Cavernous malformations

To The Editor: We read with great interest the article written by Cheng-Chia Lee and colleagues (Lee CC, Pan DHC, Chung WY, et al: Brainstem cavernous malformations: the role of Gamma Knife surgery. Clinical article. J Neurosurg 117 Suppl:164–169, December 2012). The authors retrospectively reviewed the efficacy and safety of Gamma Knife surgery (GKS) in patients with brainstem cavernous malformations (CMs). Forty-nine patients with symptomatic CMs were treated by GKS between 1993 and 2010. The mean age in these patients was 37.8 years. There were 118 episodes of hemorrhage during the pre-GKS observation period. The authors calculated the pre-GKS hemorrhage rate in 49 patients who experienced more than 2 bleeding episodes. After excluding the first hemorrhage (118 − 49 = 69 episodes), the authors calculated the annual hemorrhage rate to be 31.3% (69 episodes in 220.3 patient-years). Forty-five patients (91.8%) underwent regularly scheduled follow-up MRI examinations and were available for study; the mean follow-up duration was 40.6 months and the overall observation period consisted of 172.4 patient-years. Six episodes of hemorrhage in 6 patients were documented during this period. Three of these episodes occurred within 2 years after GKS, and 3 episodes occurred more than 2 years after GKS.

Lee et al.2 calculated the annual hemorrhage rate during the first 2 years after GKS to be 3.33% (3 hemorrhages/90.0 patient-years), which was not difficult to understand. However, they calculated the annual hemorrhage rate after the initial 2-year follow-up to be 1.74% (3 hemorrhages/172.4 patient-years). We examined several other studies1,3–5 in which annual hemorrhage rates were calculated. We found the method used by Lee et al. to determine the annual hemorrhage rate after the initial 2-year follow-up period to be quite different from the method used in those studies. We therefore recalculated the annual hemorrhage rate for this period and found it to be 3.64% (3 hemorrhages/172.4 − 90.0 patient-years) rather than 1.74% (3 hemorrhages/172.4 patient-years) as described by Lee et al. We did this because 172.4 patient-years was the overall observation period and 82.4 patient-years (172.4 − 90.0 patient-years) was the precise observation period after the initial 2-year follow-up. The calculation method used in the study by Lee et al. to determine the post-GKS annual hemorrhage rate after the initial 2-year follow-up is not quite reasonable. It reduces the annual hemorrhage rate after 2 years and leads to a misunderstanding of the effectiveness of GKS on CMs. Using our method of calculation, the annual hemorrhage rate after the initial 2-year period (3.64%) was higher than that during the first 2 years (3.33%). This finding can be contrasted with the conclusions of the study by Lee et al., which state that the annual hemorrhage rate decreased within the first 2 years and further decreased after those 2 years.

In recent years, the positive therapeutic effect of GKS on intracranial CMs, including brainstem CMs, has been confirmed by many studies.1,3–6 In a future study, a randomized controlled prospective multicenter trial is recommended to compare the effectiveness between different treatment methods—surgery and GKS—and observation with close follow-up evaluation.

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Disclosure
The authors report no conflict of interest.

References

Response: We appreciate the efforts that Dr. Da Li and Dr. Jun-Ting Zhang took to read and recalculate our
statistics, and we thank them for sharing their thoughts with the Journal of Neurosurgery readers and us. We are pleased to have the opportunity to revise our data and continue to provide important information on CM therapies.

The point raised in the comments by Drs. Li and Zhang is related to the method we used to calculate the post-GKS annual hemorrhage rate. To clarify the problem, we returned to our original data and recalculated the hemorrhage rate more than 2 years post-GKS. We found, however, that the real problem lies in the way in which we calculated patient-years during the initial 2 years of follow-up.

