

Neurosurgery Concepts

Neurosurgery concepts: Key perspectives on deferoxamine and chronic hydrocephalus from intraventricular hemorrhage, laboratory dissection training in neurosurgical residency, tetanus toxoid and dendritic cell vaccines for glioblastoma, and intracranial hypertension after surgery for craniosynostosisWinward Choy, Angela M. Bohnen, Panayiotis Pelargos¹, Sandi Lam², Isaac Yang¹, Zachary A. SmithDepartment of Neurosurgery, Feinberg School of Medicine, Northwestern University, Chicago, IL, ¹Department of Neurosurgery, David Geffen School of Medicine, University of California, Los Angeles, CA, ²Department of Neurosurgery, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, USAE-mail: Winward Choy - winward.choy@northwestern.edu; Angela M. Bohnen - angela-bohnen@northwestern.edu; Panayiotis Pelargos - ppelargo@uci.edu; Sandi Lam - sandilam@gmail.com; Isaac Yang - iyang@mednet.ucla.edu; *Zachary A. Smith - zsmith@nmff.org

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Key Words: Craniosynostosis, deferoxamine, glioblastoma, hydrocephalus, tetanus**DEFEROXAMINE ALLEVIATES CHRONIC HYDROCEPHALUS AFTER INTRAVENTRICULAR HEMORRHAGE THROUGH IRON CHELATION AND WNT1/WNT3A INHIBITION^[4]****Study Question:** Does deferoxamine (DFX) alleviate posthemorrhagic chronic hydrocephalus (PHCH) by chelation of iron and suppression of the Wnt1/Wnt3a cellular pathway?

To explore the putative role and mechanism by which iron may mediate PHCH resultant from intraventricular hemorrhage (IVH), the authors utilized a PHCH animal model comprising rats receiving intraventricular injections of blood (IVH) or iron (Fe) either alone or in combination with DFX, an iron chelator shown to be neuroprotective in intracerebral hemorrhage. Intraventricular injections of saline were used as controls. Blood and iron injections increased rates of hydrocephalus significantly at 1 (80% and 60%) and 4 (80% and 70%)

weeks compared to saline controls, which did not produce any hydrocephalus. Treatment with DFX drastically decreased rates of hydrocephalus down to 20% and 10% when given alongside IVH or Fe, respectively. DFX treatment additionally significantly decreased the severity of hydrocephalus following IVH and Fe injections. DFX treatment significant decreases in CSF iron and brain ferritin levels following blood and iron injections thereby decreases frequency and severity of hydrocephalus following IVH and iron injections. Treatment with DFX decreased elevated Wnt1/Wnt3a messenger RNA and protein levels induced by IVH. Finally, treatment with

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DFX following IVH significantly improved performance on the Water Morris navigation test, a measure of rat behavior.

Perspective: PHCH is a common complication following IVH. Prognosis remains poor resulting in neurological disability and possible mortality. Management is challenging to do limited understanding of the underlying pathogenesis of PHCH. Previous studies have collectively demonstrated (1) Increased iron in mediating posthemorrhagic neurotoxicity, (2) aberrant iron and ferritin levels following hydrocephalus secondary to IVH, (3) subarachnoid fibrosis is key pathological sequelae following intracranial hemorrhage, and (4) Wnt1/Wnt3a is involved with fibrosis in a variety of pathological processes. The present study is the first to describe the role of DFX in the treatment of PHCH and elaborate on the cellular pathway involved. Findings suggest that iron, a product of red blood cell catabolism, may stimulate the Wnt1/Wnt3a pathways, which may be involved with subarachnoid fibrosis, following intracerebral hemorrhage. Importantly, the data demonstrates the therapeutic promise of DFX, which suppresses posthemorrhagic induction of Wnt expression and decreases the severity and frequency of consequent hydrocephalus.

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

THE ROLE OF LABORATORY DISSECTION TRAINING IN NEUROSURGICAL RESIDENCY: RESULTS OF A NATIONAL SURVEY^[3]

Study Question: What is the role of laboratory dissection training in neurosurgery residency programs within the United States?

A detailed survey regarding the use of laboratory dissections and other stimulators and its role in the residency program was sent to 100 neurosurgical programs from the American Association of Neurological Surgeons residency directory database. In total, 65% of institutions responded, 93.8% of which used dissection as an educational adjunct. Common reasons for not utilizing lab time were limitations in: Resident time, available lab director, specimen procurement, and storage. Dissection lab opportunities were variable and included: Scheduled sessions plus independent free time (58.3%), scheduled sessions only (31.7%), and independent resident study time only (10%). Number of scheduled sessions varied from 1 to 26 per year, but most offered 4–6 dissections (39.3%). Formal curriculum for the dedicated laboratory time was common in programs offering > four sessions per year (55%). Approaches taught included cranial approaches (100%), spinal approaches (88.5%), spinal instrumentation (80.3%), endoscopy (50.8%),

microvascular anastomosis (50.8%), and peripheral nerve procedures (34.4%). Eight programs are formulated a grading regimen to evaluate the residents' surgical skills. Funding primarily came from industry alone (33.3%) or from both industry and the institution (33.3%). In addition, to cadaver or animal use, 31 programs (47.7%) also implemented training with other types of simulators. Most programs advised better learning was obtained from the dissections; however, 30.8% of programs did express equal learning from both dissections and simulators. Moreover, 89% agreed that a universal lab curriculum and dissection manual would be beneficial to resident training.

