

Update Morbus Basedow

Georg Zettinig

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Carl Adolph von Basedow

- “ 1799-1854, Merseburg
- “ 1840 Erstbeschreibung der Basedow'schen Krankheit im deutschen Sprachraum
- “ Merseburger Trias:
Tachykardie, Struma, Exophthalmus



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Morbus Basedow

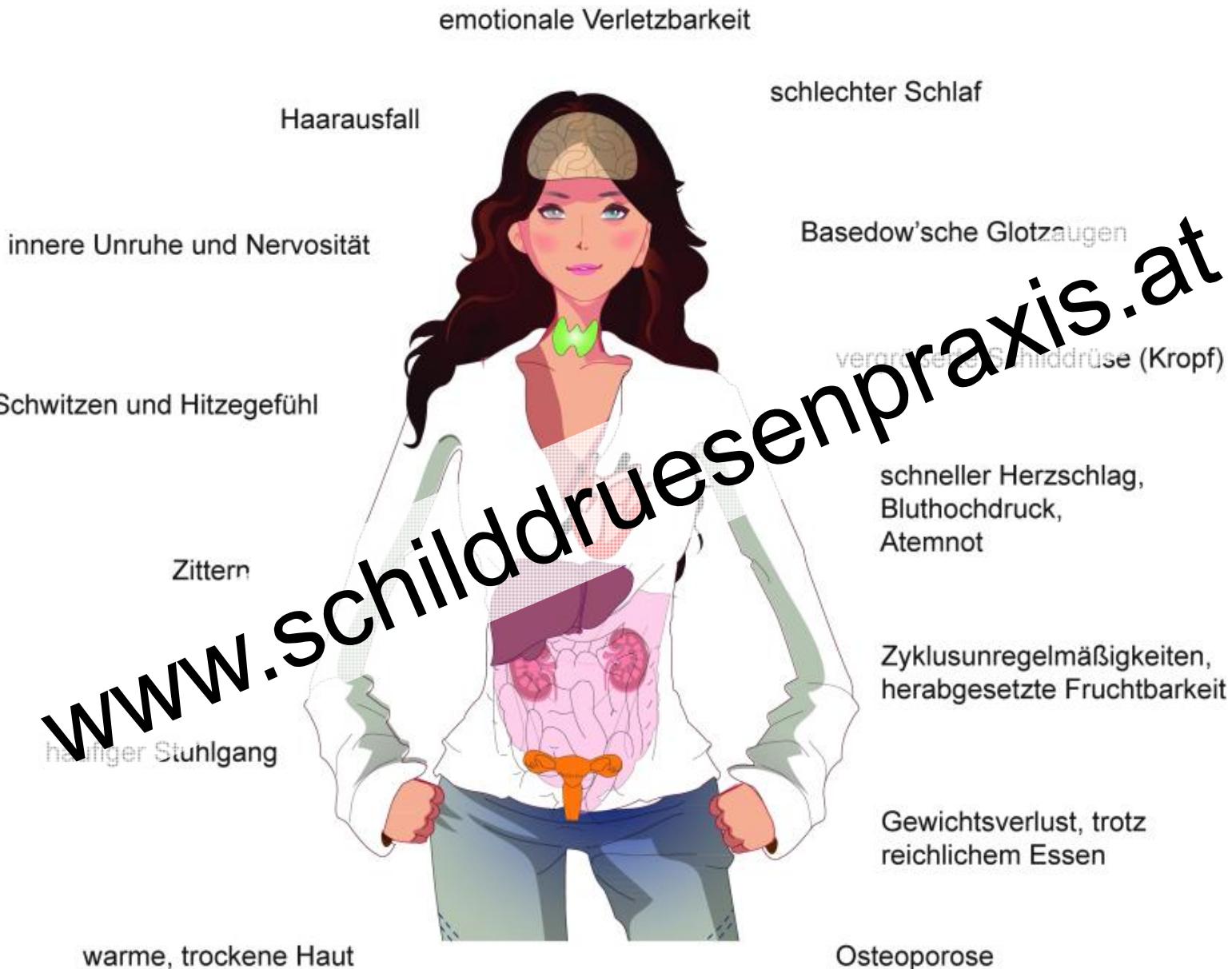
- „ Autoimmunerkrankung
- „ Thyreoidale und extrathyreoidale Manifestationen
- „ Pathogenetische Grundlage: TRAK
TSH-Rezeptor Antikörper

