# Human African Trypanosomiasis (sleeping sickness)

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# Human African Trypanosomiasis (HAT)-Sleeping Sickness

*Trypanosoma brucei rhodesiense* - East Africa

*Trypanosoma brucei gambiense* - West Africa

Estimated 60 million people at risk from HAT

Approx. 100,000 existing cases of HAT in Africa

Transmitted by tsetse fly of Glossina species

Invasion of CNS leads to meningoencephalitis which is invariably fatal

Melarsoprol treatment is given for CNS disease. This treatment kills about 5% of patients from the PTRE

# FACTORS LEADING TO RE-EMERGENCE OF HAT

- SOCIO-ECONOMIC INSTABILITY-AS DISRUPTS DISEASE SURVEILLANCE AND PUBLIC HEALTH SYSTEM (incl. War in Angola)
- INADEQUATE FINANCIAL ALLOCATION OF CRITICAL RESOURCES TO DISEASE DURING PEACETIME
- INCREASING PARASITE DRUG RESISTANCE
- CHANGES IN CLIMATE AND VEGETATION
- UNPREDICTED POPULATION MOVEMENTS OF ANIMAL RESEVOIRS
- CHANGES IN HOST DISEASE SUSCEPTIBILITY

# Stages of sleeping sickness

Early **haemolymphatic stage**

Late **encephalitic stage**-disease course is slower in *gambiense* ( many months-years) compared to *rhodesiense* ( weeks-few months)

- The 2 stages may merge into eachother
- Accurate staging is crucial for effective treatment
- No fully reliable clinical suspicion criteria for early-stage disease

# Clinical features of African trypanosomiasis(both stages) in European patients

*(based on Duggan & Hutchington,1966)*



| | Percentage |
|---|---|
| **Constitutional signs and symptoms** | |
| fever | 74.3 |
| debility | 38.5 |
| headache | 24.5 |
| oedema | 24.5 |
| anaemia | 19.6 |
| **Cutaneous signs** | |
| rash | 50 |
| chancre | 22.6 - 45.8 |
| pruritus | ? |
| **Cardiovascular signs** | |
| tachycardia | 36.6 |
| **Gastro intestinal signs** | |
| hepatomegaly | 23.8 |
| splenomegaly | 23.8 |
| **CNS symptoms and signs** | |
| somnolence | 37.8 |
| hyperaesthesia | 26.6 |
| Tremor, abnormal movements | 25.7 |
| psychiatric symptoms | 20.1 |
| ataxia | 16.6 |
| slurred speech | 10.6 |
| **Other symptoms or signs** | |
| lymphadenopathy | 50 |

# Central Nervous System involvement in late-stage human trypanosomiasis

| *Mental disturbances* | *Motor System Disturbances* | *Sensory System Involvement* | *Abnormal Reflexes* |
|---|---|---|---|
| Indifference | Extrapyramidal features | Deep Hyperaesthesia | Pout |
| Lassitude | | Generalised pruritis | Palmarmental |
| Irritability | Chorea or oscillatory movements | Paraesthesia | Babinski |
| Somnolence | Pyramidal weakness | Anaesthesia | |
| Anxiety | Tremors of tongue and fingers | | |
| Agitation/mania | Slurred speech | | |
| Episodes | Muscle fasciculation | | |
| Uncontrolled sexual Impulses | Cerebellar ataxia | | |
| Violent mood | Myelopathy, myelitis | | |
| | Peripheral motor neuropathy | | |
| Delirium and Hallucinations | | | |
| Suicidal tendencies | | | |

# Frequency of Neurological Features in HAT

## Based on 2541 cases over 3 yr (Blum et al 2006)

- Sleep disorder-74.4%
- Headache-78.7%
- Motor weakness-35.4%
- Behaviour disturbance-25%
- Gait disturbance-22%
- Tremor-21.2%
- Speech impairment-14.2%
- Abnormal movements-10.7%

# Sleep disturbances in trypanosomiasis

- Loss of attention and distractibility
- Narcoleptic features
- Daytime somnolence alternating with nocturnal insomnia
- Continuous urge to sleep in final stage
- Recent evidence for alterations of sleep structure in stage 2 disease with particular onset of REM phases. Potential use in diagnosis and monitoring response to therapy (Buguet et al 2005 Acta Trop.)