Perspective: Changes in neurosurgical training and healthcare have added obstacles to providing trainee's with comparable levels of exposure as those who proceed the current time. Implementation of the 80-h work week has limited the clinical exposure and operative experience of residents since 2003 and has been met with strong opposition. Surgeons are now faced with increasing scrutiny following the advent of quality improvement initiatives, which may ultimately limit resident autonomy and experience as well. There is a strong need for educational adjuncts to provide trainees with the skills they may not obtain or master during residency. While the present study demonstrates that, most residency programs offer cadaveric dissection sessions and find them useful in improving resident technique and surgical comprehension, only 21 programs had a formal curriculum of incorporation. Neurosurgical education and curriculum adaptation seem to be lesser progressed when compared to our general surgery colleagues. After identifying a significant gap of knowledge in general surgery residents attempting to obtain certification, the Surgical Council on Resident Education task force was developed alongside numerous initiatives aimed at strengthening surgical education and standardizing a national curriculum. For example, the Residency Review Committee for Surgery requires a skills lab implemented into training, and the Surgical Skills Curriculum Task Force works to promote "operating room readiness" among residents by teaching through modules prior to performing in the OR where the participant learns via video, practices, and then is judged for proficiency.^[1] The surgery program at Northwestern University revamped its training structure in 2003 that allowed the organization to not only meet their work-hour restrictions, but also improve the quality of education. The changes promoted better perceived quality of life by trainees, improved American Board of Surgery In-Training Examination scores, and allowed for increased operative experience.^[6]

Neurosurgery is dynamic. Our training should be as well. From a resident's perspective, we ought to look to other specialty for solutions to help ensure competency upon graduation. The most frightening concept is to go

through years of training only to feel inept at the end. The sponge mentality is no longer acceptable as our time in the hospital is limited. Our education needs to be supplemented and excuses such as lack of resident time and lack of resources should not be satisfactory. Requiring lab time and practice prior to contributing to critical portions of a case should be standard, and at some point, one should have to prove themselves technically skillful to their institution and arguably to a National Committee prior to graduation. Mental performance on an oral board exam may not represent the skill behind the applicant.

Summary Written by: Angela M Bohnen, MD

TETANUS TOXOID AND CCL3 IMPROVE DENDRITIC CELL VACCINES IN MICE AND GLIOBLASTOMA PATIENTS^[5]

Study Question: Can vaccine site preconditioning with tetanus/diphtheria (Td) toxoid improve dendritic cell vaccines for glioblastoma (GBM) multiforme?

The authors^[5] conducted a randomized, blinded clinical trial of 12 newly diagnosed GBM multiforme patients who had gross total resection, residual radiographic contrast enhancement on postresection magnetic resonance imaging ≥ 1 cm in diameter in two perpendicular axial planes, and a Karnofsky performance scale score of ≥ 80 were eligible for the clinical study. Patients completed a 6-week course of external beam radiotherapy to a dose of 60 Gy with concurrent temozolomide (TMZ) at a targeted daily dose of 75 mg/day/m. Exclusion criteria were a subtotal resection, use of 5-aminolevulinic acid dye during resection, receiving intensity-modulated radiation therapy, receiving steroid therapy >2 mg/day of dexamethasone, or radiological evidence of progressive disease. The first vaccine was administered on day 21 ± 2 of TMZ cycle 1. The first three dendritic cell (DC) vaccines were administered bi-weekly. At the time of administration of vaccine four, patients were randomized to preconditioning of the vaccine site with either mature, unpulsed, autologous DCs or Td toxoid unilaterally before bilateral vaccination with DCs pulsed with *Cytomegalovirus* phosphoprotein 65 (pp65) RNA. The authors reported that the accumulation of injected DCs in vaccine site draining lymph nodes was significantly greater in patients given Td (two sample *t*-test, $P = 0.049$). Progression-free survival and overall survival were significantly increased in Td-treated patients compared to DC-treated patients (log-rank test, $P = 0.013$). Using both a previously published recursive partition analysis and the European Organization for Research and Treatment of Cancer nomogram for predicting outcome of patients with GBM, the authors found that Td-treated patients exceeded expected survival times by a far greater degree than did DC-treated

patients in both cases by nearly the same amount.

