

HEPATIC ENCEPHALOPATHY

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DEFINITIONS:

- HEPATIC ENCEPHALOPATHY (HE) is a complex neuropsychiatric disorder that results from impaired liver function, i.e. impaired clearance from blood of toxins (ammonia), which eventually enter the brain.

- HEPATIC RETINOPATHY (HR) – a manifestation of HE in the retina of the eye.

HE classified according to causes

Type A: HE due to acute liver failure (ALF) resulting from inflammatory and/or necrotic liver disease of rapid onset.

Type B: HE resulting from portacaval shunting, a treatment for high blood pressure in the liver.

Type C: HE associated with **chronic liver failure (liver cirrhosis)**.

Type “A upon C” (or “acute upon chronic”), reflecting rapid deterioration imposed on chronic balanced condition.

Type C *is the most frequent form of HE*

COMMON CAUSES OF HEPATIC CIRRHOSIS:

- Alcohol abuse (60 to 70 percent)*
- Chronic hepatitis B or C (10 percent)*
- Biliary obstruction (5 to 10 percent)*
- Nonalcoholic fatty liver disease (obesity) (10 percent)*
- *Hemochromatosis (excessive accumulation of iron) (5 to 10 percent)*

OTHER CAUSES OF HEPATIC CIRRHOSIS:

- *Drugs and toxins*: (Paracetamol, Aldomet, antihypertensive; Cordarone, arrhythmia; Isoniazid, against mycobacterium tuberculosis; *Vitamin A, heroin, cocaine*)
- Genetic metabolic diseases (Wilson's disease; urea cycle defects, e.g., ornithine carbamoyltransferase deficiency)
- Infections (brucellosis; congenital or tertiary syphilis)

STATISTICAL DATA ON CIRRHOSIS AND HE IN EU

*~ 1 000 000 are affected with liver cirrhosis,
most show symptoms of HE,
with average survival time ~ 15 years*

*Average yearly treatment cost of 1 patient (lactulose, 1
hospitalization) ~ 9 000 euro (estimate from Neff et al.,
Transpl Proc. 38, 3552, 2006)*

90 000 cirrhotic patients die every year

DEATH RATES ASSOCIATED WITH DIFFERENT DISEASES IN EU (2006)

DISEASE	DEATHS/100 000
Cancer	175
Ischemic heart failure	94.4
Stroke	75.4
<i>Diseases of nervous system (all, incl. Alzheimer's disease)</i>	17.2
<i>Pneumonia</i>	15.5
<i>CHRONIC LIVER FAILURE</i>	13.7
<i>Diabetes</i>	13.4
<i>Car accidents</i>	9.1
Alcoholic abuse	2.7
Drug dependence	0.6
<i>AIDS</i>	1

(Eurostat; http://ec.europa.eu/health/ph_information)

GRADES (CLINICAL STAGES) OF HE

Stage	Mental state
I	Mild confusion, euphoria or depression, <u>decreased attention</u> , <u>slowing of ability to perform mental tasks</u> , untidiness, slurred speech, irritability, reversal of sleep rhythm
II	Drowsiness, lethargy, <u>gross deficits in ability to perform mental tasks</u> , obvious personality changes, inappropriate behaviour, intermittent disorientation (especially for time), lack of sphincter control
III	Somnolent but rousable, unable to perform mental tasks, persistent disorientation with respect to time and/or place, <u>amnesia</u> , occasional fits of rage, speech present but incoherent, pronounced confusion
IV	<u>Coma</u> , with (IVA) or without (IVB) response to painful stimuli

Albrecht and Jones, J Neurol Sci, 170, 138-46, 1999

SUBCLINICAL HE (SHE; MHE)

Mild cognitive, attention and motor skill deficits that escape detection with routine clinical tests and, thus, fall in the category below stage I of HE.

Among cirrhotic patients : 51–62% have evidence of SHE (MHE)

(US statistics; Leevy & Phillips, Dig Dis Sci (2007) 52:737–741)

SHE patients suffer *decreased quality of life and impaired working efficiency*, and pose *increased risks of motor vehicle accidents*.

DIAGNOSIS OF SHE*

Procedure	Comments (Pitfalls)
Psychometric tests (NCT)	Easy to perform, but score depends upon the patient's education level and/or age, complicating statistical evaluation
PMR spectroscopy	Sensitive and accurate, but difficult access (only in well-off Medical Centers)
Critical flicker frequency (CFF)	Patient's visual discrimination ability of red light. Easy to perform, and score independent upon the patient's education, but requires tedious standardization and specified attention of a patient – good at the bedside, not for outpatients.
Blood biochemical test (a desired modality)	Light at the end of the tunnel: Increased cyclic GMP recorded in blood of SHE patients (C. Montoliu et al., J Mol Med 85, 237-245, 2007)

*compiled from Albrecht and Węgrzynowicz, J Mol Med 85, 203-205, 2007

MECHANISM(S) OF HE

Extremely complex: Mostly associated with interference of **ammonia** with various aspects of brain metabolism, leading to **imbalance of neural transmission**.

Primary involvement of **astrocytes** (the cells supporting neurons), which are the locus of ammonia metabolism. This makes impaired **astrocyte-neuron** interactions a key player.

This mechanism is distinct from those underlying stroke or neurodegenerative diseases (AD, PD etc.), which are primarily associated with **nerve cell** damage.

SEQUENCE OF EVENTS LEADING TO
DEATH
IN THE ACUTE PHASE of HE (types A and A upon C):

brain cell (astrocytic) swelling



brain edema (mostly cytotoxic)



increased intracranial pressure (**ICP**)

AVAILABLE TREATMENTS OF HE

Stages I-III: Reduction of production and absorption of ammonia in the gut using non-absorbable disaccharides (lactulose) and/or non-absorbable antibiotics (rifaximin)

Stage IV: Liver transplantation. Moderate hypothermia (cooling blankets) to depress energy consumption in the brain: employed to prevent **death of acute HE patients with increased **ICP** before transplantation (as a „bridge”) (executed in two European centers only: R. Jalan in London, F. Larsen in Copenhagen).**

REASONS TO INTENSIFY JOINT RESEARCH ON HE IN EU

HE is a significant socioeconomic burden to EU states: it affects the life quality and productivity of millions of EU citizens.

Mechanisms of HE involve extremely complex impairments of brain function which remain to be elucidated to implement effective causative treatment, and to extend symptomatic treatment beyond transplantation.

Diagnosis of SHE needs further fine-tuning

Improved coordination of the work of the few EU laboratories studying HE will serve well **European patients** and **European research** alike.