Ätiologie

- „ multifaktoriell
- „ Genetik
- „ Immunologie
- „ Umwelteinflüsse
- „ Psychosoziale Faktoren

TRAK

- “ Sonderstellung gegenüber anderen Antikörpern
- “ Bindung am TSH Rezeptor der Schilddrüse
- “ Stimulierende und auch blockierende AK
- “ Unkontrollierte Aktivierung am TSH Rezeptor führt zur Hyperthyreose
- “ TSH Rezeptor-Expression auch an anderen Organen: retrobulbär



2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis

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**One or more of the authors are military service members (or employees of the U.S. Government). The

Thyroid
Guidelines for Diagnosis and Management of Hyperthyroidism and other causes of Thyrotoxicosis (doi: 10.1089/thy.2016.0229)
has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.

ATA 2016 B1

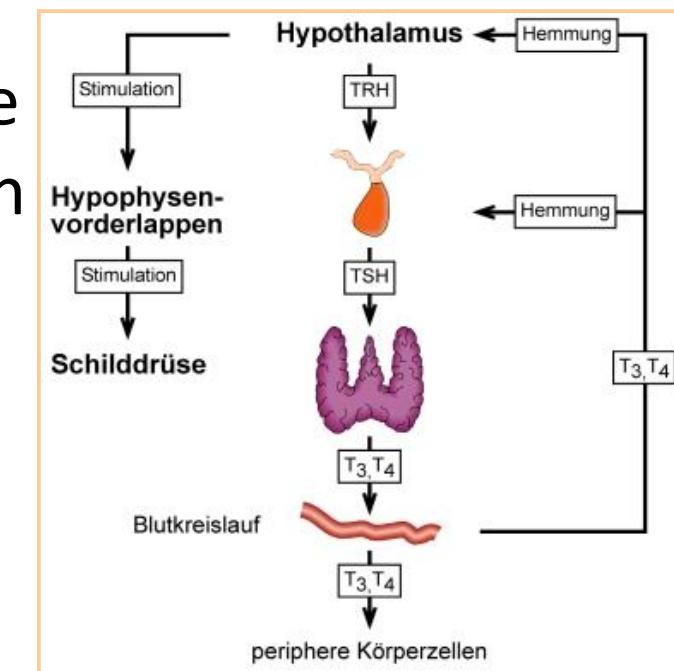
- „ Clinical evaluation
- „ While it might be anticipated that the severity of thyrotoxic symptoms is proportional to the elevation in the serum levels of free T4 and T3, in one small study of 25 patients with GD, the Hyperthyroid Symptom Scale did not strongly correlate with free T4 or T3 and was inversely correlated with age assessment of disease severity.
- „ The ratio of T3 to T4 helpful for differential diagnosis



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TSH nur bedingt aussagekräftig

- „ TSH Wert spiegelt die Situation der letzten letzten 6 Wochen wider
- „ Beim Mb. Basedow jedoch schnelle Änderung der Schilddrüsenfunktion
- „ Meist fT4 und ev. fT3 zur Funktionsbestimmung erforderlich
- „ Schnelle Änderungen unter thyreostatischer Therapie



aus: Zettinig, Buchinger. Schilddrüse - kurz und bündig. 3. Auflage 2014

Typischer Fall

- „ 32 Jahre, weiblich,
Therapie mit Thiamazol 20 mg 2x1
- „ TSH: * 0.08 (normal: 0.40 - 3.00 mU/l)
fT4: * 0.41 (normal: 0.80 – 1.85 ng/dl)
fT3: 2.03 (normal: 1.90 – 4.20 pg/ml)
- „ Diagnose: Beginnende manifeste Hypothyreose



