ALBUMIN FOR ACUTE EPISODIC HEPATIC ENCEPHALOPATHY (ALFAE STUDY)

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Albumin for Acute Episodic Hepatic Encephalopathy (Alfae Study): Background

- Episodic hepatic encephalopathy (HE) is frequently precipitated by factors that may induce:
  - circulatory dysfunction
  - cause oxidative stress-mediated damage
  - enhance astrocyte swelling

- The administration of albumin could modify these factors and improve the outcome of HE
Albumin for Acute Episodic Hepatic Encephalopathy (Alfae Study): Aim

- Assess the efficacy of albumin on episodic HE in a multicenter, prospective, double-blind, placebo-controlled trial (ClinicalTrials.gov number, NCT00886925)
Cirrhotic patients with an acute episode of HE (grade II-IV) were randomized to receive albumin (1.5 g/Kg on inclusion -day 0- and 1.0 g/Kg on day 2) or isotonic saline, in addition to the usual treatment (laxatives, rifaximin 1200 mg per day)

Primary end point: proportion of patients in which HE was resolved on day 3

Secondary end points: included survival and the mean length of hospital stay
Albumin for Acute Episodic Hepatic Encephalopathy (Alfae Study): Results

- Fifty-six patients
  - HCV= 18
  - Alcohol= 24
  - Males= 42
  - Age= 65±10 years

- Randomly assigned to albumin (ALB, n=26) or saline (SAL, n=30)
  - stratified by the severity of HE (II-III vs IV)

- Both groups were comparable with regard to demographic data, liver function (MELD 16.5±4.5), precipitating factors (44.6% infections) and characteristics of the HE episode
Percentage of patients without HE at day 3 did not differ between both groups (ALB: 62.5% vs. SAL: 57.1%; p > 0.05)

Differences were not found neither in the mean duration of the HE (ALB: 4.12 days vs. SAL: 3.42 days; p > 0.05) nor in the mean length of stay (ALB: 8.6 days vs. SAL: 10.3 days; p > 0.05)

However significant differences in mortality were found in the follow-up at 1.5 months (ALB: 7.7% vs. SAL: 36.7%; p = 0.01) and at 3 months (ALB: 24% vs. SAL: 50%; p = 0.048)
• Albumin does not improve the evolution of HE during hospitalization.

• However, differences in survival after hospitalization suggest that the development of HE may identify a subgroup of patients with advanced cirrhosis that may benefit from the administration of albumin.
A GENETIC VARIANT IN THE PROMOTER OF PHOSPHATE ACTIVATED GLUTAMINASE (GLS) GENE PREDICTS THE RISK OF DEVELOPING HEPATIC ENCEPHALOPATHY

Abstract 216

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Hepatic encephalopathy (HE) is one of the major complications of liver cirrhosis and impairs patients' survival.

Exact pathogenesis of HE is unknown.

Recently an association between a microsatellite in the promoter region of the phosphate activated glutaminase (GLS) gene and the risk of developing HE has been detected by Romero-Gomez et al. (Ann Int Med 2010).

Aim was to assess whether the described GLS variant increases the risk of developing HE in cirrhotic patients.
A Genetic Variant in the Promoter of Phosphate Activated glutaminase (GLS) Gene Predicts the Risk of Developing Hepatic Encephalopathy: Patients and Methods

- 158 patients recruited
  - 104 males
  - 54 females
  - mean age 59 years
  - with liver cirrhosis mainly due to alcoholic liver disease (59%) or chronic viral hepatitis (19%)

- Mean MELD score at the time of admission was 14 (range 6 - 35); 61% of the patients presented with Child-Pugh scores B or C
• In all patients, HE was quantified by critical flicker frequency (CFF), and individuals with CFF ≤ 39 Hz were regarded as cases.

• The GLS variants were genotyped by PCR-based assays with 5-nuclease and fluorescence detection.
A Genetic Variant in the Promoter of Phosphate Activated glutaminase (GLS) Gene Predicts the Risk of Developing Hepatic Encephalopathy: Results

- (significant, $p < 0.05$): Mean CFF value in cohort was 38.98 Hz (range 26-58)
- 53% of the patients displayed abnormal CFF results
- GLS genotype distributions were consistent with Hardy-Weinberg equilibrium
- Genetic variants of the GLS microsatellite classified in homozygous minor, homozygous major and heterozygous alleles were carried by 32 (20%), 51 (32%) and 75 (48%) individuals, respectively
CFF values significantly differed between the three groups (ANOVA).

