Lucile Packard Children's Hospital Stanford

Lucile Packard Children's Hospital at Stanford is a children's hospital which is part of the Stanford University system. It is located adjacent to the campus at 725 Welch Road, Palo Alto, California. It was founded in 1991. It is staffed by over 650 physicians and 4,750 staff and volunteers.

1. Ultrasound Obstet Gynecol. 2019 Jan 8. doi: 10.1002/uog.20212. [Epub ahead of print]

Prenatal brain imaging for predicting postnatal hydrocephalus treatment in fetuses that had neural tube defect repair.

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OBJECTIVES: To determine if fetal brain imaging in fetuses that underwent prenatal repair of neural tube defect (NTD) can predict the need for postnatal hydrocephalus treatment (HT) in the first year postpartum. METHODS: This was a prospective study of fetuses diagnosed with open neural tube defect that had in-utero myelomeningocele repair between April 2014 and April 2016. Independent variables were collected from four chronological sets of fetal images: pre-surgery ultrasound, pre-surgery MRI, 6-week post-surgery MRI and pre-delivery ultrasound. The following independent variables were collected from all image sets unless otherwise noted: gestational age, head circumference, mean ventricular width, ventricular volume (VV, MRI only), hindbrain herniation (HBH) score (MRI only), and level of lesion, defined as the upper bony spinal defect (🤣, pre-surgery US). Based on these measurements, additional variables were defined and calculated including change in degree of HBH, ventricular width growth (mm/week), and ventricular volume growth (ml/week). The need for hydrocephalus HT (by either ventriculoperitoneal shunt or endoscopic third ventriculostomy and choroid plexus cauterization (ETV-CPC)) was determined by a pediatric neurosurgeon using clinical and radiographic criteria; a secondary analysis was performed using the MOMS trial criteria for hydrocephalus. The predictive value of each parameter was assessed by ROC-curve and logistic regression analyses. RESULTS: Fifty affected fetuses were included in the study, of which 32 underwent open hysterotomy and 18 fetoscopic repair. Two cases of neonatal death were excluded from the analysis. The mean gestational ages for the pre-surgery ultrasound, pre-surgery MRI, post-surgery MRI and pre-delivery ultrasound were 21.8 ± 2.1 weeks, 22.0 ±1.8 weeks, 30.4 ±1.6 weeks and 31.0 ±4.9 weeks, respectively. A total of 16 subjects required HT. Area under the curve (AUC) of predictive accuracy for HT showed that HBH grading on post-surgery MRI had the strongest predictive value (0.86; p<0.01), outperforming other predictors such as mean ventricular width on pre-surgery US (0.67; p=0.05), post-surgery MRI VV (0.73; p=0.03), MRI VV growth (0.79; p=0.01), change in HBH (0.82; p<0.01), and mean ventricular width on pre-delivery US (0.73; p=0.01). Other variables such as 🤣, mean ventricular width on pre-surgery and post-surgery MRI, and ventricular growth assessment by MRI or US, had an AUC<0.7. Optimal cut-offs of the variables with the highest AUCs were evaluated to improve prediction. A combination of ventricular volume growth ≥ 2.02 ml/week and/or HBH of 3 on post-surgery MRI were the optimal cut-offs for the best prediction [OR: 42 (95% CI:

4 - 431), accuracy: 84%]. Logistic regression analyses also showed that persistence of severe HBH 6 weeks after surgery by MRI is one of the best predictors for HT [OR 39 (95% CI: 4 - 369), accuracy: 84%]. There was no significant change in the results when the MOMS trial criteria for hydrocephalus were used as the dependent variable. CONCLUSIONS: Persistence of HBH on MRI 6 weeks after prenatal NTD repair independently predicted the need for postnatal HT better than any US- or MRI-derived measurements of ventricular characteristics. These results will aid in prenatal counseling and add support to the hypothesis that HBH is a significant driver of hydrocephalus in myelomeningocele patients. This article is protected by copyright. All rights reserved.

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2. Proc Natl Acad Sci U S A. 2019 Jan 2. pii: 201721434. doi: 10.1073/pnas.1721434116. [Epub ahead of print]

Microglia are effector cells of CD47-SIRPα antiphagocytic axis disruption against glioblastoma.