# Visual involvement in HAT

- Diplopia
- Optic neuritis
- Papilloedema
- Optic atrophy
- Iritis,keratitis,conjunctivitis,choroidal atrophy

# Drug-induced neurological disease in HAT

- Peripheral neuropathy
- PTRE
- Multifocal inflammatory syndrome
- Seizures

# Specific Laboratory Diagnostic tests

- Direct demonstration of the parasite
- Antibody detection
- Antigen detection
- DNA detection

# Diagnosis of sleeping sickness

- This can be difficult. Malaria may also coexist
- Based on a combination of clinical and investigative criteria
- In *rhodesiense* parasite detection in blood or lymph node aspirates often successful
- But in *gambiense* parasitaemia is cyclical so serological tests very important-CATT is used. But many false positives, so CATT dilution is used wherever possible to increase specificity
- All CATT-positive patients need CSF analysis
- CSF PCR has been used but problems with assay reproducibility and not used in the field
- Newer serological tools eg CSF IgM quantitation by latex agglutination assay

# Investigations in HAT

Haematology and Biochemistry

Specific neurological investigations:

CSF

Neuroradiology - CT, MR

EEG

# Investigations in HAT



## Lumbar Puncture

Pleiocytosis (lymphocytosis), raised protein, high IgM.

Trypanosomes not so easy to detect (modified simple centrifugation increasingly used)

# Reported range of CSF values in HAT*

- **WBC**-median 93/µL, interquartile range 22-266/µL, max 430/µL
- **CSF protein**-median 78.7mg/100ml, interquartile range 45.4-106.5mg/100ml, max 203.8 mg/100ml

* 181 patients with late-stage *gambiense* HAT. Lejon et al J.Infect.Dis 2003, 187:1475-1483

# Criteria for CNS involvement

- WHO criteria are parasites in CSF or a CSF WBC count of >5/microlitre
- But in Angola and Ivory Coast criteria have been 20 WBC/microlitre in CSF
- Reports of some *gambiense* patients successfully treated with pentamidine with up to 20 WBC/microlitre in CSF
- Recent suggestion of 10 WBC/microlitre in CSF ( Chappuis et al 2005)

# Key Therapeutic Problems with HAT Staging

- **If get it wrong and don't treat late stage** CNS disease then the patient will die
- **If get it wrong and treat early stage** with melarsoprol then 5% risk of death from PTRE
- There is a lack of 100% congruence between the biological definition of CNS involvement and the ground for therapeutic choices
- Perhaps there is an 'intermediate stage' where Tryps can cross BBB without invading and damaging brain structures-hence pentamidine.

# EEG - 3 patterns described

1 Sustained low-voltage background (early cerebral impairment)

2 Paroxysmal waves (acute cerebral involvement)

3 Various types of high and low delta wave bursts (meningoencephalitis)

These abnormalities resolve with treatment

# CURRENT DRUGS FOR SLEEPING SICKNESS

- **Suramin**(early 1920s) stage 1 IV *T.b.rhodesiense*
- **Pentamidine** (1940) stage 1 IM *T.b.gambiense*
- **Melarsoprol** (1949) stage 2 IV both types
- **DFMO (eflornithine)** (1981) stage 2 IV *T.b.gambiense*
- **Nifurtimox** (1977) stage 2 ? Oral *T.b.gambiense*

- Note that nifurtimox is not registered for HAT
- No registered oral drug for early or late stage disease
- Combination therapy DFMO/nifurtimox (*gambiense*)

# TREATMENT OF HUMAN AFRICAN TRYPANOSOMIASIS

**Early stage :**

**Suramin (IV) (*rhodesiense*) or**

**Pentamidine (IM) (*gambiense*)**

**Late stage:**

**Above drugs followed by Melarsoprol (IV)**

**Alternative( gambiense)-DFMO(IV)**

# Post-treatment Reactive Encephalopathy (PTRE) or 'Melarsoprol-related Encephalopathic syndrome'

- Also known as 'reactive arsenical encephalopathy'
- Occurs in about 10% of treated patients
- Can prove fatal in up to 50% of cases
- Characterised by severe meningoencephalitis
- Rarely presents as acute haemorrhagic leukoencephalopathy
- Pathogenesis unclear

