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Neurosurgery concepts: Key perspectives on intrathecal fluorescein for detecting intraoperative cerebrospinal fluid leak during endoscopic endonasal surgery, spinal intraarterial chemotherapy, oligoastrocytoma classification by *in situ* molecular genetics, and prenatal myelomeningocele closure and the need for cerebrospinal fluid shunt placement

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SENSITIVITY AND SPECIFICITY OF INTRATHECAL FLUORESCIN AND WHITE LIGHT EXCITATION FOR DETECTING INTRAOPERATIVE CEREBROSPINAL FLUID LEAK IN ENDOSCOPIC SKULL BASE SURGERY: A PROSPECTIVE STUDY^[2]

Study Question: What is the diagnostic value of intrathecal fluorescein to identify an intraoperative cerebrospinal fluid (CSF) leak during endoscopic endonasal skull base surgery?

The authors review a prospectively accrued database of consecutive patients to assess the effectiveness of the off-label routine use of intrathecal fluorescein to

detect an intraoperative cerebrospinal fluid (CSF) leak during endoscopic endonasal skull base surgery. Patients were pretreated with intravenous dexamethasone and diphenhydramine prior to administration of 25 mg of fluorescein injected immediately before surgery via lumbar puncture or lumbar drain. Basic white light illumination from the endoscope was used to identify the presence of unstained or fluorescein-tinged CSF during the procedure. A dural reconstruction algorithm

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developed by the authors, based on leak severity and location/size of the skull base defect, was used for skull base reconstruction. A valsalva maneuver was then performed to assess reconstruction integrity and ensure no visualization of fluorescein at the conclusion of the procedure. Temporary postoperative CSF drainage was performed with duration dependent on the treated pathology. Lesion type and location, endonasal approach corridor, reconstruction method, operative time, and presence of postoperative CSF leak were analyzed.

A total of 419 patients were included in this study over nearly a 10-year period at a single institution. Of 269 patients who had an identified intraoperative CSF leak, 250 (92.9%) of them had fluorescein-stained CSF identified during the procedure and were labeled as true positives. The remaining 19 (7.1%) patients had clear, unstained CSF that was identified and were categorized as false negatives. There were no false positives. This data generated the sensitivity and specificity of low-dose intrathecal fluorescein to detect an intraoperative CSF leak to be 92.9% and 100%, respectively. An overall total of 7 (1.7%) patients developed a postoperative CSF leak within the 1st month. All of these patients were true positives. Lesion type, approach corridor, reconstruction method, and operative time were not risk factors predictive of a postoperative CSF leak.

Perspective: While retrospective, this well-organized study underscores the significance of intraoperative identification of a CSF leak during endoscopic endonasal skull base surgery. The authors note that intrathecal fluorescein can help identify intraoperative CSF leaks with high sensitivity and specificity. The overall false negative rate of 4.5% was hypothesized to be due to arachnoidal scarring, lumbar stenosis, inadequate time for circulation, and/or unclear physiology. None of the false negative patients developed postoperative CSF leaks, substantiating the 25 mg dosage of fluorescein. No side effects related to intrathecal fluorescein were noted. Recognized limitations of this study include lack of a randomized controlled study, inability to identify patients with small, postoperative leaks that spontaneously resolve, and absence of an objective measurement tool to assess for intraoperative leaks.

Multiple other high-volume institutions that perform such surgery without routine fluorescein administration report similar intraoperative and postoperative CSF leak rates while avoiding the infrequent side effects of fluorescein, dexamethasone, and diphenhydramine, as well as the rare complications of accessing the lumbar cistern via needle or catheter. In addition, 150 of the 419 patients in this article did not have an intraoperative CSF leak, negating any potential benefit from intrathecal fluorescein. We recognize the advantage of intrathecal fluorescein and favor its judicious use to help identify unclear leak sites in patients with suspected spontaneous or traumatic CSF leaks. Furthermore, we

have observed that good pulsation of the reconstruction at the conclusion of surgery usually confirms a watertight closure and may provide an additional objective data point to ensure good coverage of an iatrogenic known dural defect. A randomized controlled study would be needed to provide stronger conclusions on the utility of routine intrathecal fluorescein.