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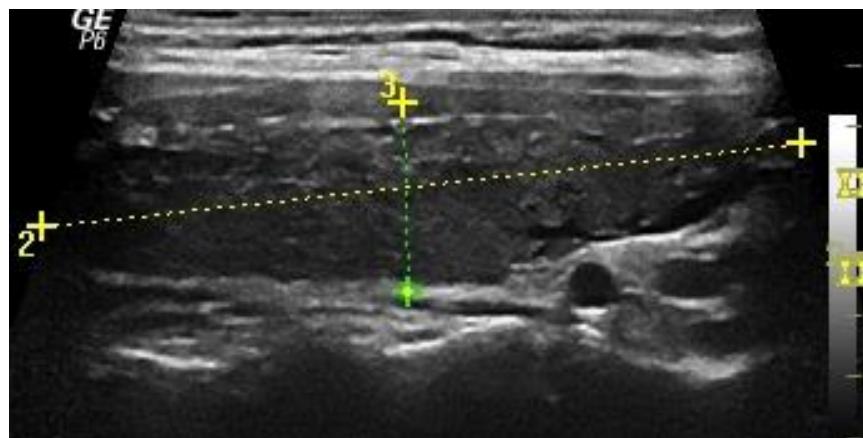
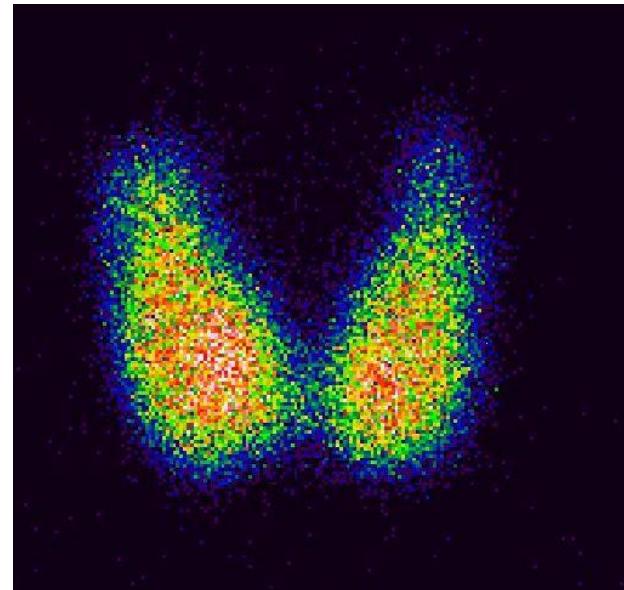
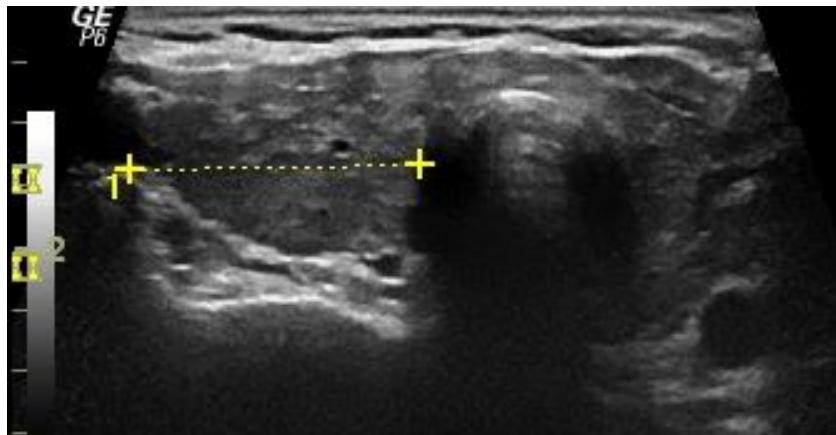
