# A hydrodynamic hypothesis for the pathogenesis of glymphatic system impairment in hepatic encephalopathy

*To the Editor:*

The interesting study by Hadjihambi *et al.*[1] demonstrated, in the bile duct ligation model, the role of glymphatic system impairment in hepatic encephalopathy. However, mechanisms underlying this finding were not stated.

The glymphatic system is a brain-wide glial dependent perivascular network that functions to remove interstitial metabolic waste products.[2] Interstitial-cerebrospinal fluid (CSF) exchanges are finely regulated at the level of Virchow-Robin spaces, prompted by the driving force of aquaporin-4, expressed in the astrocyte end-feet of the brain microvasculature.[2] There are disorders arising from glymphatic system dysfunction, as well as clinical conditions that damage this system by altering intracranial pressure and/or the blood circulation. Indeed, the glymphatic system is a key component of an interstitial-CSF clearance system that encompasses systolic heart forces, arterial wall pulsatility, CSF brain circulation, venous circulation and meningeal lymphatic vasculature drainage.[3–5] Derangement of any component of this integrated hydrodynamic system may lead to glymphatic malfunctioning by impacting on the CSF dynamics.[3,5,6] Changes in arterial pulsatility may contribute to accumulation and deposition of toxic solutes, including amyloid ß, in the aging brain and Alzheimer's disease.[7] A recent glymphatic magnetic resonance imaging study demonstrated that delayed clearance of CSF and impaired glymphatic function lead to neurodegeneration, and eventually dementia in normal pressure hydrocephalus, a neurological condition of the elderly caused by failure in CSF dynamics.[8] Abnormalities of the venous system associated with cerebral-venous outflow reduction may change CSF dynamics, contributing to the pathophysiology of several neurological diseases, such as multiple sclerosis, leukoaraiosis, vascular dementia,[3] idiopathic intracranial hypertension.[5] Notably, minimal increases in cerebral-venous pressure may result in congestion of the glymphatic system.[5] Finally, it has been proposed that dysfunction of meningeal lymphatic vessels, also through reduced CSF drainage, may lead to reduction of interstitial macromolecule renewal at the glymphatic level, thus triggering neurodegeneration.[4]

In seeking explanations for the glymphatic impairment in hepatic encephalopathy, it could be interesting to look at this liver complication in a global, closed-loop vision of human circulation. We speculate that, in the advanced phases of liver cirrhosis, glymphatic damage could be the end-stage phenomenon of a cascade of hydrodynamic events starting from the establishment, even if only in a small percentage of patients, of the so-termed "hyperdynamic circulation". The latter is characterized by the onset of a vast number of artero-venous shunts developing in several organs and apparatuses.[9] This condition, in the presence of retention of sodium and water in the splanchnic circulation (overflow theory) and, eventually, reduction of central blood volume (underfilling theory), results in a complex hemodynamic derangement, according to the proposed unifying peripheral vasodilatation hypothesis.[10] Finally, a venous overload at the level of inferior and superior vena cava may occur; consequently, venous blood stagnates at the level of jugular veins, which appear dilated, resulting in reduced venous outflow.[11] Incidentally, transjugular intrahepatic porto-systemic shunt stenting is contraindicated in this setting, due to possible occurrence of severe heart failure and/or pulmonary hypertension.[12] This warning is particularly advisable in the presence of cirrhotic cardiomyopathy, a complication present in about 50% of patients with end-stage cirrhosis undergoing liver transplantation.[13] Reduction of jugular vein outflow may in turn induce a reduction of cerebral-venous outflow and consequently, impairment of CSF circulation,[3] derangement of aquaporin-4 based clearance, accumulation of waste molecules and fluids, glymphatic congestion and occurrence of inflammatory processes.[5,6] Moreover, persistent reactive gliosis, which is associate with these events, may contribute to further glymphatic damage in a self-perpetuating pathogenetic mechanism.[6] This cascade of events, started and propelled by hydrodynamic driving forces, may result in the final *noxa* of hepatic encephalopathy, consisting of the accumulation of toxic substances and metabolites in the brain interstitium.

Studies on glymphatic flow modification in the context of a global vision of fluid dynamics in patients with liver cirrhosis and hepatic encephalopathy might help to explore this theory.

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## Authors' contributions

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## Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.02.010.

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# Reducing mother-to-child transmission of HCV: Is it attainable with a multidisciplinary approach?

*To the Editor:*

We read with great interest Modin *et al.* in the November 2018 edition of *Journal of Hepatology*.[1] Given the demonstrated long-term disease sequelae for children infected with hepatitis C virus (HCV) particularly through mother-to-child transmission (MTCT), we agree that there is a need for earlier detection and treatment of HCV in children. However, in the absence of universal guidelines for HCV screening during pregnancy, the antepartum case definition of HCV is inadequate, and coordination of maternal care is challenging. Therefore, MTCT is insufficiently prevented, and HCV diagnosis in children is suboptimal. With preliminary data of our experience with a cohort of women with HCV during pregnancy in New York State, we would like to emphasize the importance of improving the prevention of MTCT of HCV.

In the study by Modin *et al.*,[1] early diagnosis and treatment of childhood HCV was recommended, because cirrhosis occurred at high rates and significantly impacted mortality in individuals who acquired HCV through MTCT. Of the measured risk factors, cirrhosis was the only risk factor that increased mortality in patients with childhood HCV infection (odds ratio [OR] 6.2; 95% CI 2.6–14.7; $p$ <0.001).[1] Perinatally infected children (11%, n = 1,049) developed cirrhosis at a far earlier age (36 years, range 17–53) than those who acquired HCV as adolescents through other means.[1] Given the earlier age of cirrhosis onset, treatment of HCV should not be delayed beyond childhood.

Despite the importance of preventing childhood HCV, perinatal HCV is difficult to detect due to a lack of screening, slow-onset symptoms, and poor adherence (43%) to the required 18 months of follow-up after birth.[2] Given the long follow-up required for diagnosis, these low rates indicate a need for improved maternal education, coordination of care, and patient-physician relationships.[3]

We sought to address these gaps in care by bringing together a multidisciplinary team of obstetricians, pediatric infectious disease providers, and hepatologists to coordinate care for women with HCV during pregnancy at 1 urban (n = 13) and 1 suburban (n = 21) center in New York State since September 2017. In total, 34 patients with HCV during pregnancy were seen and managed in our practices. Upon detection of HCV during routine prenatal care, 26/34 (76%) attended at least 1 liver specialty visit while pregnant. However, of the 18 women who delivered at the primary institution, only 8 (44%) returned to the liver clinic postpartum. This contrasts with the 15/20 (75%) women who returned to the obstetrics clinic postpartum. This data suggests that care coordinators are sorely needed to improve adherence, particularly during the postpartum period, to match that of the obstetrics clinic.

In addition to coordinating care, we sought to treat HCV as soon as possible. Six patients were treated for HCV with direct-acting antivirals post-delivery, most after cessation of breastfeeding. One patient, who was co-infected with HIV and had acquired HCV through MTCT herself, was treated intrapartum to decrease the risk of MTCT. Earlier treatment benefits women with HCV and active injection drug use, as they are less likely to use contraception (56% *vs.* 81%)[4] and are at greater risk of unplanned pregnancy than the general population (89% *vs.* 31–47%).[5] Furthermore, earlier treatment utilizes Medicaid's expanded inclusion criteria for women during pregnancy and