Indeed, 29 patients were followed up for more than 2 years, and 16 were followed up for less than 2 years. Therefore, we cannot simply use 90 for the number of patient-years (45 patients × 2 years) in the initial 2 years. Please refer to the following recalculated data (Fig. 1):

- Initial 2 years post-GKS: 70.0 patient-years = (29 patients × 2 years) + (16 patients × various follow-up periods)
- After the initial 2 years post-GKS: 82.4 patient-years = (29 patients × various follow-up periods) – (29 patients × 2 years)

So, the recalculated annual hemorrhage rates after GKS are:

- Initial 2 years post-GKS: 4.29% = 3 hemorrhage episodes/70.0 patient-years
- After the initial 2 years post-GKS: 3.64% = 3 hemorrhage episodes/82.4 patient-years

We are preparing an erratum notice that will reflect changes throughout our article. The original Figure 2 showing changes over time in the post-GKS annual hemorrhage rate has been revised (Fig. 2) and is shown below.

We still can conclude that GKS is effective in reducing the rate of recurrent hemorrhage in patients with brainstem CMs. In our study, the annual hemorrhage rate decreased from 31.3% to 4.29% within 2 years and further decreased to 3.64% after 2 years.

Certainly, we agree that the positive therapeutic effect of GKS on intracranial CMs has been confirmed by many studies, and that a randomized controlled prospective multicenter trial is necessary to compare the effec-
tiveness between different treatment methods. In the field of brainstem CM therapies, we still have a lot of work to do in the future.

**References**


**Disclosure**

The authors report no conflict of interest.

**Current Study**

To gain insight into the impact of pregnancy on cra-
niospinal hemangioblastomas and associated cysts in VHL, we prospectively evaluated female patients with VHL disease of anticipated reproductive age (16–35 years) with serial (at 6-month intervals except during pregnancy) longitudinal clinical and MRI over long-term follow-up (mean follow-up 7.5 ± 2.3 years [± SD]). We compared the radiographic development and progression of 177 craniospinal hemangioblastomas and 28 associated cysts in patients with VHL disease who became pregnant (pregnancy cohort; 9 patients with 13 pregnancies) with those patients who did not become pregnant (nonpregnancy cohort; 27 patients). We found that there was no increase in hemangioblastoma or hemangioblastoma-associated cyst development or progression (growth) during pregnancy compared with the nonpregnancy cohort or nonpregnant periods in the pregnancy cohort. Finally, there were no VHL-related complications associated with pregnancy or delivery in these patients.

Frantzen and Colleagues’ Study

In their Letter to the Editor, Dr. Frantzen and colleagues discuss 2 recent studies that suggested that pregnancy is associated with hemangioblastoma progression in patients with VHL. Because the study by Abadie and colleagues\(^1\) mentioned has not been published (data were presented at a medical symposium and we do not have access to that information), we can only comment on the study by Frantzen and colleagues.\(^3\) The Frantzen study retrospectively examined records from VHL centers in the Netherlands of 29 patients with VHL who became pregnant 48 times (49 newborns) between the years 1966 and 2010 (40% became pregnant before 1990). Only 15 pregnancies (31%) had imaging records available to assess the effect on craniospinal hemangioblastoma progression. Overall, they found that 17% of all pregnancies had VHL-related complications, including 3 patients (10%) who had craniospinal hemangioblastoma–related complications. Finally, they found that cerebellar hemangioblastomas (not hemangioblastomas in other regions of the nervous system) had a significant (p = 0.049) change in “progression score” before and after pregnancy.

Study Differences

There are several critical methodological and patient disparities between the study by Frantzen and colleagues\(^3\) and ours that underlie the differences in findings, conclusions, and recommendations. These study disparities include study design, number of tumors analyzed, method for determining tumor progression, presence of a control group, and VHL diagnosis in patients.

Study Design. The Frantzen report is a retrospective analysis of patient records collected over a 44-year span from multiple VHL centers (the mean length of follow-up is not reported). Because of the retrospective nature of that study, it has a number of associated inherent limitations, which is the reason that we chose to perform a prospective analysis to serially and systematically study patients with VHL longitudinally over a prolonged period of time. The serial clinical and imaging follow-up in our study was designed specifically to determine the impact of pregnancy on the natural history of craniospinal hemangioblastomas in VHL.

Along these lines, a particularly potent limitation of retrospective nature of the Frantzen study is that it did not use a systematic approach to the MRI of hemangioblastomas. Patients had “1 or 2 measurements during the 4 years before pregnancy and 1 or 2 measurements within 4 years of delivery.”\(^3\) Neither the rate of hemangioblastoma (or cyst) development nor the rate of tumor (or cyst) growth surrounding pregnancy was quantified. Moreover, the precise timing and length of imaging follow-up after pregnancy, which is critical to the veracity of the data, are not reported. Consequently, it is not possible to form definite conclusions about the actual effect of pregnancy on development and growth/progression of hemangioblastomas from their study.