Summary Written by: Anand V Germanwala, MD

SPINAL INTRAARTERIAL CHEMOTHERAPY: INTERIM RESULTS OF A PHASE I CLINICAL TRIAL^[1]

Study Question: Is spinal intraarterial chemotherapy (SIAC) safe and feasible for the treatment of metastatic spinal epidural tumors in patients who have exhausted standard therapeutic options?

Patsalides *et al.* reported the interim outcomes of an ongoing single arm prospective Phase I clinical trial investigating the role of SIAC for advanced metastatic spinal tumors that are no longer candidates for resection or radiotherapy. Patients older than 18 years of age with metastatic spinal disease causing cord compression on imaging disease causing cord compression on imaging were included in the study. Determination of those who are not candidates for resection or radiotherapy was made based on prior consensus among radiation oncologists and neurosurgeons. Those with severe cord compression where the subarachnoid space was completely occluded were excluded. In addition, patients with <3 months life expectancy or have the same segmental arteries supplying the spinal cord and the tumor on diagnostic angiography were excluded. Nine patients with 7 different tumor types underwent selective spinal angiography and received 19 IA treatments of melphalan, an alkylating agent. After diagnostic angiography of segmental arteries at the level of cord compression, including one level above and below, the ventral branch of the segmental arteries were occluded with coils to maximize chemotherapy delivery along the dorsal branch supplying the tumor while minimizing its delivery to adjacent healthy tissue.

Melphalan was chosen based on its established and promising IA use in a variety of other malignancies including colorectal metastases to the liver and lung metastases. Total injected dose was 16 mg/m², representing the recommended systemic dose. Patients were allowed up to 3 SIAC procedures in 1 sitting, repeated up to ever 3 weeks. Patients were followed up with, at minimum, one spinal magnetic resonance imaging (MRI) with contrast at 4 weeks following SIAC to determine possible complications and tumor control. Follow-up ranged from 1 to 7 months. One patient experienced neutropenic fevers, and no other adverse effects were noted. Only 4/9 patients received the planned 3 separate IA treatments.

While tumor size was stable in 7 and decreased in 1, disease progression was noted at spinal levels where SIAC was not given.

Perspective: The authors report their experience thus far in an ongoing Phase I trial utilizing SIAC for progressive spinal metastasis with cord compression in patients for which conventional therapies have failed. Although advances in microsurgical technique and radiotherapy have improved the rates of tumor control for patients with metastatic spinal disease, there remains a subset of patients that fail or are no longer candidates for standard therapies. For these patients, prognosis remains grim, and innovative treatment modalities are essential, as inevitable neurological deterioration secondary to progressive cord compression will occur.

Selective IA delivery of chemotherapy offers a number of pharmacokinetic advantages of maximizing local drug concentration and minimizing systemic toxicity. While its use in other malignancies has been reported, this is the first report of its application in spinal metastasis. Early results are promising, with only 1 incidence of myelosuppression and neutropenic fevers. In addition, tumor control at the levels treated was seen in all but 1 patient. Indeed, efficacy should be interpreted with caution due to short length of MRI follow-up due to advanced stage of disease in patients. Moreover, the optimization of SIAC for the treatment of these metastatic lesions requires further investigation. While melphalan has demonstrated efficacy by IA route in other cancers, clinical response is likely tumor-dependent, and the present study included a variety of metastatic tumor types. Optimal patient selection to minimize complications and identification of ideal chemotherapeutic agents for differing tumor types requires further elaboration from larger data sets. However, despite the small study size and limited follow-up, the study highlights SIAC as a novel therapeutic that can benefit patients who have exhausted their therapeutic options.

Summary Written by: Winward Choy, BA and Zachary A Smith, MD

FAREWELL TO OLIGOASTROCYTOMA: IN SITU MOLECULAR GENETICS FAVOR CLASSIFICATION AS EITHER OLIGODENDROGLIOMA OR ASTROCYTOMA^[3]

Study Question: What is the impact of molecular genetics in glioma classification and the subsequent treatment of these patients?