# CNS Pathology in Late-Stage Sleeping Sickness

- Cellular infiltrates and perivascular cuffs composed mostly of macrophages, lymphocytes and plasma cells, Russell body-containing plasma cells and morular plasma cells
- PTRE associated with an exacerbation of above changes

# PTRE/melarsoprol-related encephalopathy - possible suggested causes

1. Release of parasite antigens within CNS as a consequence of chemotherapy
2. Subcurative chemotherapy
3. Immune complex deposition
4. Autoimmune mechanism(s)
5. Other immune mechanisms e.g. neuropeptide involvemenT.
6. Recent evidence for HLA association eg C*14/B*15

# Experimental PTRE in Mice

## (FRANK JENNINGS MODEL OF PTRE)

- CD1-mice
- Infected IP with 4 x $10^4$ trypansomes of T.b. brucei (cloned stabilate GVR35/C1.5)
- Develop chronic infection with parasites established in CNS by day 21
- Treated day 21-28 p.i. With Berenil (diminazene aceturate 40mg/kg, i.p.)
- **Berenil treatment is subcurative and leads to PTRE**
- Mice killed at various times post-Berenil
- Different treatment regimes usually given for 7-10 days before and/or after Berenil

# PTRE in Mice
# - Astrocyes and Cytokines

- Astrocytes become activated between days 14-21 post-infection before detectable inflammatory lesions in the brain
- Astrocyte response therefore presumably not a secondary response to CNS inflammatory cell infiltration
- Production of several cytokine transcripts correlates with astrocyte activation.

# Drug Treatment of Experimental PTRE in Mice

| | |
|---|---|
| Azathioprine | Immunosuppressant |
| Eflornithine (DFMO) | Ornithine decarboxylase inhibitor |
| RP-67,580 | SP antagonist |

# EFLORNITHINE-DFMO

- Shown to be effective in *T.b.gambiense* disease in the 1980s
- Then became an orphan drug.
- Expensive and non-profitable for drug companies
- Became available for HAT treatment through a contract between WHO and Aventis Pharma
- Has been used in melarsoprol-refractory *gambiense* disease and also more recently as first line therapy with nifurtimox
- But still has potentially serious toxic effects

# Pharmacological effects of DFMO

- ornithine decarboxylase inhibitor
- trypanostatic not trypanocidal

# DFMO chemotherapy:

- prevents the development of the PTRE
- ameliorates an existing PTRE
- effects are only partially due to ODC blockade
- effects are transitory

# RP-67,580

- substance-P receptor antagonist
- non-peptide
- specifically binds to NK-1 receptor

