - 9 g

- Sometimes benzodiazepines and bzd receptor agonists are required

Modafinil

- EBM class 1 studies

<table>
<thead>
<tr>
<th>Studie</th>
<th>N</th>
<th>Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Billard 1994</td>
<td>50</td>
<td>12 W, cross-over 300 mg Modafinil fixed Dosis</td>
</tr>
<tr>
<td>Broughton 1997</td>
<td>75</td>
<td>6 W, cross-over 3 Arme (Placebo, 200 mg, 400 mg)</td>
</tr>
<tr>
<td>US Modafinil in narcolepsy</td>
<td>283</td>
<td>9 W, DB, randomisiert  Placebo vs. 200 mg vs. 400 mg</td>
</tr>
<tr>
<td>multicenter study group 1998</td>
<td></td>
<td></td>
</tr>
<tr>
<td>US Modafinil in narcolepsy</td>
<td>271</td>
<td>9 W, DB, randomisiert  Placebo vs. 200 mg vs. 400 mg</td>
</tr>
<tr>
<td>multicenter study group 2000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sodium oxybate

- EBM Class 1 studies

<table>
<thead>
<tr>
<th>Studie</th>
<th>N</th>
<th>Design</th>
<th>Primäre Endpunkte</th>
</tr>
</thead>
<tbody>
<tr>
<td>SXB-15</td>
<td>228</td>
<td>8 W, doppelblind, randomisiert</td>
<td>ESS, CGI</td>
</tr>
<tr>
<td>SXB-22</td>
<td>278</td>
<td>8 W, doppelblind, randomisiert</td>
<td>MWT</td>
</tr>
<tr>
<td>GHB2</td>
<td>136</td>
<td>4 W, Placebo vs. 3 g vs. 6 g vs. 9 g</td>
<td>Kataplexie</td>
</tr>
<tr>
<td>SXB-21</td>
<td>55</td>
<td>4 W, Withdrawal design</td>
<td>Kataplexie</td>
</tr>
</tbody>
</table>
Sodium oxybate:

- Research and off label use for narcolepsy since the 70ies
- 2007 licenced by EMEA for adult narcolepsy with cataplexy
- Postulated mechanism of action: similar to GABA, dopamine release?
- Only drug with class 1 evidence for EDS, cataplexy and sleep disturbance
- Very short plasma half life

Adverse events with sodium oxybate

Potential AR worsening as rare side effect
Abuse potential

Other treatment attempts

Hypocretin Replacement?
Immune modulation?

Histamin H3 Rezeptor Antagonists
- First studies with pitolisant have been published, non inferiority with modafinil has been demonstrated

Waiting for EMEA decision
• Excessive daytime sleepiness (EDS) affect around one third of PD patients
  (Ondo, Neurology 2001; Tan, Neurology 2002; Ghorabay, Mov Disord 2007)

• Sleepy phenotype in PD:
  − In multiple sleep latency test >50% fell asleep within a mean 5 min; 41%
    have at least 2 sleep onset REM
  (Arnulf, Neurology 2002; Razmy, Arch Neurol 2004; Ry e, J Sleep Res 2005)
  − Hypnagogic hallucinations
  (Arnulf, Neurology 2000)
  − In large groups of PD patients, the longer sleep time at night is associated
    with more severe daytime sleepiness, an association suggestive of central
    hypersomnia
  (Arnulf, Neurology 2002; Razmy, Arch Neurol 2004; Ry e, J Sleep Res 2005)
  − Sleep apnea, periodic leg movements, REM sleep behavior disorder and
    sleep fragmentation do not correlate with the severity of daytime sleepiness
  (Arnulf, Neurology 2002; Razmy, Arch Neurol 2004; Ry e, J Sleep Res 2005; De Cock, Brain 2007)

• Excessive daytime sleepiness and sleep attacks are common side-effect of all classes of
  dopamine agonists, and sometimes of levodopa alone and other PD medications.

• Treating patients with stimulants such as modafinil is only partially efficacious, while trials
  of anti-H3 drugs and sodium oxybate seem more active. Eventually, the recent stimulation
  of the pedunculopontine nucleus has stimulant or sedative effects in patients, depending
  on the frequency of stimulation.

