Hyperuricemia and gout are two of the most common metabolic diseases in industrial countries. The exacerbated forms of uricemia are the acute gout attack and chronic gout. They are caused by the incorporation of crystalloid salts of uric acid (urate) into the joints. In the following article, we will present all relevant facts concerning gout. This way, you are perfectly prepared for all exams in the clinical part of the medical studies and for your final exams.

Definition of Hyperuricemia and Gout

Hyperuricemia

Hyperuricemia is defined by uric acid level > 6.4 mg/dl. This corresponds to the solubility of uric acid in plasma water at 37 °C and a pH of 7.4. If the uric acid level rises, the risk to become infected with gout increases simultaneously. The following threshold values show:
- At values between 6.4 and 7 mg/dl: only 2 % develop manifested gout.
- At values > 8 mg/dl: 40 % develop manifested gout.

Manifested gout

Manifested gout is defined by uric acid precipitation in the tissue (joints, tophi and kidneys). An acute gout attack represents exacerbated hyperuricemia.

Epidemiology of Hyperuricemia and Gout

Distribution of hyperuricemia and gout

In Western industrial nations, 25 % of all men are affected by hyperuricemia. Men can be affected independently of their age, while women mostly sicken post-menopausally since estrogens have a uricosuric effect.

1.5 % of the population suffers from gout. The disease primarily manifests between the ages 40 – 60. Roughly, every tenth patient with hyperuricemia develops gout.

**Note:** Men and women are affected by gout at a ratio of 9 to 1.

Classification of Hyperuricemia and Gout

Hyperuricemia is a metabolic disorder. It is divided into a primary (genetic) and a secondary form (genesis via another disease).
Primary familiar hyperuricemia

95% of hyperuricemia cases are primary. Two causes can be distinguished:

**Polygenetically induced a decrease of renal-tubular uric acid secretion (in 99% of the cases):** if the decreased elimination capacity of the kidney is exceeded at uric acid precipitation, uric acid tailback occurs. If the affected person has an appropriate diet, the kidneys can cope with the hyperuricemia, even if caused by genetic predisposition. Thus, for the most part, primary hyperuricemia is a genetically inherited disease, which manifests at malnutrition.

**Genetic defects causing overproduction of uric acid:** deficiency of the enzyme hypoxanthine-guanine-phosphoribosyl-transferase at X-chromosomal-recessively inherited Lesch-Nyhan syndrome.

Secondary hyperuricemia

- **Increased uric acid precipitation at cell destruction:** develops at myelo- or lymphoproliferative diseases, hemolytic anemia, tumor lysis syndrome, cytostatic therapy.
- **Reduced renal uric acid elimination:** via kidney insufficiency, medication, ketosis (fasting, diet rich in fats, decompensated diabetes mellitus), intoxications (lead, CO), endocrine diseases (functional disorders of the parathyroid gland, hypothyreosis, acromegaly), lactate acidosis, alcohol abuse.

Pathogenesis of Hyperuricemia and Gout

Development of hyperuricemia

The final product of purine metabolism is uric acid. In purine metabolism, the nucleotide bases adenine and guanine, along with purines absorbed exogenously via consumed food, are metabolized. Every day, 350 mg of uric acid accumulates in the body and are then excreted via the kidneys and the feces. The uric acid level in the plasma and other extracellular fluids increases in case of a positive uric acid balance. Chronic precipitation and acute gout attacks occur if the solubility threshold of 6.4 mg/dl is exceeded.
Development of gout

An acute gout attack develops via an exacerbation of the uric acid level, which, along with the uric acid solubility, can be influenced by different events:

- **Supernutrition**: gout is a manifestation factor of the metabolic syndrome.
- Alcohol consumption: acidification of the fluids in the extracellular space leads to inhibited uric acid excretion in the kidneys.
- Fasting
- Tissue trauma
- Surgical interventions
- Medication: diuretics; aspirin in low doses can influence uric acid excretion.

Hyperuricemia often occurs in patients with hyperlipidemia, diabetes mellitus, obesity, and hypertension. Thus, a connection between these diseases is discussed.

Clinic of Hyperuricemia and Gout

Symptoms of acute gout

In ca. 65 % of the cases, a gout attack often occurs at night with monarthitis, at which the lower extremity is affected in 90 % of the cases: gout attack in the toe basal joint (podagra). Rarer is the gout attack in the thumb basal joint (chiragra). Mostly, patients suffer from complaints in the joints for one week. In older patients, polyarthritic attacks also occur.

