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A Novel Technique Regarding the Pathophysiology of Normal Pressure Hydrocephalus: Glymphatic Magnetic Resonance Imaging?

Normal Basınçlı Hidrosefali Patofizyolojisi Üzerine Yeni Bir Teknik: Gilenfatik Manyetik Rezonans Görüntüleme?

Halil Önder

Yozgat City Hospital, Clinic of Neurology, Yozgat, Turkey

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The glymphatic system represents a large network that plays a role in the clearance of waste metabolites from the brain. This system functions through fluid transport through the interstitial space, which is regulated by aquaporin 4 (AQP 4) channels in the astrocytic perivascular extensions. Previous studies have suggested that the glymphatic system has a fundamental function in the clearance of waste metabolites from the brain interstitial space, and that it is an effective pathway in the development of brain pathologies such as Alzheimer's disease (AD) and brain trauma, as well as normal ageing (1). Assessment of the glymphatic system through administration of the gadolinium-based Gd-DTPA contrast agent into the subarachnoid space was first performed in the mouse brain (2). In humans, glymphatic contrast enhancement was reported in a patient for cerebrospinal fluid (CSF) leakage as a single case report (3).

Recently, Ringstad et al. (1) reported the results of their studies aiming to determine CSF flow characteristics and glymphatic system function in patients with idiopathic normal pressure hydrocephalus (INPH) using glymphatic magnetic resonance imaging (MRI). The imaging protocol included T1-weighted MRI with equal sequence parameters before and at multiple time points through 24 h after intrathecal injection of the contrast agent gadobutrol at the lumbar level. Several axial T1-sequence MRIs were recorded before and 24 hours after intrathecal gadobutrol injection at the lumbar level in the imaging protocol. Gadobutrol enhancement was measured at all imaging time points at predefined locations (brain parenchyma, subarachnoid and intraventricular space, and inside the sagittal sinus), and gadobutrol enhancement and clearance patterns were compared between the two groups.

Fifteen patients with INPH and eight reference subjects were included in the study. In the analysis results, delayed enhancement was observed at the extraparenchymal subarachnoid space (foramen magnum, pontine cistern, Sylvian fissure) in patients with INPH. This delay was found to be statistically higher adjacent to the frontal gyrus (adjacent to the inferior frontal gyrus, $p<0.05$) and at the vertex of the brain (precentral sulcus, $p<0.01$). Periarterial contrast enhancement was found to be significantly delayed in patients with INPH. Evidence of ventricular reflux in patients with INPH was presented regarding significantly higher ventricular contrast enhancement in the fourth, third, and lateral ventricles in patients with INPH. In the brain parenchyma, especially in the periventricular white matter and inferior frontal gyrus, gadobutrol contrast enhancement was found to be higher in the INPH group. However, there was no increase in gadobutrol enhancement in central venous areas.

As a result, the authors described ventricular reflux and transependymal migration from the lateral ventricles towards the periventricular white matter in patients with INPH as characteristic findings of NPH. It was emphasized that, at the brain surfaces, gadobutrol propagated antegradely along large leptomeningeal arteries in all study subjects before adjacent brain

Address for Correspondence/Yazışma Adresi: Halil Önder MD, Yozgat City Hospital, Clinic of Neurology, Yozgat, Turkey
Phone: +90 537 683 68 64 E-mail: halilnder@yahoo.com ORCID ID: orcid.org/0000-0002-1823-2278
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tissue. This result was interpreted by the authors as a finding that intracranial arterial pulsation plays a pivotal role for glymphatic function. Delayed enhancement ($p<0.05$) and decreased clearance ($p<0.05$) at the Sylvian fissure were determined in patients with INPH. Parenchymal contrast enhancement was found to peak overnight in both study groups, which correlated with increased glymphatic function during sleep. The authors interpreted the results of the study as findings of reduced glymphatic clearance in patients with INPH and hypothesized that reduced glymphatic function might be a key mechanism in the development of dementia in these patients.

On the other hand, the reference subjects in the study were younger than the INPH group and they also differed in terms of sex. Two of the reference subjects had a diagnosis of CSF leakage, a condition in which the CSF flow pattern is not normal. These situations constitute important limitations of the study, as mentioned by the authors. The authors emphasized the lack of contrast enhancement in the brain convexity, suggesting that this could lead to a debate on the role of arachnoid villi in CSF absorption. Another striking interpretation of the authors, based on previous study results suggesting that glymphatic dysfunction is associated with a reduction in the clearance of interstitial substances such as amyloid-B, might be their hypothesis suggesting that a common pathogenetic mechanism may play a role in INPH-related dementia as well as AD, in which amyloid-B is a key feature. The results of further larger case reports seem necessary to support these views. Despite these limitations, this study is valuable in that it is the first study to evaluate glymphatic function in patients with INPH by using intrathecal contrast injection and that results provide considerable perspectives. The authors presented glymphatic MRI as a promising method for imaging of the metabolic functions of the human brain.

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