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Glioblastoma multiforme (GBM) is a highly aggressive malignant brain tumor with fatal outcome. Tumor-associated macrophages and microglia (TAMs) have been found to be major tumor-promoting immune cells in the tumor microenvironment. Hence, modulation and reeducation of tumor-associated macrophages and microglia in GBM is considered a promising antitumor strategy. Resident microglia and invading macrophages have been shown to have distinct origin and function. Whereas yolk sac-derived microglia reside in the brain, blood-derived monocytes invade the central nervous system only under pathological conditions like tumor formation. We recently showed that disruption of the SIRPα-CD47 signaling axis is efficacious against various brain tumors including GBM primarily by inducing tumor phagocytosis. However, most effects are attributed to macrophages recruited from

the periphery but the role of the brain resident microglia is unknown. Here, we sought to utilize a model to distinguish resident microglia and peripheral macrophages within the GBM-TAM pool, using orthotopically xenografted, immunodeficient, and syngeneic mouse models with genetically color-coded macrophages (Ccr2 RFP) and microglia (Cx3cr1 GFP). We show that even in the absence of phagocytizing macrophages (Ccr2 RFP/RFP), microglia are effector cells of tumor cell phagocytosis in response to anti-CD47 blockade. Additionally, macrophages and microglia show distinct morphological and transcriptional changes. Importantly, the transcriptional profile of microglia shows less of an inflammatory response which makes them a promising target for clinical applications.

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Conflict of interest statement: Conflict of interest statement: S.G., S.S.M., S.H.C., and I.L.W. are coinventors on patents regarding the use of CD47 antibody targeting brain tumors. I.L.W. is the inventor of multiple patents regarding CD47 antibody targeting non-CNS tumors that have been licensed to Forty Seven, Inc. He serves on the board of directors and as a consultant. He has equity ownership in Forty Seven, Inc.

3. AJNR Am J Neuroradiol. 2018 Dec 6. doi: 10.3174/ajnr.A5899. [Epub ahead of print]

MR Imaging-Based Radiomic Signatures of Distinct Molecular Subgroups of Medulloblastoma.

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BACKGROUND AND PURPOSE: Distinct molecular subgroups of pediatric medulloblastoma confer important differences in prognosis and therapy. Currently, tissue sampling is the only method to obtain information for classification. Our goal was to develop and validate radiomic and machine learning approaches for predicting molecular subgroups of pediatric medulloblastoma. MATERIALS AND METHODS: In this multi-institutional retrospective study, we evaluated MR imaging datasets of 109 pediatric patients with medulloblastoma from 3 children's hospitals from January 2001 to January 2014. A computational framework was developed to extract MR imaging-based radiomic features from tumor segmentations, and we tested 2 predictive models: a double 10-fold cross-validation using a combined dataset consisting of all 3 patient cohorts and a 3-dataset cross-validation, in which training was performed on 2 cohorts and testing was performed on the third independent cohort. We used the Wilcoxon rank sum test for feature selection with assessment of area under the receiver operating characteristic curve to evaluate model performance. RESULTS: Of 590 MR imaging-derived radiomic

features, including intensity-based histograms, tumor edge-sharpness, Gabor features, and local area integral invariant features, extracted from imaging-derived tumor segmentations, tumor edge-sharpness was most useful for predicting sonic hedgehog and group 4 tumors. Receiver operating characteristic analysis revealed superior performance of the double 10-fold cross-validation model for predicting sonic hedgehog, group 3, and group 4 tumors when using combined T1- and T2-weighted images (area under the curve = 0.79, 0.70, and 0.83, respectively). With the independent 3-dataset cross-validation strategy, select radiomic features were predictive of sonic hedgehog (area under the curve = 0.70-0.73) and group 4 (area under the curve = 0.76-0.80) medulloblastoma. CONCLUSIONS: This study provides proof-of-concept results for the application of radiomic and machine learning approaches to a multi-institutional dataset for the prediction of medulloblastoma subgroups.

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4. J Neurooncol. 2018 Nov 27. doi: 10.1007/s11060-018-03060-4. [Epub ahead of print]

Correction to: International experience in the development of patient-derived xenograft models of diffuse intrinsic pontine glioma.

Tsoli M(1), Shen H(1), Mayoh C(1), Franshaw L(1), Ehteda A(1), Upton D(1), Carvalho D(2), Vinci M(2), Meel MH(3), van Vuurden D(3), Plessier A(4), Castel D(4), Drissi R(5), Farrell M(6), Cryan J(6), Crimmins D(7), Caird J(7), Pears J(8), Francis S(9), Ludlow LEA(10), Carai A(11), Mastronuzzi A(12), Liu B(1), Hansford J(10), Gottardo NG(13), Hassall T(14), Kirby M(15), Fouladi M(5), Hawkins C(16), Monje M(17), Grill J(4), Jones C(2), Hulleman E(3), Ziegler DS(18)(19).