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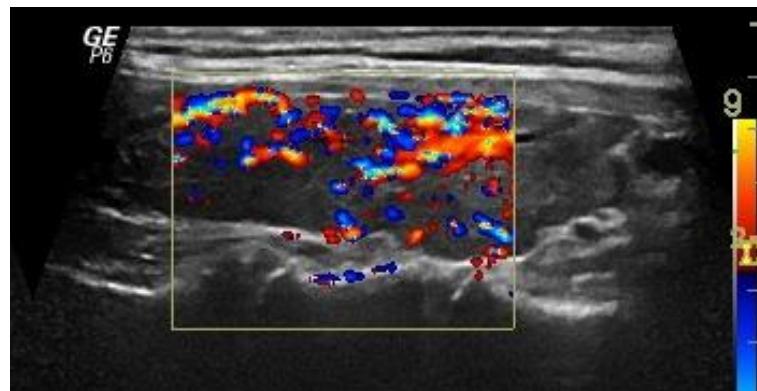
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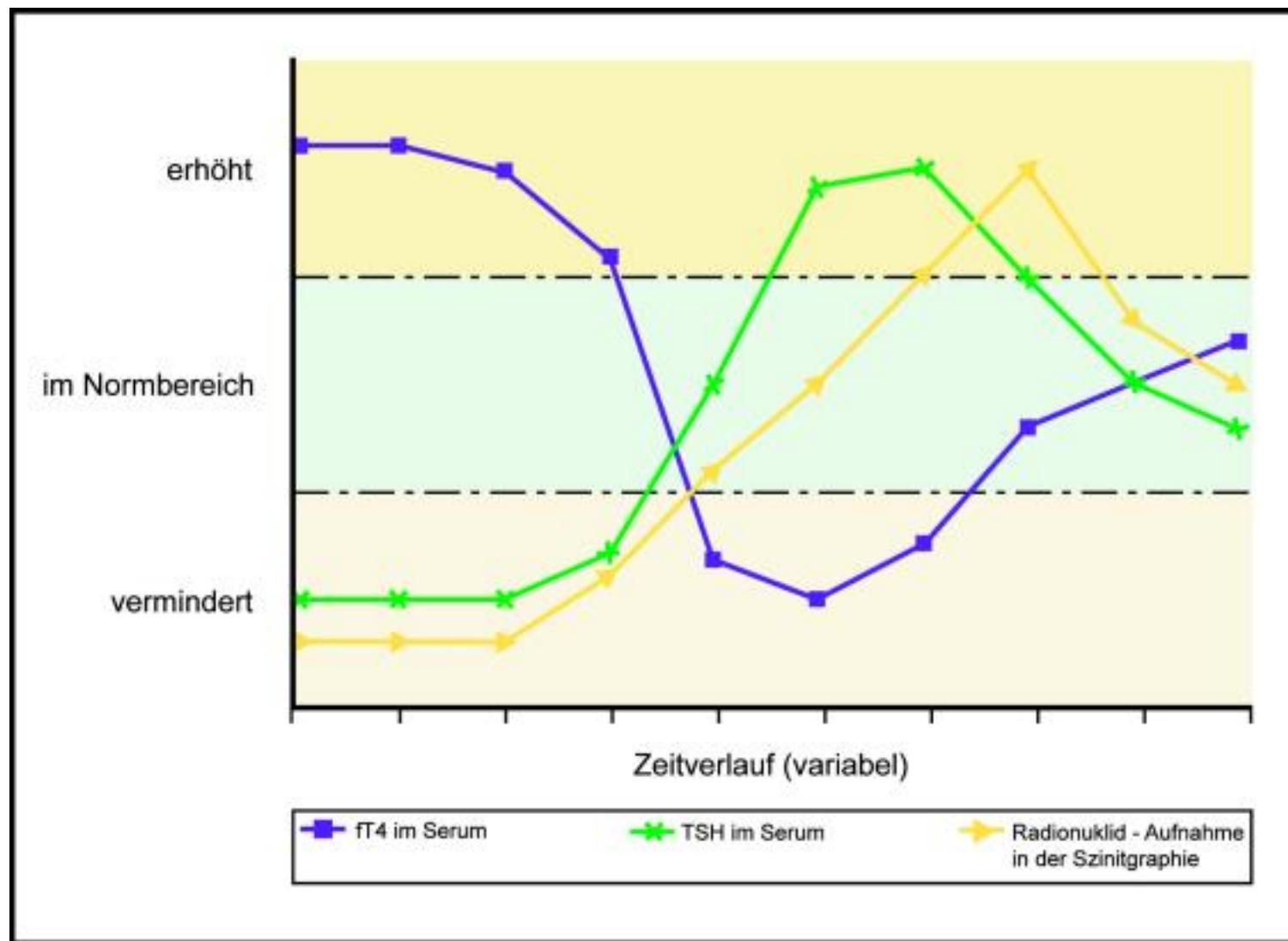
Bildgebung

