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Research Letter In-Press Preview Aging Neuroscience

Impact of SGLT2 inhibitors on cerebrospinal fluid dynamics and implications for hydrocephalus management

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Conflict-of-Interest Statement: ABH holds equity in Caris Life Sciences, serves on the advisory board of WCG Oncology, receives research support from Alnylam Pharmaceuticals and AbbVie, and is an inventor on the following patents: “Biomarkers and combination therapies using oncolytic virus and immunomodulation” (US20140377221A1);” miRNA for treating cancer and for use with adoptive immunotherapies” (US20170312304A1); “Concurrent chemotherapy and immunotherapy” (US9399662B2); and “Low intensity ultrasound combination cancer therapies.” (WO2022192323A).

To the Editor:

Sodium/glucose cotransporter 2 (SGLT2) inhibitors (SGLT2-I) are increasingly used for glycemic control, cardiovascular and renal protection, and weight loss in type 2 diabetes mellitus (DM) (1). DM incidence ranges from 15-18% in idiopathic normal pressure hydrocephalus (INPH) patients, increased from general populations (2). SGLT2 (*SLC5A2*) is expressed in the choroid plexus epithelial and ependymal cells in humans, potentially influencing cerebrospinal fluid (CSF) production (3). INPH is a syndrome affecting up to 3% of individuals 65 and older, characterized by dementia, gait impairment, and urinary incontinence (4). INPH is treated with ventriculoperitoneal shunts (VPS), but no approved pharmacological treatments exist. We observed a reduction in ventricular size in a patient with INPH after initiating an SGLT2-I (Case 2), prompting a review of our institutional cohort to assess the impact of SGLT2-I on ventricular size. The Institutional Review Board approved this study.

Three INPH patients with imaging before and after SGLT2-I treatment were identified. Radiographic changes in ventricle size were quantified using Evan's Index (EI) and the callosal angle (CA) at the anterior commissure (AC), posterior commissure (PC), and splenium (5). The last brain imaging before SGLT2-I initiation was compared to the first scan after SGLT2 inhibition (Figure 1A). For patients with a programmable VPS, shunt settings remained unchanged between scans.

The mean age at INPH diagnosis was 74 years (SEM: 3.3). Two patients were male, and one female. All patients underwent VPS placement and showed postoperative improvement in NPH symptoms. Each patient started SGLT2-I therapy after VPS placement (Figure 1B). The average time from VPS placement to pre-SGLT2-I scan was 11.4 months (SEM: 4.9), from pre-

SGLT2-I scan to SGLT2-I initiation was 11.7 months (SEM: 2.2), and from SGLT2-I initiation to first post-SGLT2-I scan was 5.7 months (SEM: 1.8).

Only the CA at the splenium and EI were measurable in all patients pre- and post-SGLT2-I therapy. One patient experienced dramatic ventricle size reduction, rendering the CA at the AC and PC unmeasurable due to ventricular collapse (Figure 1A, Case 2). This patient required a VPS valve adjustment post imaging to reduce CSF drainage. The mean pre-SGLT2-I EI was 0.34 (SEM: 0.1), and post-SGLT2-I therapy EI was 0.26 (SEM: 0.1; 2-tailed T-test, p= 0.2597). The mean pre-SGLT2-I CA was 88.1º (SEM: 15.3), and post-SGLT2-I therapy CA was 105.1º (SEM: 17.9; 2-tailed T-test, p=0.0225), with all patients showing increased CA (Figure 1C). Ventricular volume changes were analyzed via segmentation before and after SGLT2-I therapy. (Supplementary Figure 1).

This study reports ventriculomegaly changes following SGLT2-I therapy in patients with INPH. The CA at the splenium increased by a mean of 17.0º, which is the only radiographic parameter that predicts improvement in INPH symptoms (5). Supplementary volumetric analysis confirmed reduced ventricular volume after initiation of SGLT2-I treatment. Patients showing ventricular changes post-VPS may have a greater propensity to respond further to SGLT2-I, though a larger study is needed. Given potential CSF drainage interactions in INPH patients after initiating SGLT2-I therapy, practitioners should monitor these patients closely.

SGLT2 expression in the choroid plexus epithelium (2), combined with these observations, suggests SGLT2 inhibition may modulate CSF production and ventricular size. Furthermore, SGLT2 is upregulated in brain tissue after traumatic brain injury (TBI), and up to

46% of ICU-admitted TBI patients develop hydrocephalus (6,7). Thus, SGLT2 inhibition may be a rational strategy for the treatment of post-traumatic hydrocephalus.