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Erratum for

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J Neurooncol. 2018 Nov 16;:.
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There are two errors and one omission in the original article. Author Gottardo's correct name is Nicholas G. Gottardo, author Hulleman's correct affiliation is no. 3 (VUMC, Amsterdam), and the Acknowledgements should include the following sentence: “We would like to thank Dr Angel Montero Carcaboso (Hospital Sant Joan de Deu, Barcelona, Spain) for generously supplying the HSJD-DIPG007 cells.”

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5. J Neurooncol. 2018 Nov 16. doi: 10.1007/s11060-018-03038-2. [Epub ahead of print]

International experience in the development of patient-derived xenograft models of diffuse intrinsic pontine glioma.

Tsoli M(1), Shen H(1), Mayoh C(1), Franshaw L(1), Ehteda A(1), Upton D(1), Carvalho D(2), Vinci M(2), Meel MH(3), van Vuurden D(3), Plessier A(4), Castel D(4), Drissi R(5), Farrell M(6), Cryan J(6), Crimmins D(7), Caird J(7), Pears J(8), Francis S(9), Ludlow LEA(10), Carai A(11), Mastronuzzi A(12), Liu B(1), Hansford J(10), Gottardo N(13), Hassall T(14), Kirby M(15), Fouladi M(5), Hawkins C(16), Monje M(17), Grill J(4), Jones C(2), Hulleman E(4), Ziegler DS(18)(19).

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Erratum in

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J Neurooncol. 2018 Nov 27;:.
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PURPOSE: Diffuse intrinsic pontine glioma is the most aggressive form of high grade glioma in children with no effective therapies. There have been no improvements in survival in part due poor understanding of underlying biology, and lack of representative in vitro and in vivo models. Recently, it has been found feasible to use both biopsy and autopsy tumors to generate cultures and xenograft

models. METHODS: To further model development, we evaluated the collective international experience from 8 collaborating centers to develop DIPG pre-clinical models from patient-derived autopsies and biopsies. Univariate and multivariate analysis was performed to determine key factors associated with the success of in vitro and in vivo PDX development. RESULTS: In vitro cultures were successfully established from 57% of samples (84.2% of biopsies and 38.2% of autopsies). Samples transferred in DMEM media were more likely to establish successful culture than those transported in Hibernate A. In vitro cultures were more successful from biopsies (84.2%) compared with autopsies (38.2%) and as monolayer on laminin-coated plates than as neurospheres. Primary cultures successfully established from autopsy samples were more likely to engraft in animal models than cultures established from biopsies (86.7% vs. 47.4%). Collectively, tumor engraftment was more successful when DIPG samples were directly implanted in mice (68%), rather than after culturing (40.7%). CONCLUSION: This multi-center study provides valuable information on the success rate of establishing patient-derived pre-clinical models of DIPG. The results can lead to further optimization of DIPG model development and ultimately assist in the investigation of new therapies for this aggressive pediatric brain tumor.

DOI: 10.1007/s11060-018-03038-2 PMID: 30446898

6. Nat Commun. 2018 Nov 2;9(1):4651. doi: 10.1038/s41467-018-07182-1.

Publisher Correction: Notch1 regulates the initiation of metastasis and self-renewal of Group 3 medulloblastoma.

Kahn SA(1)(2)(3)(4), Wang X(5), Nitta RT(6), Gholamin S(7)(8)(6), Theruvath J(7), Hutter G(7), Azad TD(7), Wadi L(9), Bolin S(7)(10), Ramaswamy V(5), Esparza R(7)(6), Liu KW(11), Edwards M(6)(12), Swartling FJ(10), Sahoo D(13), Li G(6), Wechsler-Reya RJ(11), Reimand J(9)(14), Cho YJ(12), Taylor MD(5), Weissman IL(8)(12), Mitra SS(7)(8)(6)(12)(15), Cheshier SH(16)(17)(18)(19)(20).

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Erratum for

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Nat Commun. 2018 Oct 8;9(1):4121.
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The original version of this Article omitted Suzana A. Kahn, Siddhartha S. Mitra & Samuel H. Cheshier as jointly supervising authors. This has now been corrected in both the PDF and HTML versions of the Article.