**Signs of acute joint gout**

- Reddening, swelling, and extreme contact pain
- Fever (due to cytokine production development of systemic inflammation)
Symptoms of chronic gout

Tophi and crystalloid arthropathy

If mononatrium uric acid accumulates in the bones, cartilage, synovia and the tendons, a local inflammatory reaction is triggered, leading to a destruction of the respective tissue and to fibrotic reactions. These lead to the formation of connective tissue nodes, the so-called tophi. If the joint is chronically damaged, one speaks of crystalloid arthropathy.

Tophi are the ‘mirror’ to the outside, concerning the severity and duration of gout. They are small, non-relocatable, indolent, firm nodes, which can develop all over the body, except for the CNS.

<table>
<thead>
<tr>
<th>Soft Tissue Tophi</th>
<th>Bone Tophi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm (ulna), auricle, Achilles tendon, pressure spots (heel, olecranon)</td>
<td>Ureter in x-ray</td>
</tr>
</tbody>
</table>

Renal manifestation

The kidney is the second most frequent lesion location after the locomotor system. Uric acid nephropathy means uric acid stone formation in the kidney. Over 80% are pure uric acid stones, the rest are mixed calcium oxalate stones or calcium phosphate stones. Stones form due to increased uric acid excretion, acidic urine and substances decreasing uric acid solubility.

Uric acid nephropathy exclusively develops at very high serum-uric acid levels. The consequence is uric acid accumulation in the lumen of the tubules, which leads to oliguria, anuria and vomiting. Interstitial precipitations result in mild proteinuria and low-degree kidney insufficiency.

Course of gout

According to CDC (Centers for Disease Control and Prevention), the course of gout can be divided into four stages.

<table>
<thead>
<tr>
<th>I</th>
<th>Asymptomatic hyperuricemia (pre-gout)</th>
<th>Last years to decades</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>First manifestation</td>
<td>Gout arthritis or nephrolithiasis</td>
</tr>
<tr>
<td>III</td>
<td>Asymptomatic stage (intercritical phase)</td>
<td>Free from symptoms for months or years after the first attack; often recurs during the first year; intercritical phases become shorter in between attacks.</td>
</tr>
</tbody>
</table>
Diagnosis of Hyperuricemia and Gout

The suspected diagnosis gout immediately suggests itself if a patient with swollen anterior foot without socks, shoes or bandage limps into the practice on one foot.

If gout is suspected at hyperuricemia, the diagnosis can mostly be made quickly due to the typical symptomatic picture. In medical history, there are often previous gout attacks in the patient and/or gout in family history.

Laboratory in hyperuricemia and gout

The elevated uric acid level (> 6.4 mg/dl) can be detected in the blood. Possible fluctuations due to meals have to be considered. Also, the uric acid level can be within normal range despite the clinical presentation of an acute gout attack.

Note: In one-third of the patients with an acute gout attack, the serum uric acid is not elevated.

The following inflammatory parameters can be elevated:

- BSR ↑
- CRP ↑
- Leukocytes ↑

Imaging in hyperuricemia and gout

In the event of chronic courses, destructive changes at the joint and tophi can be detected in an x-ray. With urography, uric acid stones can indirectly be detected.
Joint puncture

In case of diagnostic insecurity, a direct joint puncture can occur, especially if septic arthritis can be excluded or if a first monoarthritis is present. Evidence of an acute gout attack are phagocytized uric acid crystals in leukocytes (double refraction in polarization microscopy).

Differential Diagnosis of Hyperuricemia and Gout

Similar diseases such as chronic gout

- Rheumatoid arthritis
- Arthrosis with accompanying arthritis
- Chondrocalcinosis
- Reiter’s syndrome
Similar diseases such as acute gout attack

- Bacterial arthritis
- Arthritis at infections
- Traumas
- Rheumatic fever
- Gonorrhea
- Psoriasis arthritis

**Note:** The most important differential diagnosis of the acute gout attack is septic arthritis.

**Therapy of Hyperuricemia and Gout**

The goals of therapy are freedom from further attacks and prevention of kidney and joint damages, accomplished via the decrease of the uric acid level to < 6 mg/dl.