All patients had a CT scan at least 3 months after VPS placement, without change in shunt drainage setting, so ventricular size is expected to be stable. However, this retrospective study cannot rule out a delayed decrease in ventricular size in response to VP shunting, although this is unlikely and a limitation of this study. While excess CSF production is a potential mechanism for INPH, its etiology is still unclear, with factors such as ependymal cilia dysfunction and impaired CSF absorption implicated. It is uncertain if SGLT2 inhibition functions in the brain similarly to its role in the kidneys. Alternatively, systemically administered SGLT2-I could reduce ventricular size secondary to diuresis, as SGLT2 is highly expressed in the kidneys. However, no changes in serum electrolytes or kidney function were observed in these patients. Further research is required to determine the mechanism of SGLT2 action in the brain and ependyma and its impact on CSF dynamics. Recent reports have shown that glucagon-like peptide 1 receptor agonists can decrease intracranial pressure, but this mechanism also remains unknown, highlighting the importance of monitoring for off-target effects of novel medications that may impact and modulate CSF dynamics (8). These observations provide the foundation for prospective clinical trials to evaluate the efficacy, safety, and long-term benefits of SGLT2 inhibition in treating INPH or post-traumatic hydrocephalus alongside the rationale to investigate the mechanistic role of SGLT2 in modulating CSF dynamics.

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Figure Legend

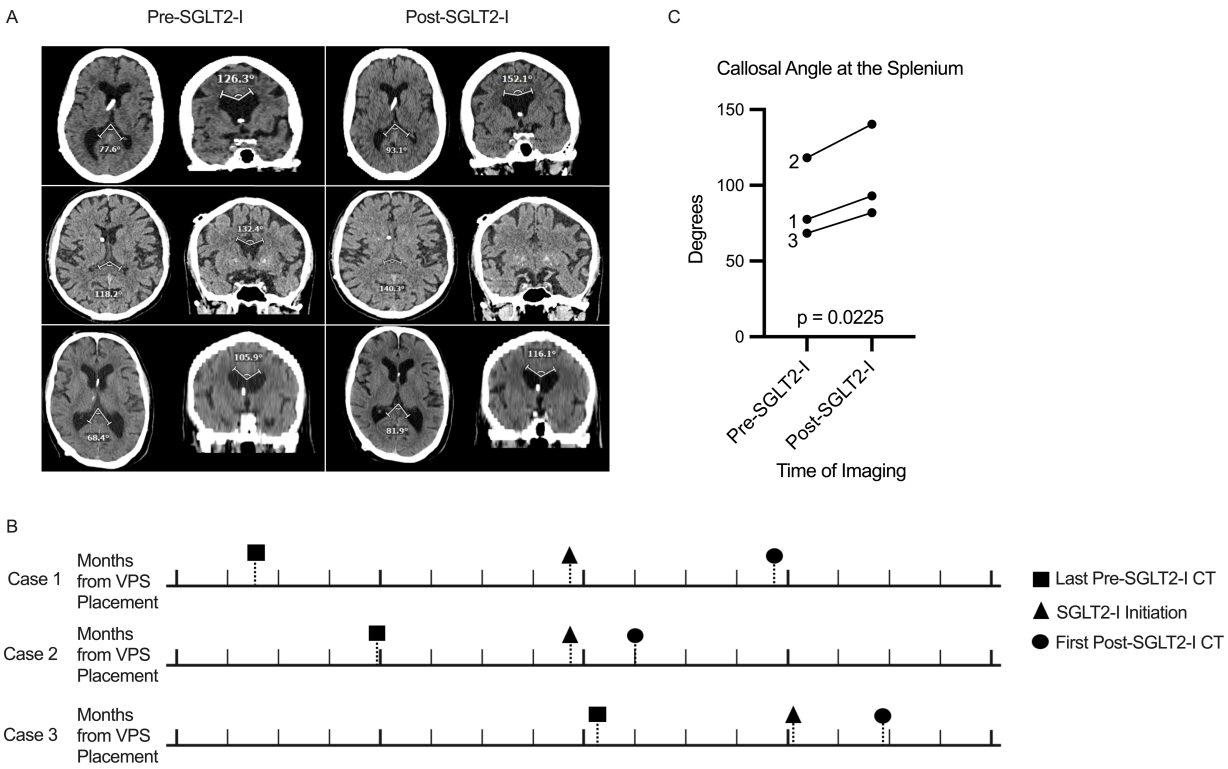

Figure 1. Effect of SGLT2 inhibition on ventricular size (A) Axial and coronal CT showing callosal angle (CA) at the splenium and anterior commissure (AC) pre- (left) and post-SGLT2 inhibition (right). (**B) Imaging** timeline after VPS placement and initiation of SGLT2-I. (**C)** Quantification of change in CA pre- and post-SGLT2 inhibition (2-tailed Student's t-test, p=0.0225).