The authors evaluated 43 oligoastrocytoma specimens with the presence of the IDH1 R132H mutation as well as at least 1 cm² of intermingled histology. The specimens were then evaluated with immunohistochemistry for

the ATRX and p53 mutations. Fluorescence *in situ* hybridization was used for analysis of the 1p/19q co-deletion. The authors confirmed that all tumor cells with p53 or ATRX mutation or 1p/19q co-deletion also stained for the IDH1 R132H mutation. The authors identified 30 cases with the IDH1 R132H exclusively in histology consistent with oligodendroglioma. This portion of the tumor displayed the 1p/19q co-deletion. In contrast, the “astrocytic” portion of these specimens was devoid of the IDH1 R132H, p53, or ATRX mutations or 1p/19q loss. This “astrocytic” portion was consequently inferred to be reactive. The authors also identified 11 cases with both ATRX and p53 mutations without 1p/19q co-deletion, indicative of an astrocytoma despite some areas of oligodendroglial histology. One case displayed 1p/19q co-deletion in both the astrocytic and oligodendroglial portions without the ATRX or p53 mutations and was interpreted as an oligodendroglioma. The last specimen was resected from a patient with a prior history of irradiation and displayed the ATRX and p53 mutations as well as the 1p/19q co-deletion in both the astrocytic and oligodendroglial portions of the specimen. Of note, radiation has previously been associated with p53 and ATRX mutations, which may explain the findings in this specimen.

Perspective: The authors of this study aim to evaluate the diagnosis of oligoastrocytoma via *in situ* molecular genetics. Recent literature establishes that pure astrocytomas display mutations in both ATRX and TP53, whereas true oligodendrogliomas display 1p/19q co-deletion. Oligodendroglioma patients typically display a significantly longer overall survival as compared to patients with astrocytoma. This difference partly correlates with response to chemotherapy, as seen in patients with the 1p/19q co-deletion. The diagnosis of oligoastrocytoma was previously defined by the WHO as a mixture of histologic features of astrocytoma and oligodendroglioma on histology. However, no guidelines exist on the minimal percentage of each subtype complicated by the typically minor total tumor fraction provided intraoperatively.

This study provides data that delineates between the diagnosis of oligodendrogliomas and astrocytoma beyond histology alone. Molecular genetics will serve as a key component to the diagnosis of gliomas. Recent data from such trials as Radiation Therapy Oncology Group 9802 indicate that patients with WHO Grade II gliomas may benefit from chemotherapy and/or radiation. As upcoming trials look to study the efficacy of temozolomide versus procarbazine, lomustine, and vincristine chemotherapy in lower grade gliomas, differences in outcome in astrocytic versus oligodendroglial subtypes using the molecular genetic distinctions as described in this study may help distinguish the true role of these treatment regimens. In

addition, the use of molecular genetics will certainly play a key role in differentiating Grade IV from lower grade gliomas, which will impact enrollment into future clinical trials.

Summary Written by: Jonathan H Sherman, MD

PRENATAL MYELOMENINGOCELE CLOSURE AND THE NEED FOR CEREBROSPINAL FLUID SHUNT PLACEMENT^[4]

Study Question: What are the 1 year outcomes from the Management of Myelomeningocele Study (MOMS) trial? Are specific risk factors associated with benefit from prenatal surgery?

MOMS was a multicenter randomized trial comparing both safety and efficacy of prenatal and postnatal closure of myelomeningocele (MMC).^[1] Pregnant women with a fetus prenatally diagnosed with MMC between 19 and 25 weeks of gestation were randomized at one of the 3 maternal-fetal surgery centers to either prenatal or postnatal surgical MMC repair. In the trial, the primary outcome was defined as a composite of fetal loss or any of the following: Infant death, cerebrospinal fluid (CSF) shunt placement, or meeting prespecified criteria for shunt placement before 1 year of age. In this paper, the authors examine primary outcome, actual shunt placement, and shunt revision surgery rates for patients who underwent prenatal and postnatal repair. The criteria for placement of CSF shunt were re-examined. The authors noted that during almost a decade of recruitment, the management of pediatric hydrocephalus had changed. In the published cohort, about one-fourth of patients in the prenatal surgery group and one-tenth of patients in the postnatal surgery group met the criteria for CSF shunt placement, but did not have actual CSF shunt placement. This observation led the authors to conduct this current investigation (it is important to note there was a blinded adjudication process for the evaluation of hydrocephalus in the MOMS trial). The authors also speculate whether it is possible to identify which fetuses are likely or unlikely to benefit from prenatal surgery. Logistic regression was used to examine for interactions between the type of MMC repair surgery and prenatal risk factors for shunt placement. These included MMC lesion level, gestational age, amount of hindbrain herniation, and ventricle size.