Number of Tumors Analyzed. While both studies did not contain a large number of patients, there was a large number of craniospinal hemangioblastomas analyzed in our series of patients (177 hemangioblastomas). Each hemangioblastoma in these patients represents an independent longitudinal data set that can be impacted by a systemic event, such as pregnancy, and used for comparative purposes. Specifically, analysis reveals that the number of tumors in our study is sufficient to detect medium and large effects in both paired and unpaired analyses. It is not clear from the Frantzen report how many, or if any craniospinal hemangioblastomas were individually analyzed for progression.

Method for Determining Tumor Progression. Frantzen and colleagues used a progression score that did not actually quantify growth of hemangioblastomas during pregnancy. Because tumor and/or cyst size and growth (progression) underlie symptom formation,\(^2,7\) the objective of our study (as stated in the manuscript) was to determine if pregnancy affected craniospinal hemangioblastoma development or growth. Consequently, because hemangioblastomas enhance vividly and discretely with contrast administration, we used MRI volumetric analysis to determine tumor development/growth as it is the most precise method for assessing hemangioblastoma development/growth.\(^2\)

Control Group Analysis. The Frantzen study did not include controls. To determine if pregnancy impacts hemangioblastoma development and growth, it is critical to have an age-matched, nonpregnant female cohort for comparison in a prospective manner. Furthermore, because of the saltatory growth pattern that hemangioblastomas exhibit, it is essential to serially observe patients who become pregnant for a prolonged period of time after pregnancy (years), which was done in our study, to determine if hemangioblastomas develop or progress at a greater rate during preganant periods compared with nonpregnant periods.

VHL Diagnosis in Patients. All of our study patients knew they had VHL at the time of first pregnancy and that they were in a VHL tumor surveillance program,\(^3\) but 59% of patients in the Frantzen report did not know they had VHL at the time of first pregnancy. Lack of VHL
diagnosis in a patient before pregnancy has potentially life-threatening implications associated with the effects of VHL-related lesions. Physicians with patients not diagnosed with VHL will miss early signs and symptoms and/or laboratory/ imaging findings of VHL-related lesions, which can lead to the pregnancy-related complications seen in the Frantzen study. These complications were not seen in our patients, who were all diagnosed with VHL before pregnancy and in a surveillance program.

Clinical Implications

Based on their study demonstrating a change in progression score for cerebellar hemangioblastomas, Frantzen and colleagues recommended additional imaging of the cerebellum at 4 months’ gestation and before delivery. It is not apparent why these imaging time points were recommended based on the data contained in their report or data from natural history studies of VHL-associated hemangioblastomas. Furthermore, it is not clear if Frantzen and colleagues would recommend resection of asymptomatic hemangioblastomas that demonstrate radiographic progression during pregnancy, which would put the mother and fetus at significant unnecessary risk.

Nevertheless, because VHL-associated craniospinal hemangioblastomas grow in a saltatory pattern and because radiographic progression is not an indication for surgical resection of craniospinal hemangioblastomas, we would not recommend removal of hemangioblastomas that demonstrate growth on MRI during pregnancy unless they were symptomatic. Consequently, it is not clear how additional imaging during pregnancy enhances the management of asymptomatic pregnant patients. Furthermore, as we described in our report, MRI with contrast enhancement (the most accurate modality to determine hemangioblastoma progression) during pregnancy is currently not feasible, based on the lack of established guidelines to safeguard the fetus.

Because we did not find that pregnancy accelerated the development or growth of craniospinal hemangioblastomas compared with controls or in pregnant patients during nonpartum periods, we recommended that “serial imaging of prospective mothers with VHL disease before conception and after delivery, with resection of symptomatic hemangioblastomas appears to be a most reasonable management approach.” This recommendation is based on the known natural history of VHL-associated hemangioblastomas, the lack of guidelines for fetal safety for contrasted MRI during pregnancy, and the fact that serial clinical observation permits early symptom detection and safe resection of VHL-associated hemangioblastomas, when necessary.