To validate these results and investigate the mechanism of the response to Td preconditioning, the authors performed analogous studies in the mouse model where vaccine sites of Td-immune mice were preconditioned with Td and subsequently administered a bilateral vaccine of ovalbumin RNA-pulsed DCs. Similar to their finding in humans, Td-immune mice that received Td preconditioning had a 3-fold increase in DCs within the afferent inguinal lymph nodes (two sample *t*-test, $P = 0.0001$). The authors found that this effect is mediated by CD4+ T cells (*post-hoc* Tukey *t*-test, $P = 0.005$) and is generalizable to other CD4+ T-cell-dependent protein antigens (*post-hoc* Tukey *t*-test, $P < 0.05$). Unilateral Td preconditioning was also observed to increase DC migration bilaterally in both humans and mice. Furthermore, the ability of Td preconditioning and CD4+ T-cells to increase DC migration is dependent upon the expression of chemokines CCL3 (two sample *t*-test, $P = 0.023$ and $P = 0.029$, respectively) and CCL21 (two sample *t*-test, $P < 0.05$). Similar to the clinical trials, Td preconditioning significantly inhibited tumor growth and increased progression-free and overall survival in an antigen-dependent manner in a mouse subcutaneous tumor model.

Perspective: There is limited data examining the mechanism underlying DC vaccines. In this study, the authors use a randomized, blinded clinical trial and analogous studies in a mouse model to examine the value and underlying mechanism of preconditioning a DC vaccine site with a potent recall antigen, such as Td, for the treatment of GBM. The authors reported that: (1) Preconditioning the DC vaccine site with Td resulted in increased progression-free and overall survival in humans and in mice, (2) preconditioning with Td improved DC migration to lymph nodes bilaterally, and (3) the underlying mechanism of this response was mediated by CD4+ T-cells, CCL3, and CCL21. Their findings suggest that modulation of DC vaccines with Td preconditioning increases the migratory capacity of DCs and may improve clinical outcomes in GBM patients. The authors suggest that DC migration should be further investigated as a predictive biomarker for immunotherapy studies.

Summary Written by: Panayiotis Pelargos and Isaac Yang, MD

INTRACRANIAL HYPERTENSION AFTER SURGICAL CORRECTION FOR CRANIOSYNOSTOSIS: A SYSTEMATIC REVIEW^[2]

Study Question: What is the incidence of intracranial hypertension (IH) after surgery for craniosynostosis?

Craniosynostosis is typically diagnosed and surgically treated in childhood. In untreated patients, up to 8–15% of single suture synostosis and at least 33% of multisuture synostosis patients are affected by elevated intracranial pressure (ICP). Postsurgical IH has also been described to occur up to years after surgical remodeling, such as with restenosis at the surgical site or synostosis at another suture. The incidence and circumstances of such occurrences have been reported in single institution series. The authors performed a systematic review of the English language literature on pediatric patients published between 1985 and 2014 to further characterize the incidence of IH following craniosynostosis surgery.

Seven studies representing over 700 patients met the authors' inclusion criteria for analysis of the primary outcome, which was defined as the incidence of IH after surgery, with confirmation by ICP monitoring. Other studies not included in the calculations reported IH based on lumbar puncture, papilledema findings, and/or clinical symptoms. Other signs and symptoms reported to suggest raised ICP in this population include decreasing head circumference percentiles, worsening head shape deformity, bulging fontanelle/craniectomy defects, headaches, irritability, and developmental delay. The authors found insufficient data on syndromic patients. Patients who had specifically nonsyndromic sagittal synostosis surgery had a 5% incidence of postoperative IH. The incidence of postoperative IH for all nonsyndromic craniosynostosis patients (single or multiple suture involvement) was 4%.

There was a variety of surgical techniques described in the reviewed studies, which limited the ability to describe outcomes based on technique. The authors grouped surgery type by cranial remodeling procedures without frontal orbital advancement versus cranial remodeling procedures with advancement. In postoperative nonsyndromic craniosynostosis patients, 23/471 (5%) patients without craniofacial advancement had IH after surgery while 3/255 (1%) patients developed IH after craniofacial advancement surgery.

Perspective: The incidence of postoperative IH in the pediatric craniosynostosis population is difficult to study.

The mechanism for the development of postoperative IH is not completely understood. There is variation in the determination of IH. Screening is not standardized. Noninvasive detection methods are often not optimally sensitive or reliable. Lack of papilledema does not guarantee lack of elevated ICP. As pediatric patients age (>8 years old), this finding becomes more sensitive. Currently, imaging techniques and findings do not reflect ICP. A long-term multidisciplinary clinical follow-up on an at least annual basis until school age is recommended for patients who have had surgery for any type of craniosynostosis.

Chronic elevated ICP in children may have long-term sequelae in neurocognitive and visual domains though the association and consequences are not clearly established. Recent literature suggests an impact of earlier age and more extensive surgery on more favorable neuropsychological outcomes in children with craniosynostosis. There are no Class I studies to guide practice at this time. There remain many unanswered questions in craniosynostosis management and outcomes; bringing this issue of postoperative IH to light points to the need for well-designed multicenter studies to accumulate data and knowledge about the large spectrum of craniosynostosis care.

Summary Written by: Sandi Lam, MD

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