The MOMS trial was stopped early with demonstrated efficacy of prenatal surgery when 158 of 183 pregnancies were reported. Here, the authors report on results from 183 pregnancies: 91 women with prenatal surgery and 92 women randomized to postnatal surgery. Using the definition above, the primary outcome occurred in 73% of infants in the prenatal surgery group and 98% of infants in the postnatal surgery group ($P < 0.0001$). Actual shunting

rates were 44% and 84%, respectively ($P < 0.0001$). For the decisions of actual shunt placement, it appeared that treating pediatric neurosurgeons incorporated evaluation of clinical signs of increased intracranial pressure rather than relying on progressive ventriculomegaly on radiographic findings alone. The authors revised the most commonly met criteria to include overt clinical signs of increased intracranial pressure, such as split cranial sutures, bulging fontanelle, or sun-setting eyes, in addition to increasing head circumference or hydrocephalus. Using these proposed modified criteria, only three patients in each group met criteria, but did not undergo actual shunt placement. For the revised composite outcome, there was a difference between the prenatal and postnatal surgery groups: 49.5% versus 87.0% ($P < 0.0001$). In the prenatal surgery group, 20% of those with ventricle size < 10 mm at initial screening, 45.2% of those with ventricle size of 10–15 mm, and 79.0% of those with ventricle size ≥ 15 mm received a shunt. In the postnatal group, 79.4%, 86.0%, and 87.5%, respectively, underwent CSF shunt placement ($P = 0.02$). Only ventricle size was significantly associated with CSF shunt placement or with the revised composite outcome, with odds ratios of 1.46 (95% confidence interval [CI] 1.20–1.79) and 1.57 (95% CI 1.26–1.97), respectively. Lesion level, gestational age, sex, and degree of hindbrain herniation were not significantly associated with receiving CSF shunt on multivariable logistic regression.

Perspective: This study reported on updated results from an important randomized trial of prenatal versus postnatal surgery for repair of MMC. Of the prenatal risk factors that may predict the future need for CSF shunt placement, only ventricle size was significantly associated with the need for shunting. Larger ventricles at initial screening are associated with increased need for CSF shunting among those in the prenatal surgery group. From this knowledge, the authors conclude that during prenatal counseling for parents, care should be exercised in predicting beneficial effects on the need for shunting after undergoing fetal surgery for MMC in patients with ventricles 15 mm or larger at the time of initial screening; prenatal surgery does not appear to improve outcome in this group. The revised criteria proposed in this study may be useful as guidelines for treating hydrocephalus in this group. This study found that pediatric neurosurgeons are more likely to rely on clinical signs of increased intracranial pressure by assessment of the anterior fontanelle or cranial sutures than on traditional radiological signs of ventriculomegaly or growth of head circumference for treating hydrocephalus. This finding is in keeping with the body of contemporary pediatric neurosurgery literature. Postnatal criteria of surgical intervention for hydrocephalus have been evolving, both with the practice of permissive ventriculomegaly and with the current interest in and evaluation of endoscopic

third ventriculostomy/choroid plexus coagulation as an attractive alternative to CSF shunting in MMC patients. Overall, there appears to be a trend toward reduction in CSF shunting rates for patients with MMC in the past decade. The field is in evolution, and our new understanding is yet to be completely defined.

Summary Written by: Sandi Lam, MD MBA

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Conflicts of interest

There are no conflicts of interest.

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