Conclusions

Based on currently available natural history data for craniospinal hemangioblastomas, we continue to recommend serial clinical evaluation during pregnancy with imaging performed before conception and after delivery, as well as contemporaneously during pregnancy with development of any neurological symptoms/signs (similar to the management of other nonpregnant patients with VHL). Until objective parameters (for example, tumor/cyst size, tumor/cyst growth rate, or other features) can be identified to predict hemangioblastoma symptom formation and the time course over which symptoms will develop in patients with VHL, this management paradigm will avoid unnecessary imaging and surgery, maximizing the safety of mother and fetus.

References


Decompression for ischemia

To The Editor: We read with interest the article by Kenning et al. (Kenning TJ, Gooch MR, Gandhi RH, et al: Cranial decompression for the treatment of malignant
intracranial hypertension after ischemic cerebral infarction: decompressive craniectomy and hinge craniotomy. Clinical article. *J Neurosurg* 116:1289–1298, June 2012). Decompressive operations were performed in 28 patients with ischemic cerebral infarction; 19 (68%) underwent decompressive craniectomy, with a striking 89% survival, and 9 had hinge craniotomies, with 56% survival. The authors report a *p* value of 0.04 for this association, which was apparently based on a 2-tailed chi-square statistic without Yates’ correction. This can be quite misleading for small numbers. The Fisher exact test gives *p* > 0.06, and the chi-square test with Yates’ correction results in the much larger *p* value of 0.12 (http://www.graphpad.com/quickcalcs/ConfInterval1.cfm). At least 57 tests of statistical significance, each with an accepted threshold of 0.05, are mentioned in this publication. Should not a lower *p* value have been required because of so many tests of significance? Not surprisingly, patients who underwent decompressive craniotomies required cranioplasty more often (100%) than did those who had hinge operations (20%). Many neurosurgeons would not consider the need for cranioplasty after craniectomy for decompression to be included in postoperative complications as shown in the authors’ Table 9.

Although all deaths in each group occurred when supportive care was withdrawn “… due to lack of early clinical improvement and in accordance with the patient’s previously stated wishes,” all patients who died had “excellent postoperative [intracranial pressure] control.” Although 4 (44.4%) of 9 families whose loved ones underwent hinge operations chose to withdraw care, only 2 (10.5%) of the 19 families of patients who underwent decompressive craniotomies made that same choice. Were there differences not reflected in the clinical characteristics and neuroimaging that were reviewed? This seems quite likely. Or did the surgeons for the 2 groups, who had chosen different types of surgical decompression, also have different perceptions of prognosis or different tolerations of survival with neurological impairment and therefore communicated different messages to the families? Whether or not the cranial openings for the patients in each category were identical, those whose bone flaps were left beneath the scalp were definitely provided less space for expansion, by the exact volume of their respective bone flaps.

The study spanned 52 months, but at the 6- to 12-month evaluations only 3 patients were in the hinge group and 9 were in the decompressive group for functional evaluations (Glasgow Outcome Scale and modified Rankin Scale), and beyond 12 months only 1 and 5 patients, respectively, were available in the 2 categories. Some of the data in this study suggest a better outcome with hinge operations at the 1- to 3-month evaluations after surgery, but only then if survival data are ignored. The statement in the abstract that hinge operations “resulted in superior long-term functional outcomes …” is not consistent with the presented evidence. Subdural effusion, subarachnoid blood, and progression of intraparenchymal hematoma being observed more commonly after decompressive craniotomies are not easy to logically interpret but are probably best attributable to unidenti-
ing a routine adjustment for multiple comparisons is the universal null hypothesis that chance serves as the first-order explanation for phenomena that are being observed. This hypothesis undermines the basic premise of empirical research that what is being observed is not random and instead follows natural laws that are being studied through observation. Therefore, a policy of not making adjustments for multiple comparisons is preferable because it will lead to fewer errors of interpretation when the data being studied are not random but have a pattern governed by natural laws.