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7. Nat Commun. 2018 Oct 8;9(1):4121. doi: 10.1038/s41467-018-06564-9.

Notch1 regulates the initiation of metastasis and self-renewal of Group 3 medulloblastoma.

Kahn SA(1)(2)(3)(4), Wang X(5), Nitta RT(6), Gholamin S(7)(8)(6), Theruvath J(7), Hutter G(7), Azad TD(7), Wadi L(9), Bolin S(7)(10), Ramaswamy V(5), Esparza R(7)(6), Liu KW(11), Edwards M(6)(12), Swartling FJ(10), Sahoo D(13), Li G(6), Wechsler-Reya RJ(11), Reimand J(9)(14), Cho YJ(12), Taylor MD(5), Weissman IL(8)(12), Mitra SS(7)(8)(6)(12)(15), Cheshier SH(16)(17)(18)(19)(20).

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Erratum in

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Nat Commun. 2018 Nov 2;9(1):4651.
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Medulloblastoma is the most common malignant brain tumor of childhood. Group 3 medulloblastoma, the most aggressive molecular subtype, frequently disseminates through the leptomeningeal cerebral spinal fluid (CSF) spaces in the brain and spinal cord. The mechanism of dissemination through the CSF remains poorly understood, and the molecular pathways involved in medulloblastoma metastasis and self-renewal are largely unknown. Here we show that NOTCH1 signaling pathway regulates both the initiation of metastasis and the self-renewal of medulloblastoma. We identify a mechanism in which NOTCH1 activates BMI1 through the activation of TWIST1. NOTCH1 expression and activity are directly related to medulloblastoma metastasis and decreased survival rate of tumor-bearing mice. Finally, medulloblastoma-bearing mice intrathecally treated with anti-NRR1, a NOTCH1 blocking antibody, present lower frequency of spinal metastasis and higher survival rate. These findings identify NOTCH1 as a pivotal driver of Group 3 medulloblastoma metastasis and self-renewal, supporting the development of therapies targeting this pathway.

DOI: 10.1038/s41467-018-06564-9 PMCID: PMC6175869 PMID: 30297829 [Indexed for MEDLINE]

8. Neurosurg Focus. 2018 Sep;45(3):E7. doi: 10.3171/2018.6.FOCUS18226.

Stereoelectroencephalography in children: a review.

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Stereoelectroencephalography (SEEG) is an intracranial diagnostic measure that has grown in popularity in the United States as outcomes data have demonstrated its benefits and safety. The main uses of SEEG include 1) exploration of deep cortical/sulcal structures; 2) bilateral recordings; and 3) 3D mapping of epileptogenic zones. While SEEG has gradually been accepted for treatment in adults, there is less consensus on its utility in children. In this literature review, the authors seek to describe the current state of SEEG with a focus on the more recent technology-enabled surgical techniques and demonstrate its efficacy in the pediatric epilepsy population.

DOI: 10.3171/2018.6.FOCUS18226 PMID: 30173607

9. J Neurosurg Pediatr. 2018 Dec 1;22(6):710-715. doi: 10.3171/2018.5.PEDS17719.

Topical vancomycin surgical prophylaxis in pediatric open craniotomies: an institutional experience.

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OBJECTIVETopical antimicrobial compounds are safe and can reduce cost and complications associated with surgical site infections (SSIs). Topical vancomycin has been an effective tool for reducing SSIs following routine neurosurgical procedures in the spine and following adult craniotomies. However, widespread adoption within the pediatric neurosurgical community has not yet occurred, and there are no studies to report on the safety and efficacy of this intervention. The authors present the first institution-wide study of topical vancomycin following open craniotomy in the pediatric population.METHODSIn this retrospective study the authors reviewed all open craniotomies performed over a period from 05/2014 to 12/2016 for topical vancomycin use, SSIs, and clinical variables associated with SSI. Topical vancomycin was utilized as an infection prophylaxis and was applied as a liquid solution following replacement of a bone flap or after dural closure when no bone flap was reapplied.RESULTSOverall, 466 consecutive open craniotomies were completed between 05/2014 and 12/2016, of which 43% utilized topical vancomycin. There was a 1.5% SSI rate in the nontopical cohort versus 0% in the topical vancomycin cohort ($p = 0.045$). The number needed to treat was 66. There were no significant differences in risk factors for SSI between cohorts. There were no complications associated with topical vancomycin use.CONCLUSIONSRoutine topical vancomycin administration during closure of open craniotomies can be a safe and effective tool for reducing SSIs in the pediatric neurosurgical population.