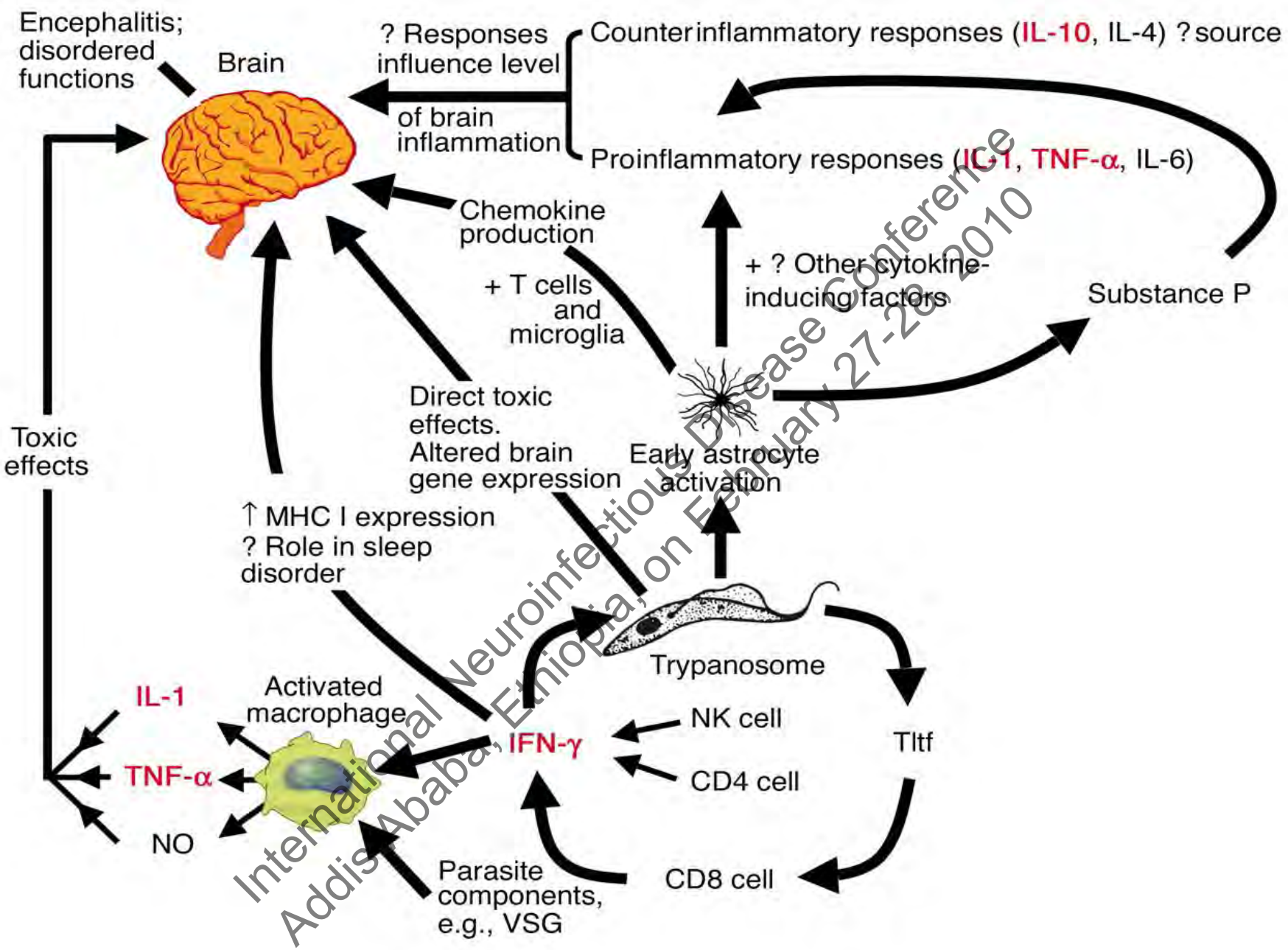
# Parameters defining the injury score allocated to the severity of neuropathology

| | Score | | | | |
|---|---|---|---|---|---|
| | 0 | 1 | 2 | 3 | 4 |
| Meningitis | None | Mild | Moderate | Severe | Severe |
| Perivascular cuffing | None | None | Mild cuffing of some vessels | Prominent cuffing of vessels | Prominent cuffing of most vessels |
| Encephalitis as defined by cellular activity in the neuropil | None | None | None | Moderate | Severe |

Injury scores are given horizontally, the parameters used are shown vertically

# Summary of Substance P Data

- SP receptor antagonist reduces clinical and neuroinflammatory responses in mouse model
- SP knockout mice were clinically improved but with more neuroinflammation after Tryp. infection
- Thus the clinical and neuroinflammatory phenotype can be dissociated
- Neuroinflammation in SP knockout mice could be prevented by NK-2 and NK-3 receptor antagonist combination. So alternative NK receptor usage
- SP plays a definite role in PTRE and suggests that neuropeptide antagonists may have an adjunct role in treatment of HAT.






Schematic representation of possible mechanisms of HAT neuropathogenesis
Kennedy PGE J.Clin.Invest.(2004)113: 496-504

# FUTURE PROSPECTS FOR CONTROL OF HAT

- Better continuous **human population surveillance** with more reliable case detection
- **Improved diagnostic test**-cheap, reliable,easy to perform, sensitive and specific. This has to go hand in hand with development of new drugs
- More **accurate staging** of CNS disease
- **More effective drug treatment** in man-better use of existing drugs eg by increasing their BBB penetration,and oral therapy development
- Further significant **reduction of man/fly contact** through ground–based strategies, eg fly traps
- Increased **understanding of HAT pathogenesis**