Genotype distribution of patients with minimal HE or grade I HE in comparison to patients without HE provided evidence for an association between the homozygous major GLS variant and the development of HE.

In multivariate analysis homozygous carriers of the major GLS variant had a significantly higher risk than heterozygous patients to develop HE independent of age and presence of transjugular intrahepatic portosystemic shunt.
A Genetic Variant in the Promoter of Phosphate Activated glutaminase (GLS) Gene Predicts the Risk of Developing Hepatic Encephalopathy: Conclusions

• The genetic analyses demonstrate that homozygous carriers of the major GLS variant display significantly lower CFF results

• Findings support a potential role of variant GLS in the development of HE

• This could be used for the identification of susceptible patients and for prevention of complications
TRANSIENT ELASTOGRAPHY IS A USEFUL CLINICAL TOOL TO DETECT MINIMAL HEPATIC ENCEPHALOPATHY IN A COHORT OF COMPENSATED CIRRHOTIC PATIENTS

Abstract 198

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Minimal hepatic encephalopathy (mHE) is a common cause of neurocognitive dysfunction in patients with cirrhosis.

- Associated with:
  - falls
  - impaired driving skills
  - the later development of overt HE
  - reduced overall survival

Treatment has been shown to improve psychometric performance, enhance quality-of-life parameters and reduce the risk of progression to overt HE.
Transient elastography is a useful clinical tool to detect minimal hepatic encephalopathy in a cohort of compensated cirrhotic patients: Introduction (cont.)

- Diagnosis is based on psychometric and/or neuro-physiological tests.
- Tests can be time-consuming, expensive and may require experienced personnel and therefore are not widely used outside of the research setting.
- Transient elastography (TE) is an established non-invasive tool to determine the severity of hepatic fibrosis.
Aim of the study was to investigate if TE could be used in a population with compensated cirrhosis to identify patients most likely to have mHE
Transient Elastography is a Useful Clinical Tool to Detect Minimal Hepatic Encephalopathy in a Cohort of Compensated Cirrhotic Patients: Methods

- All compensated, biopsy-proven, cirrhotic patients attending the outpatient department were included in the study.
- Patients with any clinical evidence of neuropsychiatric disturbance were excluded.
- Each patient completed the Psychometric Hepatic Encephalopathy Score (PHES) and had TE performed on the same day.
PHES raw data was compared to UK normative data and a score of two or more standard deviations below the mean diagnosed mHE.

TE was performed using Fibroscan (Echosens) and the median value of ten valid acquisitions gave the liver stiffness measurement (LSM) in kPa.

Statistical analysis was done using SPSS version 18.

- Diagnostic performance of LSM was assessed by using receiver operating characteristics (ROC) curves.
- The optimal cut-off value for LSM was chosen to maximize the sum of sensitivity and specificity.
Transient Elastography is a Useful Clinical Tool to Detect Minimal Hepatic Encephalopathy in a Cohort of Compensated Cirrhotic Patients: Results

- 29/86 patients (34%) had mHE on PHES

- LSM was significantly higher in those with mHE than in those without mHE (median 38.6kPa v 17.3kPa; p=0.002)

- Based on the ROC curve a cut-off of 20.8kPa had a sensitivity of 79% and a specificity of 67% to detect mHE (AUROC = 0.785, p=0.001)
• TE can be used to risk stratify patients for the presence of mHE

• All patients with a LSM >20.8kPa should either be tested for mHE or empirically treated
RIFAXIMIN IMPROVES COGNITION AND ENDOTOXEMIA IN MINIMAL HEPATIC ENCEPHALOPATHY BY SHIFTING GUT MICROBIAL FUNCTIONALITY WITHOUT ALTERING THEIR ABUNDANCE

Abstract 192

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Minimal hepatic encephalopathy (MHE) has a presumed gut-based pathophysiology.

Rifaximin, a gut-specific antibiotic, is effective in MHE but its mechanism of action is unclear.

Hypothesized that modulation of gut microbiota and their end-products by rifaximin would improve cognition in MHE.
To perform a systems biology analysis of the microbiome, metabolome and cognitive change after rifaximin in MHE
Cirrhotics with MHE underwent cognitive testing (seven recommended tests):
- endotoxin analysis
- urine/serum metabolomics (GC-Mass Spectrometry)
- fecal microbiome assessment
- (multi-tagged pyrosequencing) at baseline
- 8 weeks post-rifaximin 550mg BID
• Diet was constant during the trial
• Changes in cognition, endotoxin, serum/urine metabolites (supervised/unsupervised techniques) and microbiome (metastats, QIIME and prinicipal-component analysis) were analyzed
• Correlation networks between cognition, microbiota and metabolome were analyzed and compared pre/post-rifaximin
• Twenty cirrhotics (60 yrs, MELD 9, 55% HCV) were included and all patients completed the trial with >92% adherence and stable diet.