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10. Pediatr Crit Care Med. 2018 Nov;19(11):1033-1038. doi: 10.1097/PCC.0000000000001706.

Use of Telemedicine During Interhospital Transport of Children With Operative Intracranial Hemorrhage.

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OBJECTIVES: To analyze the impact of an intervention of using telemedicine during interhospital transport on time to surgery in children with operative intracranial hemorrhage. DESIGN: We performed a retrospective chart review of children with intracranial hemorrhage transferred for emergent neurosurgical intervention between January 1, 2011 and December 31, 2016. We identified those patients whose neuroimaging was transmitted via telemedicine to the neurosurgical team prior to arrival at our center and then compared the telemedicine and nontelemedicine groups. Mann-Whitney U and Fisher exact tests were used to compare interval variables and categorical data.

SETTING: Single-center study performed at Johns Hopkins Hospital. PATIENTS: Patients less than or equal to 18 years old transferred for operative intracranial hemorrhage. INTERVENTIONS: Pediatric transport implemented routine telemedicine use via departmental smart phones to facilitate transfer of information and imaging and reduce time to definitive care by having surgical services available when needed. MEASUREMENTS AND MAIN RESULTS: Fifteen children (eight in telemedicine group; seven in nontelemedicine group) met inclusion criteria. Most had extraaxial hemorrhage (87.5% telemedicine group; 85.7% nontelemedicine group; p = 1.0), were intubated pre transport (62.5% telemedicine group; 71.4% nontelemedicine group; p = 1.0), and arrived at our center's trauma bay during night shift or weekend (87.5% telemedicine group; 57.1% nontelemedicine group; p = 0.28). Median trauma bay Glasgow Coma Scale scores did not differ (eight in telemedicine group; seven in nontelemedicine group; p = 0.24). Although nonsignificant, when compared with the nontelemedicine group, the telemedicine group had decreased rates of repeat preoperative neuroimaging (37.5% vs 57%; p = 0.62), shorter median times from trauma bay arrival to surgery (33 min vs 47 min; p = 0.22) and from diagnosis to surgery (146.5 min vs 157 min; p = 0.45), shorter intensive care stay (2.5 vs 5 d) and hospitalization (4 vs 5 d), and higher home discharge rates (87.5% vs 57.1%; p = 0.28). CONCLUSIONS: Telemedicine use during interhospital transport appears to expedite definitive care for children with intracranial hemorrhage requiring emergent neurosurgical intervention, which could contribute to improved patient outcomes.

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11. J Neurosurg Pediatr. 2018 Nov 1;22(5):1-8. doi: 10.3171/2018.5.PEDS17718.

Robot-guided pediatric stereoelectroencephalography: single-institution experience.

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OBJECTIVEStereoelectroencephalography (SEEG) has increased in popularity for localization of epileptogenic zones in drug-resistant epilepsy because safety, accuracy, and efficacy have been well established in both adult and pediatric populations. Development of robot-guidance technology has greatly enhanced the efficiency of this procedure, without sacrificing safety or precision. To date there have been very limited reports of the use of this new technology in children. The authors present their initial experience using the ROSA platform for robot-guided SEEG in a pediatric population.METHODSBetween February 2016 and October 2017, 20 consecutive patients underwent robot-guided SEEG with the ROSA robotic guidance platform as part of ongoing seizure localization and workup for medically refractory epilepsy of several different etiologies. Medical and surgical history, imaging and trajectory plans, as well as operative records were analyzed retrospectively for surgical accuracy, efficiency, safety, and epilepsy outcomes.RESULTSA total of 222 leads were placed in 20 patients, with an average of 11.1 leads per patient. The mean total case time (± SD) was 297.95 (± 52.96) minutes and the mean operating time per lead was 10.98 minutes/lead, with improvements in total (33.36 minutes/lead vs 21.76 minutes/lead) and operative (13.84 minutes/lead vs 7.06 minutes/lead) case times/lead over the course of the study. The mean radial error was 1.75 (± 0.94 mm). Clinically useful data were obtained from SEEG in 95% of cases, and epilepsy surgery was indicated and performed in 95% of patients. In patients who underwent definitive epilepsy surgery with at least a 3-month follow-up, 50% achieved an Engel class I result (seizure freedom). There were

no postoperative complications associated with SEEG placement and monitoring.CONCLUSIONSIn this study, the authors demonstrate that rapid adoption of robot-guided SEEG is possible even at a SEEG-naïve institution, with minimal learning curve. Use of robot guidance for SEEG can lead to significantly decreased operating times while maintaining safety, the overall goals of identification of epileptogenic zones, and improved epilepsy outcomes.