- “ Schilddrüse oft massiv vergrößert
- “ Sonografie:
 - . echoarmes Muster
 - . dopplersonografisch gesteigerte Perfusion
- “ Szintigrafie:
 - . Gesteigerte Hormonproduktion führt zu vermehrter Radionuklidaufnahme
 - . Gesteigerte Anreicherung, Uptake erhöht



1 Re Schilddrüse L 2.34 cm
2 Re Schilddrüse H 6.14 cm
3 Re Schilddrüse B 1.51 cm
Re Schilddr. Vol 10.37 ml





ATA 2016 Rec 1

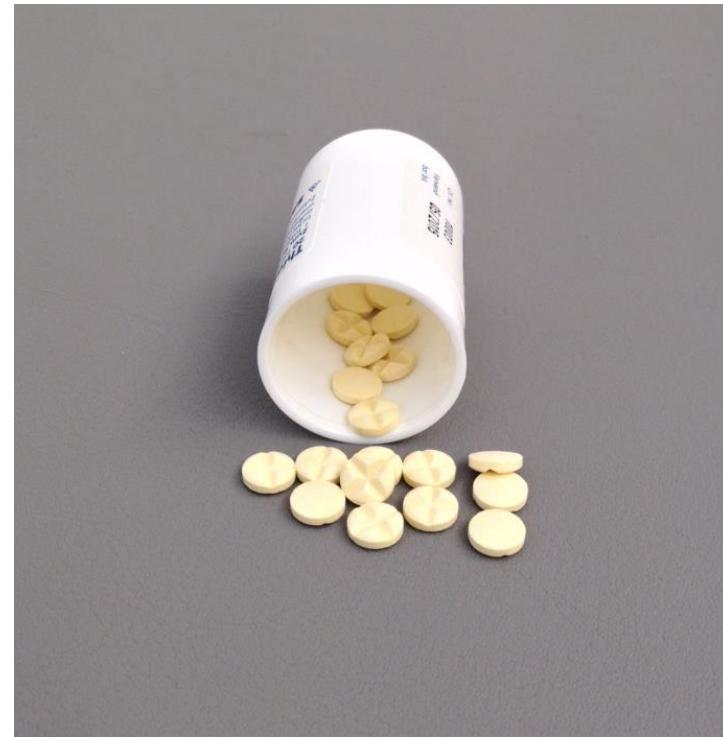
- “ The choice of initial diagnostic testing depends on cost, availability, and local expertise.
- “ TRAb is cost-effective because if it is positive it confirms the diagnosis of the most common cause of thyrotoxicosis, but if negative it does not distinguish among other etiologies, and it can be negative in very mild GD.
- “ If third generation TRAb assays are not readily available, RAIU is preferred for initial testing.

ATA Rec 1 E

- “ There are two methods for measuring TRAb:
- “ Third-generation TSH binding inhibition immunoglobulin (TBII) assays
- “ Bioassays for thyroid stimulating immunoglobulin (TSI)
- “ The newer TRAb assays are positive in 96% of patients with GD.

Therapie

- „ Thyreostatische Monotherapie
- „ Betablocker (Propranolol bzw. kardioselektive Betablocker)



Thyreostatika

- “ Thionamide (Thiamazol, Carbimazol)
 - “ Propylthiouracil
-
- “ Thiamazol: Thiamazol 20 mg
 - “ Carbimazol: Carbistad in Österreich nicht erhältlich
 - “ Propylthiouracil: Prothiucil 20 mg

Dosierung

- “ 10 mg Thiamazol äquivalent zu 16 mg Carbimazol (HWZ ca. 24 h)
- “ PTU: HWZ wesentlich kürzer, auf mehrere Einzelgaben verteilen, Dosierung 15 mal höher als Thiamazol.
- “ Achtung: In anderen Ländern andere Wirkstoffmenge pro Tablette
- “ Faustregel: $\frac{1}{4}$ Thiamazol 20 mg jeden 2. Tag entspricht 1 Tabl. PTU 20mg

Thyreostatika - 2

- “ Engmaschige Kontrollen der Schilddrüsenfunktion unbedingt erforderlich
- “ Allergische Reaktionen
- “ Leukopenie / Agranulozytose
- “ Leberschädigung
- “ Im eigenen Patientengut:
 - intensivpflichtige Agranulozytose: n=2
 - toxische Hepatitis: n=2,
 - eine weitere Patientin kam anschliessend

ATA Rec 17

- “ There is insufficient evidence to recommend for or against routine monitoring of white blood cell counts in patients taking ATDs.
- “ No recommendation, insufficient evidence to assess benefits and risks.

ATA Rec 20

- ” Minor cutaneous reactions may be managed with concurrent antihistamine therapy without stopping the ATD.
- ” Persistent symptomatic minor side effects of antithyroid medication should be managed by cessation of the medication and changing to RAI or surgery, or switching to the other ATD when RAI or surgery are not options.
- ” In the case of a serious allergic reaction, prescribing the alternative drug is not recommended.