2) Regarding the inclusion of the requirement for cranioplasty in Table 9: Postoperative complications: Although the necessity of a delayed cranioplasty as an obligate sequelae of a decompressive craniectomy may not be considered a complication in the conventional sense, this secondary operation is an additional surgical procedure with attendant morbidity as well as a not insignificant cost to the health care system. The incidence of complication with cranioplasty is often understated, and in our published series, we had a 34% immediate postoperative complication rate. The avoidance of a delayed cranioplasty by the initial utilization of a hinge craniotomy for adequate decompression holds obvious advantages.

3) Regarding the difference in inpatient mortality rates: We appreciate the recognition of the “excellent postoperative [intracranial pressure] control” that was achieved in both the hinge craniotomy and decompressive craniectomy groups, as is demonstrated in Table 6 in our article. The differences in the inpatient mortality numbers are likely most reflective of the small study size, as the inclusion of a few additional patients in each group could potentially alter the results. In order to prevent selection and observer bias from confounding our analysis, we confirmed that the baseline demographics and clinical status (Table 5) as well as the preoperative radiographic studies (Table 11) were similar between the groups.

4) Regarding the statement of “Whether or not the cranial openings for the patients in each category were identical, those whose bone flaps were left beneath the scalp were definitely provided less space for expansion, by the exact volume of their respective bone flaps.”: Our paper provides the measurements of the maximal cranial opening or craniotomy diameter (Table 12) to show that the cranial defects created were similar between the groups, and that equivalent postoperative intracranial pressure (ICP) control was not simply obtained by making the cranial opening larger in the hinge craniotomy group. Leaving the bone flap in place does indeed reduce the absolute volume of cerebral expansion (Table 11). It appears, however, that this reduction is not deleterious to ICP control despite leaving the hinged bone plate in place.

5) Regarding our assessment that the long-term functional data appear to favor the hinge craniotomy group is “not consistent with the presented evidence.”: Although we acknowledge that the statistical power of our data is limited by sample size and the number of patients lost to follow-up, hinge craniotomy functional outcome data were better in the 1- to 3-month postoperative period and comparable at every other postoperative patient follow-up visit.

6) Regarding the potentially detrimental effect of “unconstrained extracerebral herniation permitted by decompressive craniectomy”: The concern for parenchymal hemorrhage expansion as well as for venous congestion and associated hemorrhage due to the brain’s cortical surface being compressed against calvarial edges as “mushrooms” out of a cranial defect are long-acknowledged and well-known concerns with decompressive craniectomy. Examining a postoperative CT scan after a cranial decompression and citing the significant degree of extracranial brain herniation as evidence for the value of decompressive craniectomy and allowing maximum brain swelling to occur is misguided in our view. Instead, we believe that the brain will, to a degree, fill the container that it is given. If sufficient ICP control and functional outcomes can be obtained without permitting maximal brain deformation, then would such a procedure not be more desirable in comparison with decompressive craniectomy?

7) Regarding the “authors’ strong belief in the equivalency or superiority of hinge operations” and the assertion that instead the published data are instead “more supportive of genuine decompressive craniectomy”: The value of hinge craniotomy in the treatment of medically refractory ICP elevation has been suggested in a prior published series of patients with malignant intracranial hypertension predominantly attributable to trauma. Our preliminary data, in the ischemic setting, suggests that hinge craniotomy is at least a comparable procedure to decompressive craniectomy. We now believe that hinge craniotomy is a promising and effective alternative that may reduce the obligate morbidity of decompressive craniectomy. As we stated in the conclusion of our paper, the promise of hinge craniotomy as a less morbidity and more cost-effective therapy, as suggested by our data, awaits confirmation in a larger, prospective, randomized study.

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Herpes encephalitis

To The Editor: We read with a great interest the report by Tang et al. of herpes simplex encephalitis (HSE) following microvascular decompression for trigeminal neuralgia (Tang H, Falcone F, Eljamel S: Herpes simplex encephalitis following microvascular decompression for trigeminal neuralgia. Case report. J Neurosurg 118:530–533, March 2013). The patient was diagnosed with viral encephalitis after failure of antibiotic treatment for suspected bacterial meningitis and the appearance of a vesicular rash on her torso, which prompted adequate treatment with acyclovir with a good outcome. The authors reviewed the literature and found similar cases of this unusual complication, mostly after surgery on cranial nerves. Since this condition can have devastating consequences if overlooked and left untreated, we would like to share a similar experience we recently encountered in a patient who presented with subarachnoid hemorrhage (SAH) due to a ruptured intracranial aneurysm.