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12. Cancer. 2018 Sep 1;124(17):3551-3559. doi: 10.1002/cncr.31598. Epub 2018 Aug 16.

Disparities in hepatocellular carcinoma incidence by race/ethnicity and geographic area in California: Implications for prevention.

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BACKGROUND: The incidence of hepatocellular carcinoma (HCC) has been rising rapidly in the United States. California is an ethnically diverse state with the largest number of incident HCC cases in the country. Characterizing HCC disparities in California may inform priorities for HCC prevention. METHODS: By using data from the Surveillance, Epidemiology, and End Results 18-Registry Database and the California Cancer Registry, age-adjusted HCC incidence in California from 2009 through 2013 was calculated by race/ethnicity and neighborhood ethnic enclave status. A geographic analysis was conducted using Medical Service Study Areas (MSSAs) as the geographic unit, and race/ethnicity-specific standardized incidence ratios (SIRs) were calculated to identify MSSAs with higher-than-expected HCC incidence compared with the statewide average. RESULTS: During 2009 through 2013, the age-adjusted incidence of HCC in California was the highest in Asians/Pacific Islanders (APIs) and Hispanics (>100% higher than whites), especially those living in more ethnic neighborhoods (20%-30% higher than less ethnic neighborhoods). Of the 542 MSSAs statewide, 42 had elevated HCC incidence (SIR ≥ 1.5; lower bound of 95% confidence interval > 1) for whites, 14 for blacks, 24 for APIs, and 36 for Hispanics. These MSSAs have 24% to 52% higher proportions of individuals below the 100% federal poverty line than other MSSAs. CONCLUSIONS: APIs and Hispanics residing in more ethnic neighborhoods and individuals residing in lower income neighborhoods require more extensive preventive efforts tailored toward their unique risk factor profiles. The current race/ethnicity-specific geographic analysis can be extended to other states to inform priorities for HCC targeted prevention at the subcounty level, eventually reducing HCC burden in the country.

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13. Childs Nerv Syst. 2018 Jun 28. doi: 10.1007/s00381-018-3881-z. [Epub ahead of print]

Topical vancomycin for surgical prophylaxis in non-instrumented pediatric spinal surgeries.

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STUDY DESIGN: Retrospective cohort study. OBJECTIVE: To determine if topical vancomycin irrigation reduces the incidence of post-operative surgical site infections following pediatric spinal procedures. Surgical site infections (SSIs) following spinal procedures performed in pediatric patients represent a serious complication. Prophylactic use of topical vancomycin prior to closure has been shown to be effective in reducing incidence of SSIs in adult spinal procedures. Non-instrumented cases make up the majority of spinal procedures in pediatric patients, and the efficacy of prophylactic topical vancomycin in these procedures has not previously been reported. METHODS: This retrospective study reviewed all non-instrumented spinal procedures performed over a period from 05/2014-12/2016 for topical vancomycin use, surgical site infections, and clinical variables associated with SSI. Topical vancomycin was utilized as infection prophylaxis, and applied as a liquid solution within the wound prior to closure. RESULTS: Ninety-five consecutive, non-instrumented, pediatric spinal surgeries were completed between 01/2015 and 12/2016, of which the last 68 utilized topical vancomycin. There was a 11.1% SSI rate in the non-topical vancomycin cohort versus 0% in the topical vancomycin cohort ($P = 0.005$). The number needed to treat was 9. There were no significant differences in risk factors for SSI between cohorts. There were no complications associated topical vancomycin use. CONCLUSIONS: Routine topical vancomycin administration during closure of non-instrumented spinal procedures can be a safe and effective tool for reducing SSIs in the pediatric neurosurgical population.

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14. World Neurosurg. 2018 Aug;116:e1188-e1193. doi: 10.1016/j.wneu.2018.05.210. Epub 2018 Jun 5.

Safety of Dynamic Magnetic Resonance Imaging of the Cervical Spine in Children Performed without Neurosurgical Supervision.