Sleepiness in Parkinson’s disease
Isabelle Arnulf*, Smaurada Leo-Semenescu

• Sleepiness may precede PO onset (damage of arousal systems)

Sleepiness in Parkinson’s disease
Isabelle Arnulf*, Smaurada Leo-Semenescu

<table>
<thead>
<tr>
<th>Area in Parkinson’s Disease</th>
<th>Neurotransmitter</th>
<th>Off vs On PD scores, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor contribution</td>
<td>Mesocorticoniches</td>
<td>40–60</td>
</tr>
<tr>
<td>Higher emotion</td>
<td>Serotonines</td>
<td>26–40</td>
</tr>
<tr>
<td>Vertical positioning</td>
<td>Dopaminergic</td>
<td>95</td>
</tr>
<tr>
<td>Paralimbic structures</td>
<td>Noradrenergic</td>
<td>53%</td>
</tr>
<tr>
<td>Limbic dopamine receptors</td>
<td>Histaminergic</td>
<td>5%</td>
</tr>
<tr>
<td>Lateral hypothalamic areas</td>
<td>Glutaminergic</td>
<td>25–62%</td>
</tr>
<tr>
<td>Frontal lobe</td>
<td>Oxytocinergic</td>
<td>12–13%</td>
</tr>
</tbody>
</table>

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  dopamine agonists, and sometimes of levodopa alone and other PD medications.

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  of the pedunculopontine nucleus has stimulant or sedative effects in patients, depending
  on the frequency of stimulation.

Daytime REM Sleep in Parkinson’s Disease

- Multi PD patients
  - UHDRS, modified Hoehn & Yahr Stage, Mini-Mental State Exam (MMSE), questionnaire dealing with restless
  legs symptoms
- 24-hour laboratory protocol
  - Polysomnography (PSG): periodic leg movements in sleep, apnea/hypopnea index
  - Maintenance of Wakefulness Test (MWT): REM sleep, sleep latency, sleep efficiency

- Chart showing data on Parkinson’s Disease and Parkinson’s disease patients.
How to assess sleepiness in PD

- Sleep history
- Scales
- MSLT / MWT
- Other tests, e.g. pupillography

Subjective assessment of sleep and sleepiness in PD – Sleep history I

- Defining the problem: basic symptoms: a) inability to sleep as desired, b) excessive daytime sleepiness and c) abnormal phenomena or behaviors during or around the sleep period
- Sleep/wake Schedule
- Behavior before sleep: including questions regarding restless legs syndrome, detailed scrutiny of the type and schedule of antiparkinsonian agents, intake of caffeine, other stimulants, alcohol or other drugs
- Behavior during sleep and final awakening:
  - number, duration and time of nocturnal awakenings, type of activities during the awakenings, appearance of motor symptoms, time needed to fall asleep again, and time and type (spontaneous or induced) of the final awakening in the morning
  - questions about snoring or stridor, breathing pauses and gasps during sleep should be asked to the patient and bed partner
  - talking, shouting, screaming, crying or laughing, limb or other body movements such as hitting, punching, kicking involuntarily the bed partner, or falling out of bed

Subjective assessment of sleep and sleepiness in PD – Sleep history II

- Dreaming and hallucinations: patients with obstructive sleep apnea may report anxious or frustrating dreams; patients with NREM parasomnias may recall dreams, where they (or their loved ones) are in great danger and need to escape (flight); patients with REM sleep behavior disorder (RBD), typically dream that they are threatened by other people or animals and they react against the aggressor. Sometimes aggressive dreams can also be reported by obstructive sleep apnea patients. Nocturnal hallucinations in PD should not be confused with dreams
- Daytime behavior and excessive daytime sleepiness: ask how the sleep problems affect the daytime activities of the patient; fatigue, inability to concentrate, subjective decrease in performance, problematic daytime sleepiness, "sleep attacks"
- Other symptoms: including questions about cataplexy, sleep paralysis or hypnagogic hallucinations

