Early and profound neurometabolic changes in pup rat with cholestatic liver disease compared to changes in adult rats, ^{1}H MRS study

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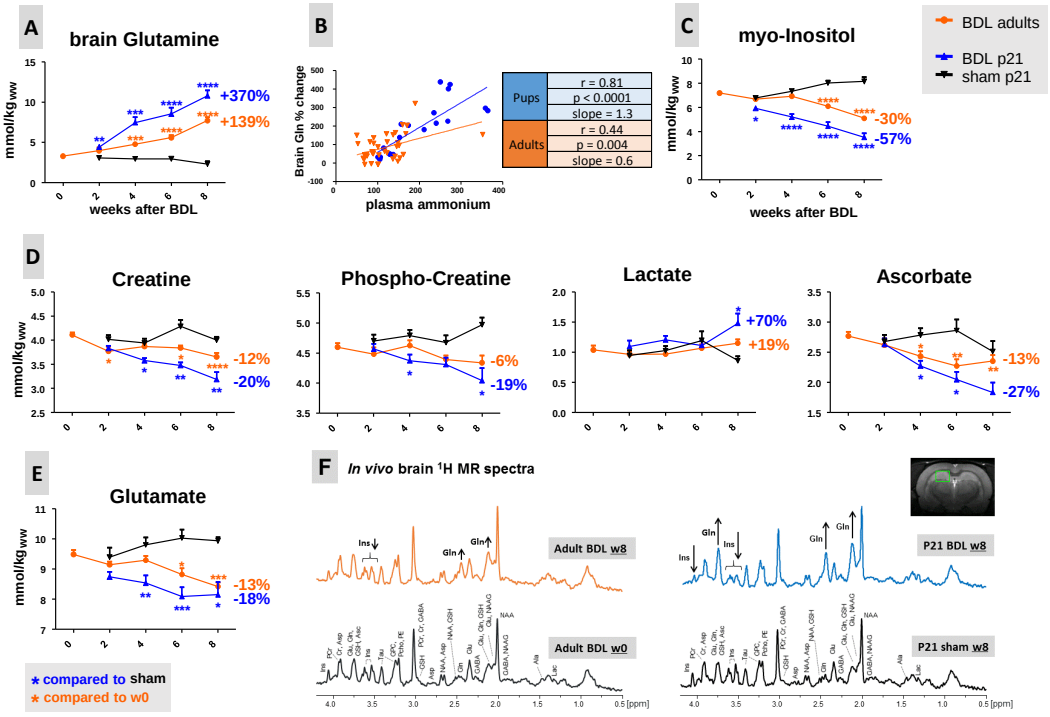
Introduction Chronic hepatic encephalopathy (CHE) is a serious neuropsychiatric disorder due to chronic liver disease (CLD) occurring in adults as well as in children. While in adults most of the neurological symptoms seem to be reversible after liver transplantation, neurocognitive deficits persist in children. The precise underlying mechanisms leading to CHE and the difference between adults and children is not completely understood. Therefore we aimed to describe and compare neurometabolic changes during the progression of CHE in adult and developing brain using an animal model of CLD – bile duct ligated (BDL) rats.

Methods ^{1}H MRS was performed in hippocampus (2x2.8x2mm^3) using SPECIAL sequence (TE=2.8ms) at 9.4T. Quantification for performed with LCModel. Rats underwent MRS and blood sampling before BDL (week 0) and at post-operative weeks 2/4/6/8. 29 rats were BDL as adults where each animal served as its own control for ^{1}H MRS (pre-BDL scan/week 0). 12 rats were BDL at post-natal day 21 (p21) and 9 rats underwent sham surgery at p21. Sham animals served as age-matched controls to take into account ongoing brain development in young rats.

Results & Discussion P21 BDL rats showed higher plasma NH_4^+ throughout the disease. From ^{1}H MRS, brain Gln in p21 BDL rats increased significantly already 2 weeks post-BDL, compared to only 4 weeks in adults and reached also higher values in young brain (**A**). Steeper slope of the linear increase between plasma NH_4^+ and hippocampal Gln (**B**) indicates differences in glutamine synthetase kinetics in developing and adult brain. The osmotic answer to Gln increase was stronger and quicker in p21 rats than in adult BDL rats (**C**). Moreover, the disturbances in energy metabolism and oxidative stress were stronger in young BDL rats (**D**). Lac increase probably represents an overall metabolic, inflammatory and oxidative stress accumulated at the end of the disease. Finally, the neurotransmitters Glu and Asp were stronger affected in young BDL rats (**E**).



Conclusion There were several striking differences between animals having undergone BDL as pups or adults: (1) all neurometabolic changes were more pronounced in the developing brain, (2) some changes appeared earlier (Gln, osmolytes mIns, tCho, neurotransmitter Glu) (3) several neurometabolic changes seem to be unique to the developing brain (Asp, Lac, PCr). Therefore, we conclude that the developing brain displays an increased vulnerability to the metabolic insults of CLD compared to adult animals. This might stand behind long-lasting cognitive and neurological problems in children even after liver transplantation.

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