Our patient was a 51-year-old woman who suffered from an SAH. Her Glasgow Coma Scale score was 13 and she had aspiration pneumonia. An external ventricular drain was placed and antibiotic therapy was started. A cerebral angiogram revealed a right V4 segment aneurysm and a small posterior inferior cerebellar artery aneurysm. The patient underwent Pipeline (ev3/Covidien) assisted coil embolization of the vertebral artery aneurysm, and a small posterior inferior cerebellar artery aneurysm. After neurosurgical intervention for trigeminal neuralgia (Tang H, Falcone F, Eljamel S; Herpes simplex encephalitis following microvascular decompression for trigeminal neuralgia (Tang H, Falcone F, Eljamel S: Herpes simplex encephalitis following microvascular decompression for trigeminal neuralgia. Case report. J Neurosurg 118:530–533, March 2013). The patient was diagnosed with viral encephalitis after failure of antibiotic treatment for suspected bacterial meningitis and the appearance of a vesicular rash on her torso, which prompted adequate treatment with acyclovir with a good outcome. The authors reviewed the literature and found similar cases of this unusual complication, mostly after surgery on cranial nerves. Since this condition can have devastating consequences if overlooked and left untreated, we would like to share a similar experience we recently encountered in a patient who presented with subarachnoid hemorrhage (SAH) due to a ruptured intracranial aneurysm.

Fig. 1. A: Coronal T2-weighted MR image showing hyperintensity and fullness within the left temporal lobe and insula. B and C: Axial apparent diffusion coefficient (ADC) map (B) and diffusion-weighted (DW) MR image (C) showing hyperintensity on the ADC map and slight changes on the DW image, suggesting an inflammatory process rather than an ischemic lesion. D: Axial FLAIR MR image showing signal changes within the left mesial temporal lobe.

Type 2), confirming the diagnosis. The patient and family did confirm at this point a previous history of herpes infection. Treatment with acyclovir was continued, and the patient had no further neurological decline. Her clinical condition improved after completion of treatment for herpes encephalitis, but she sustained permanent speech difficulties.

Despite being the most common cause of sporadic encephalitis, herpes encephalitis is a rare complication after neurosurgical procedures. Although it might be overlooked and underdiagnosed in the setting of an acute neurosurgical diagnosis or following surgery, a high index of suspicion is needed to prevent delay in diagnosis and initiation of treatment and avoid permanent neurological deficit. In our case, the symptoms were initially attributed to vasospasm as the patient did have evidence angiographic vasospasm. However, when her condition failed to improve following treatment of vasospasm, further workup was initiated, leading to the correct diagnosis and appropriate treatment. Although the differential diagnosis in similar cases is broad and several conditions can present with a similar picture, the electroencephalographic and MRI findings were extremely helpful in establishing diagnosis. The CSF analysis was not very helpful as there was an inflammatory component due to SAH, and both conditions can present with a similar pattern. Our patient did not have any skin manifestations. It is certainly pos-
Possible that the steroids she was taking contributed to the development of herpes encephalitis, as dexamethasone has a high glucocorticoid effect and therefore leads to immunosuppression. In addition, the physiological stress of her acute illness and hospitalization might have also played a role in immunosuppression. Fortunately, after adequate treatment was initiated, our patient’s condition did not decline any further, and this letter is meant to reiterate the importance of keeping a high index of suspicion for herpes encephalitis in patients with SAH or who have undergone neurosurgical procedures, especially when taking steroids, in order to prevent permanent neurological damage and irreversible complications.

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Disclosure

Dr. Hanel reports being a Pipeline proctor for Covidien (all fees paid to the Mayo Clinic).

Reference


Response: We would like to thank Dr. Navarro and colleagues for sharing their case of HSE following SAH. This is yet another example of HSE complicating acute brain conditions such as SAH and neurosurgical procedures as in our case of HSE following microsurgical vascular decompression for trigeminal neuralgia. These two cases emphasize the importance of keeping a high index of suspicion for early diagnosis and treatment.

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