Subjective assessment of sleep and sleepiness in PD – Sleep scales

<table>
<thead>
<tr>
<th>Scale</th>
<th>Type of disorder assessed</th>
<th>Best informant required</th>
<th>Period assessed</th>
<th>Population studied</th>
<th>Number of questions</th>
<th>Range of scores (cut-off value)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDSS-2</td>
<td>Nocturnal disturbance</td>
<td>Patient, informant</td>
<td>Previous week</td>
<td>Specific for PD</td>
<td>15</td>
<td>0-60</td>
<td>A previous version PDSS-1 exist with several changes.</td>
</tr>
<tr>
<td>PSQI</td>
<td>Sleep quality, both nocturnal sleep and diurnal sleepiness</td>
<td>Required</td>
<td>Previous month</td>
<td>Many populations, used also in PD</td>
<td>19</td>
<td>5 components</td>
<td>0-21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>It gives quantitative information about number of sleep hours, sleep latency, etc.</td>
</tr>
<tr>
<td>SCOPA/SLEEP</td>
<td>Sleep quality, both nocturnal sleep and diurnal sleepiness</td>
<td>May or not participate</td>
<td>Previous month</td>
<td>Designed for PD</td>
<td>12</td>
<td>0-12</td>
<td>5/6</td>
</tr>
<tr>
<td>ESS</td>
<td>Daytime sleepiness</td>
<td>Not required</td>
<td>Reporting</td>
<td>General, but used in PD several times</td>
<td>8</td>
<td>0-24</td>
<td>(&gt;10)</td>
</tr>
<tr>
<td>ISCS</td>
<td>Sudden onset of sleep</td>
<td>Not required</td>
<td>Reporting</td>
<td>PD</td>
<td>6</td>
<td>Good to investigate risk of unintended sleep episodes (sleep attacks)</td>
<td></td>
</tr>
<tr>
<td>SSS</td>
<td>Current daytime sleepiness</td>
<td>Not required</td>
<td>Reporting</td>
<td>General, but used in PD several times</td>
<td>1</td>
<td>Instantaneous measure of sleepiness, not appropriate for routine follow-up of patients</td>
<td></td>
</tr>
<tr>
<td>Stavanger</td>
<td>Daytime sleepiness</td>
<td>Required</td>
<td>Not specified</td>
<td>Specifically designed for PD</td>
<td>1</td>
<td>0-3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>It is particularly useful in patients with advanced PD disease.</td>
</tr>
</tbody>
</table>


How to treat sleepiness in PD

- As specific as possible, e.g. if sleep apnea is present and cause for EDS, treat SA
- If sleepiness is associated with dopaminergic medication intake, try to switch
- If sleepiness is severe (narcolepsy-like phenotype) consider stimulants, e.g. modafinil, methylphenidate (caveats)

Thank you for your kind attention
Narcolepsy: autoimmunity, effector T cell activation due to infection, or T cell independent, major histocompatibility complex class II induced neuronal loss?

Adriano Fontana, Henrikus Guatr, Werner Roth, Emily Rojas, Thomas Herbst and Chezlin Benoit

Table 1: Autoimmunity in narcolepsy?

<table>
<thead>
<tr>
<th>Autoimmune</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-DABA</td>
<td>Longhi et al., 1994; Moskau et al., 1993</td>
</tr>
<tr>
<td>Presence of alpha-MSH</td>
<td>Kikuta et al., 2003</td>
</tr>
<tr>
<td>Increase in anti-alpha-MSH</td>
<td>Savin et al., 2004; Kriwaczek et al., 2005</td>
</tr>
<tr>
<td>Anti-FLi antibodies</td>
<td>Billard et al., 1998; Asaad et al., 2009</td>
</tr>
<tr>
<td>Anti-IFN-β antibodies</td>
<td>Confavreux-Caramozza et al., 2010</td>
</tr>
</tbody>
</table>

No other abnormalities found in cerebrospinal fluid, including cell counts and protein levels.

No increase in IgG index.

No increased number of lymphocytes in peripheral blood.

No increased number of eosinophils in peripheral blood.

No increased number of basophils in peripheral blood.

No increased number of monocytes in peripheral blood.

No increased number of neutrophils in peripheral blood.

No increased number of platelets in peripheral blood.

No increased number of red blood cells in peripheral blood.

No increased number of white blood cells in peripheral blood.

No increased number of lymphocytes in bone marrow.

No increased number of plasma cells in bone marrow.

No increased number of B cells in bone marrow.

No increased number of T cells in bone marrow.

No increased number of natural killer cells in bone marrow.

No increased number of monocytes in bone marrow.

No increased number of eosinophils in bone marrow.

No increased number of neutrophils in bone marrow.

No increased number of basophils in bone marrow.

No increased number of mast cells in bone marrow.

No increased number of mast cells in peripheral blood.

No increased number of mast cells in bone marrow.

No increased number of mast cells in bone marrow.

No increased number of mast cells in bone marrow.

No increased number of mast cells in bone marrow.

No increased number of mast cells in bone marrow.

No increased number of mast cells in bone marrow.