The "glymphatic system" is the global waste clearance pathway of the brain, which effectively eliminates metabolites and waste products from the CNS through cerebrospinal (CSF) and interstitial fluid (ISF) exchange. This process depends on the use of the perivascular tunnels, formed by astrocytes and it is mostly active during sleep. Evidence exist indicating altered clearance of the brain during certain pathologies such as Alzheimer’s disease and traumatic brain injury. In patients with hepatic encephalopathy (HE) sleep disturbances are reported and changes in the cerebrospinal fluid composition have been identified, such as elevated acetylated compounds, amino acids and bile acids suggesting alterations in metabolic pathways. In this study we investigated whether glymphatic function is affected during HE, by using dynamic contrast-enhanced MRI to quantify glymphatic clearance in the brain of an animal (rat) model of HE (bile duct ligation [BDL]). We also aimed to correlate the effectiveness of this clearance pathway with the concentration of toxic metabolites; bile acids, in the CSF of these animals. Methods: Glympathic clearance in BDL- (n=5) and SHAM-operated (n=5) rats was measured via intracisternal infusion of gadolinium, concurrent with serial acquisition of T1-weighted MR images. In addition, bile acid concentrations from extracted plasma and CSF were assessed using liquid chromatography–mass spectrometry. Immunofluorescence and PCR was also performed on the brain of these animals to quantify the presence of the most abundant bile acid receptor, TGR5. Results: A dysfunction in the clearance pathway of the brain was observed in the BDL rats compared to sham, with the most affected areas being in the rostral brain, i.e. the olfactory bulbs and rostral region of the cortex. The caudal brain (i.e. the caudal region of the cortex, the hippocampus, thalamus and midbrain) of BDL rats however was observed to display an improvement in glymphatics inflow compared to sham controls. Blood and CSF analysis showed a significant increase of the Tauro-bile acid, which is the main rodent form. An increase in the gene and protein expression of TGR5 was also observed at the caudal brain regions of the BDL rats similar to the regions affected in the MRI experiments. Conclusions: These results show for the first time a brain clearance dysfunction occurring in chronic liver failure, which could be the cause or consequence of the toxic bile acid accumulation. Although the molecular mechanism of this disturbance is unclear, the altered glymphatic pathway in the brain could have many detrimental effects such as sleep disturbances as well as altered mood and consciousness, due to the accumulation of neurotransmitters, toxins and byproducts of cell metabolism. Collectively, this
may contribute to the chronic brain injury that is characteristic of patients with cirrhosis and HE.

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