• There was a significant improvement in cognition (six of seven tests improved, p< 0.01) and endotoxemia (0.55 to 0.48 Eu/ml, p=0.02) without MELD score change after rifaximin.

• Metabolomics showed a significant increase in serum saturated (myristic, caprylic, palmitic, palmitoleic, oleic and eicosanoic) and unsaturated (linoleic, linolenic, gamma-linolenic and arachnidonic) acids post-rifaximin without urinary changes.
• No significant microbial abundance change at the phylum/order level apart from a modest decrease in *Veillonellaceae* (2.5 to 1%) and increase in *Eubacteriaceae* (0% to 1.0%) was seen.

• On network analysis, post-rifaximin networks showed that while features of microbiome and metabolome remained same, their interaction significantly shifted compared to baseline resulting in a significant reduction in network connectivity and clustering.
Specifically, the networks centered on potentially pathogenic and HE-associated taxa; *Enterobacteriaceae*, *Porphyromonadaceae* and *Bacteroidaceae* indicated a shift from pathogenic to beneficial metabolite linkages.

Pre-rifaximin, these taxa were linked with:
- poor cognition
- aromatic amino-acids
- ammonia
- glutamate
- endotoxin

Post-rifaximin, these correlations significantly weakened or disappeared
• Networks centered on autochthonous taxa (Lachnospiraceae, Ruminococcaeae and Clostridium-ClusterXIV) however, remained similarly linked to:
  - beneficial metabolites
  - fatty acids
  - good cognition pre/post-rifaximin
Rifaximin therapy changes gut bacterial linkages with metabolites without significant change in microbial abundance that is associated with improved cognitive function and endotoxemia in MHE.
AST-120 (SPHERICAL CARBON ADSORBENT) IN COVERT HEPATIC ENCEPHALOPATHY: RESULTS OF THE ASTUTE TRIAL

Abstract 190

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• Covert hepatic encephalopathy (CHE = minimal and/or ≤ grade 1 HE) adversely affects cirrhotic patients, but no standard-of-care is yet established

• AST-120 has demonstrated efficient binding capacity for NH₃ and other gut-based toxins
AST-120 (Spherical Carbon Adsorbent) in Covert Hepatic Encephalopathy: Results of the Astute Trial: Aim

• To provide proof-of-concept and safety/tolerability for AST-120 treatment of CHE
A multi-center, double-blind, randomized, placebo-controlled, dose-ranging study of AST-120 was conducted over 8 weeks.

Compensated cirrhotic patients with MELD Score ≤ 25 were eligible.

CHE was defined as a global summary score on Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) below 10th percentile at screening and/or ≤1 HE by West-Haven criteria.
• Primary endpoint: neurocognitive improvement, defined as change in global RBANS at 8-weeks compared to baseline

• Secondary endpoints included: Psychometric HE-Score (PHES), clinical global assessment of HE (CGA-HE), and frequency of occurrences of overt HE and hospitalization

• RBANS testing was performed at screening, baseline (+1 week), and 4 and 8-weeks after assigned intervention
• 148 patients
  - mean 55 yrs
  - MELD 10
  - 53% HCV
  - randomized to AST-120 12g (n=50), AST-120 6g (n=50), or placebo (n=48)
• No significant changes were noted in the RBANS global-summary scores at week 8 (3.27±7.97 p=0.2584, 4.51±7.72 p=0.7812, and 4.57±9.50, Δ vs, baseline; AST-120 12g, AST-120 6g, and placebo respectively)
A strong learning effect on RBANS (p< 0.0001) was apparent between screening and baseline visits in all groups.

No differences in PHES, CGA-HE or overt HE/hospitalization events between groups were observed.

Over 8 weeks, venous NH$_3$ significantly decreased from baseline in both treatment groups but increased in the placebo group: Δ ammonia: -17, -14 and +5 µg/dL (AST-120 12g, AST-120 6g, and placebo, respectively).