**General measures at gout**

Just like in all the other metabolic consequential diseases, a change of lifestyle is the main focus. Asymptomatic hyperuricemia up to 9 mg/dl is only treated nutritionally:

- **Diet low in purines** (giving up giblets and generally high meat consumption)
- High fluid intake to promote uric acid excretion via diuresis
- Avoidance of uric acid-increasing drugs (e.g., diuretics, aspirin in low doses, cyclosporine, ethambutol)
- Alcohol consumption ↓ (especially beer!)
- Strive for normal weight

**NOTE:** At total fasting, catabolism can lead to a rapid increase in uric acid level and trigger a gout attack.

**Medicaments for gout treatment**

If general measures are not sufficient to decrease the uric acid level below 9 mg/dl in the case of manifested gout, medication is indicated.

**Overview of gout therapeutics**

<table>
<thead>
<tr>
<th>Therapeutics</th>
<th>Uricostatics</th>
<th>Uricosurics</th>
<th>Ureolytics</th>
<th>Colchicine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Agent</strong></td>
<td>Allopurinol, febuxostat</td>
<td>Benzbromaron, probenicid</td>
<td>Uric acid oxidase enzyme</td>
<td>Colchicum</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Inhibition of xanthine oxidase (of purine degradation).</td>
<td>Inhibition of tubular re-absorption.</td>
<td>Transfers uric acid into soluble allantoin.</td>
<td>Inhibition of mitosis and of phagocyte activity of the leukocytes</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Long-term therapy</td>
<td></td>
<td>No influence on the uric acid level, only coping with a gout attack</td>
<td></td>
</tr>
<tr>
<td><strong>Side effects</strong></td>
<td>Gastrointestinal symptoms, leukopenia, increase in transaminases.</td>
<td>Gastrointestinal disorders, headaches, exanthema, urticarial, crystalluria</td>
<td>Fever, vomiting, nausea, diarrhea, headaches, allergic reaction</td>
<td>Nausea, vomiting, abdominal pain, diarrhea, hemorrhagic enteritis</td>
</tr>
</tbody>
</table>
Interactions

<table>
<thead>
<tr>
<th>Interactions</th>
<th>Inhibits the degradation of azathioprine and theophylline.</th>
<th>ASS decreases the effect.</th>
</tr>
</thead>
</table>

Clinical application

<table>
<thead>
<tr>
<th>Clinical application</th>
<th>1-2 weeks AFTER an acute gout attack, since worsening is possible otherwise.</th>
<th>Contraindication: pregnancy, kidney insufficiency</th>
</tr>
</thead>
</table>

Therapy at acute gout attack

Besides inflammation-inhibiting medicaments (NSAIDs like diclofenac, ibuprofen, COX-2-inhibitors, and glucocorticoids), colchicine can be administered. Although the medicament, which is extracted from the autumn crocus, triggers many side effects (see table), it is still used in the event of severe gout attacks.

Concerning local therapy, the joint should be cooled and immobilized, if possible. This way, most of the pain can be minimized.

Surgical measures concerning gout

Gout tophi should be treated with surgery in acute, life-threatening situations only, e.g., if a tophus suppresses the spinal cord. The same applies to kidney stone surgery: it is only indicated at therapy-resistant urine stasis due to stone impaction.

Review Questions

The correct answers can be found below the references.

1. A 50-year-old patient comes to your practice with a swelling at the elbow. It is a painless, whitish gleaming node. In medical history, the patient has had a metabolic syndrome for several years. Which disease is the most likely cause for this knotty change?

   A. Rheumatic fever with rheumatic nodes
   B. Gout
   C. Psoriasis arthritis
   D. Rheumatoid arthritis
   E. Dermatomyositis

2. Which statement concerning the gout occurrence ratio between men and women is most likely true? Men:women are...

   A. 7:3
   B. 1:1
   C. 7:1
   D. 1:7
   E. 7:6

3. A 67-year-old patient comes to the emergency department with acute pain in the right knee joint. He has had the pain for three days during which it constantly increased. At night, he can hardly sleep. He states that there was no trauma. The knee joint presents hyperthermic and shows distinct articular effusion. Laboratory findings: BSG ↑, CRP ↑, no leukocytosis. In puncture fluid, there is an increased cell count in dull, yellowish secretion and crystalloid
forms indirect preparation. Which is most likely the diagnosis?

A. Arthrosis-induced effusion  
B. Chondrocalcinosis  
C. Purulent knee joint infection  
D. Gout attack  
E. Rheumatoid arthritis

References

doi:10.1007/978-3-211-79280-3_409

doi:10.1007/bf01662787


**Correct answers:** 1B, 2C, 3D

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