The diagnostic value of Acetylcholinesterase activity in minimal hepatic encephalopathy: an ongoing need for biomarkers ?

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Introduction

• The diagnosis of minimal hepatic encephalopathy (mHE) can be easily missed in patients with liver cirrhosis. Adequate psychometric testing is considered time consuming.

• **Early identification** and treatment of mHE is of high priority in order **to prevent further detoriation**. Reliable blood based biomarkers might improve early diagnosis.

• Acetylcholinesterase (**AChE**) is an enzyme that catalyzes the breakdown of the neurotransmitter acetylcholine for subsequent uptake into the presynaptic neuron (figure 1). In septic encephalopathy, significantly altered AChE activity was shown to represent the **severity of systemic inflammation**. Plasma **AChE activity is reduced** in loss of cholinergic neurons and associated with **delirium and cognitive decline**.

• We aimed to investigate the diagnostic value of plasma AChE activity in patients with liver cirrhosis and cognitive dysfunction according to the PSE-Syndrome Test results.

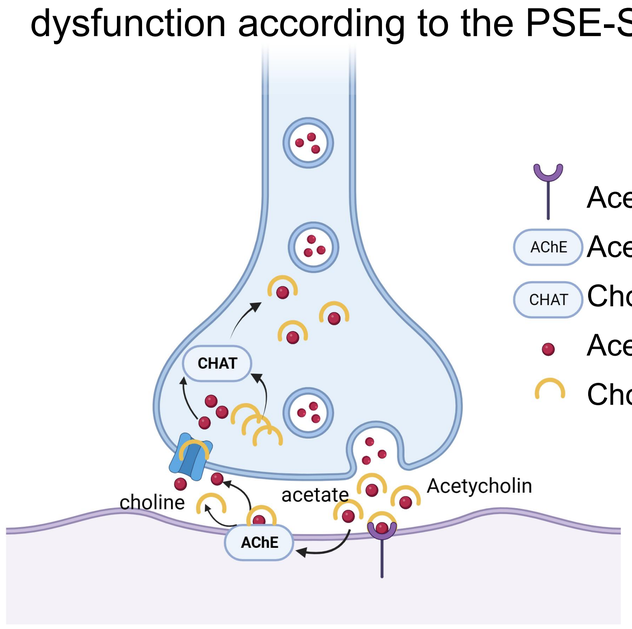

Figure 1: *Schematic illustration of the acetylcholine cycle in the synaptic cleft. Created with BioRender.com.*

Discussion

• AChE activities in the cerebrospinal fluid are equivalent to AChE activities in plasma, suggesting that erythrocytic AChE reflects the (central) cholinergic transmitter balance.

• Decreased activities of AChE indirectly indicate cholinergic deficits and apoptosis of cholinergic neurons in the context of neuroinflammation. Furthermore, the increased release of the cytokine tumor necrosis factor alpha (TNF-α) directly correlates with the severity of hepatic encephalopathy due to chronic liver failure and simultaneously causes a decrease in cholinergic neurons by inhibiting insulin-like growth factor-1, which is neurotrophic and neuroprotective.

• However, since AChE is also found throughout the body such as on erythrocytes, platelets, leucocytes and muscles, its activity measured in plasma might be biased by the systemic consequences of liver cirrhosis.

• Other biomarkers such as the neurofilament light chain might thus represent more favourable biomarkers in the serum, reflecting axonal loss in the course of severe neuro-inflammation in HE.

Materials & Methods

AChE activity in plasma was analysed in 89 patients with liver cirrhosis via a point-of-care photometric measurement. Clinical characteristics, demographic data, laboratory findings and the PHES were assessed and tested for their associations with AChE activity in serum, considering a PHES <-4 as abnormal.

Results

• Median age of the study population was 59 years (52-67), 21 % were female. Median Child Pugh-Score was 7 (6-9) and median Model for End-stage Liver Disease (MELD) Score 12 (10-15). 19 % had HE grade 1 according to the West Haven Criteria. PHES was -4 (-8- -2) in median.

• AChE activity in (U/L) was lower in patients with abnormal PHES (4108.84 vs. 3543.51, p=0.004) and HE Grade 1 (3990.91 vs. 3344.61, p=0.009) (figure 2).

• Lower AChE activity correlated with lower platelets, hemoglobin and CHE as well as higher scores of the MELD, CLIF C-AD and Child Pugh.

• In a linear regression model including the above mentioned markers AChE activity was not related to PHES. Neither was the hemoglobin adjusted AChE activity in U/g hemoglobin (Hb) associated with pathological PHES results. Instead, it correlated with elevated transaminases, bilirubin and INR.

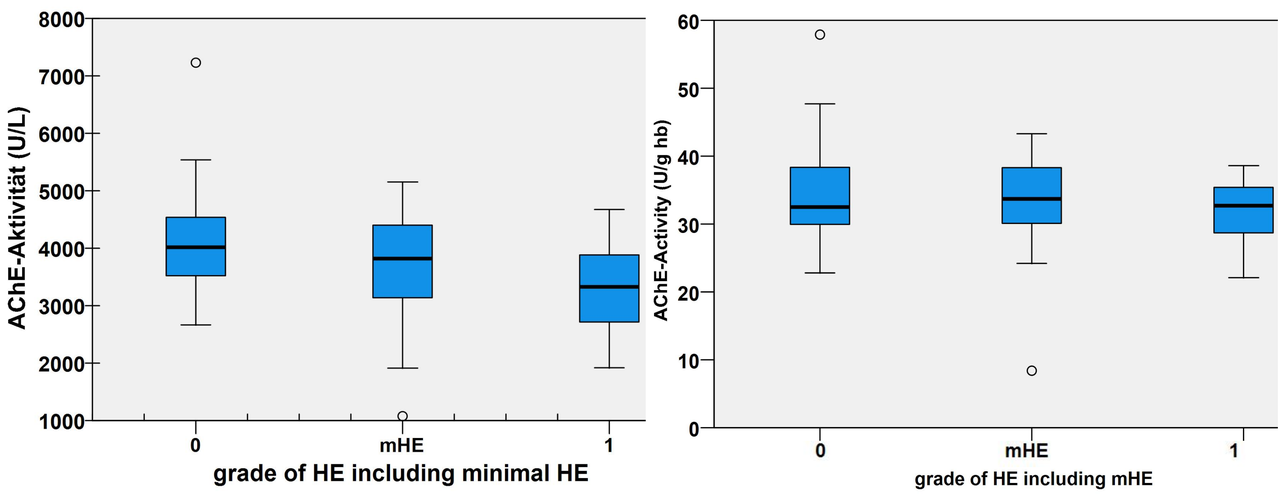

Figure 2: *Boxplots of AChE activity and hemoglobin in different grades of HE .*

	Regression coefficient B	SD error of the mean	Beta	level of significance	lower limits of 95% CI	upper limits of 95% CI
Thrombocytes	2,570	1,049	0,215	0,016	0,482	4,657
Hemoglobin	91,777	48,449	0,202	0,062	-4,622	188,176
CHE	192,275	76,767	0,319	0,014	39,531	345,018
Child Pugh Score	-21,546	54,523	-0,048	0,694	-130,030	86,939
PHES	11,862	20,076	0,055	0,556	-28,084	51,807
CLIF C-AD Score	-19,242	11,269	-0,167	0,092	-41,663	3,180

Figure 3: *linear regression model with AChE in U/l as dependent variable.*

Conclusion

Plasma **AChE activity does not emerge as a suitable blood biomarker** for the detection of mHE in patients with liver cirrhosis. The investigation of appropriate biomarkers thus continues and needs to be addressed in further studies.

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