The frequencies of treatment-emergent adverse events were similar for all groups (32%, 26% and 37.5%; AST-120 12g, AST-120 6g, and placebo, respectively, p = NS).
• Largest controlled trial yet conducted in CHE or Minimal HE

• AST-120 was well tolerated but did not achieve its primary endpoint of RBANS improvement

• Results were confounded by study design that allowed for an improvement in neurocognitive measures before drug randomization

• NH₃ improved significantly but independently of neurocognitive change
HEPATIC ENCEPHALOPATHY IS AN INDEPENDENT RISK FACTOR FOR MORTALITY IN PATIENTS AWAITING LIVER TRANSPLANTATION

Abstract 147

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Hepatic Encephalopathy is an Independent Risk Factor for Mortality in Patients Awaiting Liver Transplantation: Introduction

- Hepatic encephalopathy (HE) is a severe complication of liver cirrhosis
- HE is not accounted for in the MELD score, which is widely being used for organ allocation
- Aim of this study was to assess the impact of encephalopathy on survival of patients awaiting liver transplantation
Hepatic Encephalopathy is an Independent Risk Factor for Mortality in Patients Awaiting Liver Transplantation: Methods

- Retrospective analysis of consecutive adult patients listed for liver transplantation between 2007 and 2011 at LUMC, NL

- Clinical data were retrieved from patient records and MELD and MELDNa score were calculated

- Survival analysis was performed using Kaplan Meier and Cox proportional hazard regression analysis with death as event, censored for liver transplantation or last visit
Log-rank analysis was performed to exclude competing risk of transplantation.

Univariate analysis was performed for:
- presence of HE
- MELD score
- MELDNa score
- age
- ascites
- prior SBP
- variceal hemorrhage
- hepatocellular carcinoma

Parameters with p < 0.10 were included in multivariate analysis.
Hepatic Encephalopathy is an Independent Risk Factor for Mortality in Patients Awaiting Liver Transplantation: Results

- 168 Patients were included; 25/51 patients with HE (49%) and 64/117 (54%) patients without HE underwent liver transplantation after a mean of 7.0 ± 7.8 (HE) vs. 9.7 ± 7.8 months (no HE) (p=0.158)

- HE patients had a higher MELD score at listing than patients without HE (20 ± 9 vs. 12 ± 5, p<0.001)

- The chance to receive a liver transplantation showed a trend towards earlier OLT in patients with HE (p=0.063)
The presence of HE was independently associated with increased mortality before transplantation (HR 3.702 (95% CI 1.496-9.162), p=0.005) also after adjusting for MELD and MELDNa score in multivariate analysis.

MELD (HR 1.095 (95% CI 1.031-1.163), p=0.003) and MELDNa score (HR 1.124 (95% CI 1.051-1.202) were also independent predictors of mortality, whereas prior SBP and ascites were not.

More severe HE was associated with a higher mortality risk, i.e., grade 2 HR 4.973 (p<0.001) grade 3-4 HR 28.413 (p<0.001).

Mortality was not increased in patients with HE grade 1 (HR 1.094).
Hepatic Encephalopathy is an Independent Risk Factor for Mortality in Patients Awaiting Liver Transplantation: Conclusion

- Hepatic encephalopathy is an independent risk factor for mortality in patients awaiting liver transplantation
- Objective biomarkers for assessment of HE are needed as HE patients might deserve higher priority
Hepatic Encephalopathy is an Independent Risk Factor for Mortality in Patients Awaiting Liver Transplantation: Conclusion (cont.)

Fig. 1. Kaplan Meler survival estimate (months) of all patients until death according to the presence or absence of hepatic encephalopathy (HE) in patients listed for liver transplantation.

[Figure 1.]
PROGNOSTIC BENEFIT OF THE ADDITION OF AN ELECTROENCEPHALOGRAPHIC (EEG) INDEX TO THE MELD SCORE: THE MELD-EEG

Abstract 220

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A reduced EEG mean dominant frequency (MDF< 7.3 Hz) is indicative of hepatic encephalopathy (HE).

Since HE is not reflected in the MELD score and is an important prognostic parameter, the aim of this study was to assess the prognostic benefit of the addition of an EEG-based index to the MELD score.
Prognostic Benefit of the Addition of an Electroencephalographic (EEG) Index to the MELD Score: The MELD-EEG: Methods

- 392 consecutive patients with decompensated cirrhosis underwent an EEG with automated MDF determination
- MELD was calculated at the time of EEG
- Patients were excluded if they had advanced hepatocellular carcinoma, HE ≥ grade III or significant comorbidity
- Monitored for up to 18 months (median 12 months) in relation to the occurrence of death/liver transplantation
Prognostic value of the stand-alone/combined MELD and MDF indices was calculated using standard survival analysis techniques (patients transplanted for hepatic decompensation were considered dead on the day of transplantation, those transplanted for hepatocellular carcinoma were censored).

