evaluated 8 days after SAH with Luxol Fast Blue staining (Figure). Four brain sections taken as previously described were digitized under ×40 magnification and stained with Luxol Fast Blue. Areas without Luxol Fast Blue staining were designated as positive for myelin loss. The percent loss of myelin did not vary between WT and MMP-9 knockout mice without SAH. However, in the SAH model, the percent myelin loss was 24 ± 4% and 8 ± 1% in the WT and knockout mice, respectively. This finding supports the hypothesis that early MMP-9 overexpression is responsible for sustained white matter injury. This study reveals 3 critical findings: (1) An experimental SAH model yielded BBB disruption in white matter; (2) MMP-9 levels were elevated in SAH mice models at early time points; and (3) genetic deletion of MMP-9 associated with decreased BBB disruption and sustained white matter injury. These findings suggest that SAH induces oxidative damage to astrocytes and oligodendrocytes, which leads to overexpression of MMP-9 in the acute phase. MMP-9 subsequently causes cerebral edema by cleaving basement membrane proteins, which leads to white matter injury and demyelination. We know that cerebral edema is an independent predictor of poor prognosis for patients with SAH. Although further work is necessary, the present study suggests that early MMP-9 expression may represent a potential therapeutic target in patients with SAH.

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**REFERENCES**


**Patterns of Care and Clinical Decision Making for Recurrent Glioblastoma Multiforme**

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor. For newly diagnosed GBM, a widely adopted standard of care, including maximal surgical resection, concurrent radiation and temozolomide, and subsequent adjuvant temozolomide, was established in 2005. However, essentially all patients with GBM suffer disease progression, and there is no established standard of care for the treatment of recurrent GBM.

Once a patient treated with the Stupp regimen is diagnosed with recurrent disease, a number of treatment options may be available. These options include repeat surgical resection, repeat fractionated radiation, radiosurgery, salvage chemotherapy such as repeat temozolomide challenge, nitrosoureas, other alkylating agents, bevacizumab, tumor-treating fields, and experimental agents used in clinical trials. Given the lack of consensus on optimal management of recurrent GBM, knowledge of care patterns used for these patients and the criteria used to determine therapeutic strategy is germane to clinicians who care for these patients. In a recent study, Hundsberger et al investigated which treatments are currently being used for recurrent GBM within a single nation (Switzerland) and how clinicians are deciding to use them.

The authors surveyed Swiss hospitals with comprehensive multidisciplinary neuro-oncology practices (neurosurgery, radiation therapy, medical neuro-oncology, and a dedicated neuro-oncology tumor board) about treatment recommendations for recurrent GBM. They identified relevant clinical decision-making criteria, called diagnostic nodes or “dodes,” and compared treatment recommendations using a decision-tree format (Figure).

Eight hospitals participated. The most common treatment options for recurrent GBM were combination repeat surgical resection with temozolomide or bevacizumab, monotherapy temozolomide or bevacizumab, monotherapy temozolomide or bevacizumab, and best supportive care. Alternative therapies, including radiotherapy, were less common. Despite widespread disagreement between centers in clinical decision making, the decision-tree analysis found agreement (63%) between most centers for only 4 specific clinical scenarios. Patients without an appropriate performance status were usually managed...
with best supportive care. Patients with rapid recurrence, nonresectable tumors, unmethylated O(6)-methylguanine DNA methyltransferase (MGMT) promoter, and high performance status were usually managed with bevacizumab. Patients with late recurrence, nonresectable tumors, overt clinical symptoms, methylated MGMT promoter, multifocal disease, and high performance status were usually managed with repeat temozolomide therapy. Patients with late recurrence, nonresectable tumors, no clinical symptoms, methylated MGMT promoter, tumor multifocality, and high performance status were usually managed with temozolomide.

The findings of this study underscore the lack of effective first- and second-line treatments for GBM, and the interhospital variability in practice patterns is not surprising. It seems likely that similar heterogeneity would also be noted in a study of American neuro-oncology centers. It is interesting to note that despite the availability of an increasing number of molecular markers for GBM stratification, MGMT promoter methylation appears to be the only biological marker widely used across multiple centers in this study. It remains to be seen when and how broadly other markers such as the epidermal growth factor receptor variant III or isocitrate dehydrogenase mutations will be adopted for clinical decision making.

The authors are to be congratulated for identifying core clinical decision-making criteria that may be useful in future studies of recurrent GBM. This decision tree is an excellent reference for clinical trial development, and several active clinical trials already target the nodes identified in this study. Subsequent studies may help to determine whether similar decision trees exist in American neuro-oncologic centers now or will exist in the future.

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Lymphatics in the Brain?

That the brain lacks lymphatic drainage is a well-established dogma and an early lesson for medical students and residents. Although robust lymphatics in the central nervous system are indeed lacking, elements of neuroanatomy remain open to refinement. Indeed, 2 excellent publications by Aspelund et al and Louveau et al recently reported the existence of lymphatic structures in the brain, subsequently labeled the brain drain. Although descriptions of a lymphatic system in the brain have previously been reported, these studies were not intensively discussed until recently. A lack of research focused on understanding such a drainage system may be attributed to its location in a unique area of the brain less commonly investigated, the dura mater.

Macromolecules and waste products in the brain were previously thought to be cleared by a system of glial cells and arterial pulsations that helped to recycle fluid and lipid transport throughout the brain, called the glial lymphatic or “glymphatic” system. Although fluids were known to be exchanged between the brain interstitial fluid, cerebrospinal fluid, and the venous circulation via arachnoid granulations, the finding of subarachnoid fluid in the extracerebral lymphatic vessels and lymph nodes suggested that there was more to the drainage system of the brain than solely the glymphatic system.

Both Aspelund et al and Louveau et al investigated the existence and functionality of these lymphatic vessels. Aspelund et al investigated a lymphatic vessel “network” in the meninges under the skull bones. They created K14-VEGFR3-IgTG knockout mice with a lack of dura matter lymphatic vasculature. After fluorescent dye was administered to the knockout mice, central nervous system macromolecules could not clear without the dural lymphatic vessels (Figure). The newly found lymphatic vessels had attributes similar to the previously studied lymphatic vessels such as the peripheral lymphatic vessels. Louveau et al also alluded to the importance of the microenvironment surrounding the vessels because these vessels were larger and more complex, depending on the area of the brain. They used surgical removal of deep cervical lymph nodes in vivo to examine interactions between the meningeal lymphatic vessels and the deep cervical lymph nodes rather than the superficial lymph nodes.

The current analyses by Aspelund et al and Louveau et al reinforce the early description of a lymphatic system in the brain. This system could encompass immune cell trafficking, thereby explaining why primary brain tumors rarely metastasize into cervical lymph nodes. A disrupted brain drain could also explain the misfolded amyloid β accumulation in Alzheimer disease and other neurodegenerative diseases. These publications may engender new investigations into the neuropathology of various central nervous system disorders and reinforce the relevance of neuroanatomy not only for neurosurgery but also for neuroscience.

REFERENCES

“Inhibiting the Inhibitors” to Support Axonal Regeneration

After spinal cord injury (SCI), the disruptive interactions of chondroitin sulfate proteoglycans (CSPGs) produced by reactive astrocytes create glial scars that are major barriers to neural circuit reconnection and functional recovery. Recent work reveals a novel strategy to inhibit an inhibitor of neural

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