ATA Rec 15 - E5

- “ Aside from hematologic and hepatic adverse effects, there are other rare side effects with ATDs.
- “ PTU, and rarely MMI can cause causes antineutrophil cytoplasmic antibody (pANCA)-positive small vessel vasculitis as well as drug induced lupus.
- “ The risk appears to increase with duration of therapy as opposed to other adverse effects seen with ATDs that typically occur early in the course of treatment.
- “ While up to 40% of patients taking PTU develop ANCA positivity, the vast majority of such individuals do not develop clinical vasculitis. When the drug is discontinued, the ANCA slowly disappear in most individuals.
- “ Children seem to be more likely to develop PTU-related ANCA positive vasculitis. In most cases, the vasculitis resolves with drug discontinuation, although immunosuppressive therapy may be necessary.

2010

The screenshot shows a web browser displaying the FDA website. The URL in the address bar is www.fda.gov/Safety/MedWatch/SafetyInformation/ucm209256.htm. The page is titled "Safety" under the "MedWatch The FDA Safety Information and Adverse Event Reporting Program". The main content is about "Propylthiouracil tablets" and includes a "BOXED WARNING" section detailing severe liver injury and acute liver failure. Other sections include "CONTRAINDICATIONS", "WARNINGS", and "Agranulocytosis". The page is from April 2010.

Propylthiouracil tablets

Detailed View: Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) – April 2010

BOXED WARNING

WARNING

- Severe liver injury and acute liver failure, in some cases fatal, have been reported in patients treated with propylthiouracil. These reports of hepatic reactions include cases requiring liver transplantation in adult and pediatric patients.
- Propylthiouracil should be reserved for patients who cannot tolerate methimazole and in whom radioactive iodine therapy or surgery are not appropriate treatments for the management of hyperthyroidism.
- Because of the risk of fetal abnormalities associated with methimazole, propylthiouracil may be the treatment of choice when an antithyroid drug is indicated during or just prior to the first trimester of pregnancy (see Warnings and Precautions).

CONTRAINDICATIONS

- Propylthiouracil is contraindicated in patients who have demonstrated hypersensitivity to the drug or any of the other product components.

WARNINGS

Liver Toxicity

- Liver injury resulting in liver failure, liver transplantation, or death, has been reported with propylthiouracil therapy in adult and pediatric patients. No cases of liver failure have been reported with the use of methimazole in pediatric patients. For this reason, propylthiouracil is not recommended for pediatric patients except when methimazole is not well-tolerated and surgery or radioactive iodine therapy are not appropriate therapies.
- There are cases of liver injury, including liver failure and death, in women treated with propylthiouracil during pregnancy. Two reports of in utero exposure with liver failure and death of a newborn have been reported. The use of an alternative antithyroid medication (e.g., methimazole) may be advisable following the first trimester of pregnancy.
- Biochemical monitoring of liver function (bilirubin, alkaline phosphatase) and hepatocellular integrity (ALT, AST) is not expected to attenuate the risk of severe liver injury due to its rapid and unpredictable onset. Patients should be informed of the risk of liver failure. Patients should be instructed to report any symptoms of hepatic dysfunction (anorexia, pruritus, right upper quadrant pain, etc.), particularly in the first six months of therapy. When these symptoms occur, propylthiouracil should be discontinued immediately and liver function tests and ALT and AST levels obtained.

Agranulocytosis

- Agranulocytosis occurs in approximately 0.2% to 0.5% of patients and is a potentially life-threatening side effect of propylthiouracil therapy. Agranulocytosis typically occurs within the first 3 months of therapy. Patients should be instructed to immediately report any symptoms suggestive of agranulocytosis, such as fever or sore throat. Leukopenia, thrombocytopenia, and aplastic anemia (pancytopenia) may also occur. Propylthiouracil should be discontinued if agranulocytosis, aplastic anemia (pancytopenia), ANCA-positive vasculitis, hepatitis, interstitial pneumonitis, fever, or exfoliative dermatitis is suspected, and the patient's bone marrow indices should be obtained.