Findings were validated using a split sample technique:

- Cox regression curve was re-calculated in a random sample of 259 patients
- remaining 133 served as a test group
During the follow-up period, 107 patients died/were transplanted for hepatic decompensation.

Both the MELD and the MDF predicted mortality on Kaplan-Meier analysis, and both were independent predictors of mortality on a Cox model.

<table>
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<th>Variable</th>
<th>Beta</th>
<th>SE (beta)</th>
<th>Wald T</th>
<th>P</th>
<th>O.R.</th>
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<td>MELD</td>
<td>0.087</td>
<td>0.016</td>
<td>30.5</td>
<td>0.000</td>
<td>1.091 (CI: 1.058-1.126)</td>
</tr>
<tr>
<td>MDF</td>
<td>-0.306</td>
<td>0.068</td>
<td>20.2</td>
<td>0.000</td>
<td>0.737 (CI: 0.645-0.842)</td>
</tr>
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</table>
Based on Cox regression parameters, a novel prognostic index was devised: MELD-EEG=0.087*MELD-0.306*MDF

On ROC-curve analysis, the MELD-EEG had a higher prognostic accuracy in predicting 12- and 18-month mortality compared to MELD (AUC\textsubscript{12m}=0.69±0.03 vs. 0.62±0.04, p=0.016; AUC\textsubscript{18m}=0.71±0.03 vs. 0.64±0.03, p=0.018) and had higher Youden index (12 months: 0.31 vs. 0.18; 18 months: 0.35 vs. 0.20)

On validation, no significant differences were observed between the reference and test groups
The addition of an automatically obtained EEG-based index improves the prognostic accuracy of MELD.

Confirmation of these findings is underway.
SPLENO-SYSTEMIC SHUNTS AND COVERT HEPATIC ENCEPHALOPATHY

Abstract 245
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Spleno-Systemic Shunts and Covert Hepatic Encephalopathy: Background and Aims

- Portal-systemic shunts can involve blood from the intestine (patent paraumbilical vein, inverted left gastric vein) or from the spleen (spleno-systemic shunts [SSS])
- A peculiar condition is that of total shunt in patients with inverted portal flow
- The relationship between portal-systemic shunt and the occurrence of overt hepatic encephalopathy has long been known
However, that between SSS and the subtle neuropsychiatric alterations termed covert hepatic encephalopathy (CHE) is less clear.

Aims of this study were to:

- *i*) assess the likelihood of CHE screening in relation to the presence of SSS
- *ii*) evaluate the relationship between SSS and quantitative CHE indices
Spleno-Systemic Shunts and Covert Hepatic Encephalopathy: Methods

- Three-hundred-and-thirty-one patients with cirrhosis, independently referred for hepatic Doppler-US between Jan-2009 and August-2012 were enrolled.
- Qualified as having SSS if convoluted, anechoic spleno-renal and spleno-retroperitoneal channels were detected, and venous flow confirmed by colour-Doppler.
- Flow direction within the portal vein was also established.
- Information was obtained on independent referral of the same patients for CHE screening, including electroencephalography, within 6 months of Doppler-US.
Spleno-Systemic Shunts and Covert Hepatic Encephalopathy: Results

- Eighty-eight/331 (27%) patients were qualified as having SSS
  - spleno-renal in 17 (19%)
  - spleno-retroperitoneal in 71 (81%)

- Eight/331 (2%) patients, all with SSS, had inverted portal flow

- Forty-three/331 (13%) patients underwent CHE screening, the prevalence of which was higher in those with SSS (34 vs. 5%; \( \chi^2=47.2, p<0.0001 \))
• Significant differences in spectral EEG features were observed between patients with/without inversion of the portal flow in the entire population (EEG frequency: 8.3±2.5 vs. 10.6±1.7 Hz, p< 0.05; slow delta activity: 18±17 vs. 6±5 %, p< 0.01) and in the SSS group (EEG frequency: 8.3±2.5 vs. 10.3±1.7 Hz, p< 0.05; slow delta activity: 18±17 vs. 7±5 %, p< 0.05)

• In patients without portal flow inversion, no differences in EEG parameters were observed in relation to SSS
A significant association was observed between SSS presence and the likelihood of CHE screening.

However, EEG parameters were not different in patients with/without SSS.

In contrast, the EEG was slower in patients with inverted portal flow compared to those with SSS only, suggesting that flow inversion is a risk factor for CHE.