Therapiedauer

- “ 12-18 Monate thyreostatische Therapie
- “ Remission bei ca. Hälfte der Patienten
- “ Bei fehlender Remission bzw. Rezidiv definitive Sanierung
 - . Operation
 - . Radiojodtherapie

Rec 21

- “ Measurement of TRAb levels prior to stopping ATD therapy is suggested, as it aids in predicting which patients can be weaned from the medication, with normal levels indicating greater chance for remission.
- “ Patients with persistently high TRAb could continue ATD therapy (and repeat TRAb after an additional 12-18 months) or opt for alternate definitive therapy with RAI or surgery.
- “ In selected patients (i.e., younger patients with mild stable disease on a low dose of MMI), long-term MMI is a reasonable alternative approach

Operation bei Mb. Basedow

- „ Ziel einer Schilddrüsenoperation ist es, das gesamte krankhaft veränderte Gewebe zu entfernen und die umgebenden Strukturen zu schonen
- „ Vorteil: Totale Thyreoidektomie
- „ Nachteil: Totale Thyreoidektomie

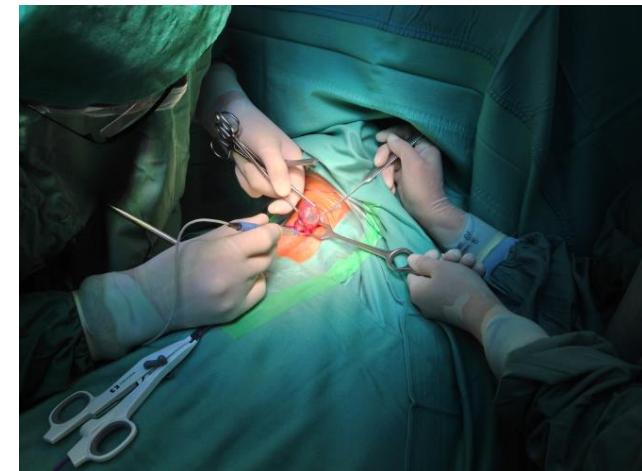


Foto: R. Prommegger

ATA - Rec 28

- “ If surgery is chosen as the primary therapy for GD, the patient should be referred to a high-volume thyroid surgeon.

Radiojodtherapie bei Mb. Basedow

- „ In USA ganz klar die erste Wahl zur definitiven Therapie
- „ Vorteile: Kein postoperativer Hypoparathyreoidismus, keine anderen operationsbedingten Komplikationen
- „ Nachteile: Hypothyreose tritt erst nach Monaten ein, posttherapeutisch TRAK Anstieg über viele Monate
 - . unmittelbar folgende Schwangerschaft
 - . endokrine Orbitopathie

ATA - Rec 3

- “ In the United States, RAI has been the therapy most preferred by physicians but a trend has been present in recent years to increase use of ATDs and reduce the use of RAI.
- “ A 2011 survey of clinical endocrinologists showed that 59.7% of respondents from the United States selected RAI as primary therapy for an uncomplicated case of GD, compared to 69% in a similar survey performed 20 years earlier.

Extrathyreoidale Manifestationen

- “ Endokrine Orbitopathie
- “ Prätibiales Myxödem: Ganz was anderes als das Myxödem in der Unterfunktion
- “ Akropachie

Clinical Activity Score

- „ Spontaner retrobulbärer Schmerz
- „ Schmerzen bei Augenbewegung
- „ Erythem der Augenlider
- „ Injektion der Konjunktiven
- „ Chemosis
- „ Schwellung der Caruncula lacrimalis
- „ Lidödem
- „ > 2 mm Zunahme der Proptose in 3 Monaten
- „ Abnahme der Sehschärfe in den letzten 3 Monaten
- „ Abnahme der Augenbewegung um 50 oder mehr in 3 Monaten







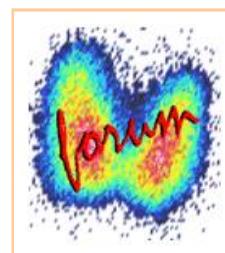
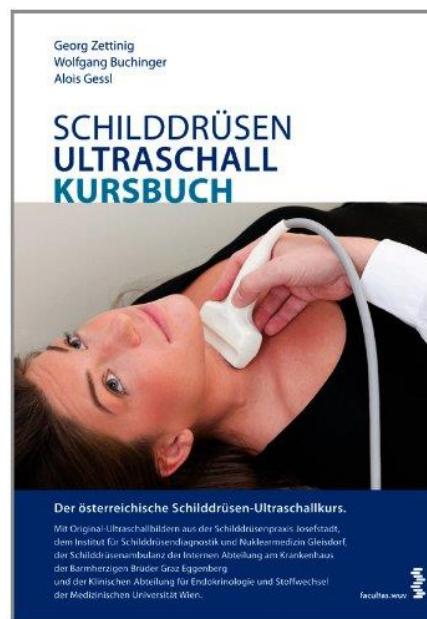
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