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OBJECTIVE: The need for neurosurgical supervision as well as the general safety and utility of dynamic magnetic resonance imaging (MRI) of the cervical spine in children remains controversial. We present the largest descriptive cohort study of cervical flexion-extension MRI scans in pediatric patients to help elucidate the safety and utility of this technique. METHODS: We retrospectively reviewed all cervical spine MRI scans performed at Lucile Packard Children's Hospital at Stanford from 2009 to 2015. We identified 66 dynamic cervical MRI scans performed in 45 children and 2 young adults for further study. RESULTS: General anesthesia was used in 43 scans. The neuroradiology team performed all scans with no direct supervision by the neurosurgery team. There were no adverse events. Dynamic MRI detected significant instability that was not clearly seen on dynamic radiographs (5 patients) and cord compression not seen on static MRI (9 patients). One patient with asymptomatic instability found on flexion-extension radiographs had no cord compression with movement on MRI and was managed conservatively. Two neonates with significant congenital malformations of the cervical spine were cleared for operative positioning for cardiac procedures based on flexion-extension MRI. CONCLUSIONS: Dynamic MRI is a safe tool for evaluating the cervical spine and cervicomedullary junction in various pediatric populations and can be performed safely without direct neurosurgical supervision. We describe for the first time the use of flexion-extension MRI to clear neonates with severe congenital cervical spine abnormalities for complex operative positioning and further care in the intensive care unit.

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15. J Neurosurg Pediatr. 2018 Sep;22(3):251-260. doi: 10.3171/2018.3.PEDS17723. Epub 2018 Jun 8.

High-resolution 3D volumetric contrast-enhanced MR angiography with a blood pool agent (ferumoxytol) for diagnostic evaluation of pediatric brain arteriovenous malformations.

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OBJECTIVE Patients with brain arteriovenous malformations (AVMs) often require repeat imaging with MRI or MR angiography (MRA), CT angiography (CTA), and digital subtraction angiography (DSA). The ideal imaging modality provides excellent vascular visualization without incurring added risks, such as radiation exposure. The purpose of this study is to evaluate the performance of ferumoxytol-enhanced MRA using a high-resolution 3D volumetric sequence (fe-SPGR) for visualizing and grading pediatric brain AVMs in comparison with CTA and DSA, which is the current imaging gold standard. METHODS In this retrospective cohort study, 21 patients with AVMs evaluated by fe-SPGR, CTA, and DSA between April 2014 and August 2017 were included. Two experienced raters graded AVMs using Spetzler-Martin criteria on all imaging studies. Lesion conspicuity (LC) and diagnostic confidence (DC) were assessed using a 5-point Likert scale, and interrater agreement was determined. The Kruskal-Wallis test was performed to assess the raters' grades and scores of LC and DC, with subsequent post hoc pairwise comparisons to assess for statistically significant differences between pairs of groups at $p < 0.05$. RESULTS Assigned Spetzler-Martin grades for AVMs on DSA, fe-SPGR, and CTA were not significantly different ($p = 0.991$). LC and DC scores were higher with fe-SPGR than with CTA ($p < 0.05$). A significant difference in LC scores was found between CTA and fe-SPGR ($p < 0.001$) and CTA and DSA ($p < 0.001$) but not between fe-SPGR and DSA ($p = 0.146$). A significant difference in DC

scores was found among DSA, fe-SPGR, and CTA ($p < 0.001$) and between all pairs of the groups ($p < 0.05$). Interrater agreement was good to very good for all image groups ($\kappa = 0.77$-1.0, $p < 0.001$). CONCLUSIONS Fe-SPGR performed robustly in the diagnostic evaluation of brain AVMs, with improved visual depiction of AVMs compared with CTA and comparable Spetzler-Martin grading relative to CTA and DSA.

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16. Am J Perinatol. 2018 Oct;35(12):1197-1205. doi: 10.1055/s-0038-1646954. Epub 2018 Apr 27.

Development of a NeuroNICU with a Broader Focus on All Newborns at Risk of Brain Injury: The First 2 Years.

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OBJECTIVE: Many critically ill neonates have an existing brain injury or are at risk of neurologic injury. We developed a “NeuroNICU” (neurologic neonatal intensive care unit) to better provide neurologically focused intensive care. STUDY DESIGN: Demographic and clinical variables, services delivered, and patient outcomes were recorded in a prospective database for all neonates admitted to the NeuroNICU between April 23, 2013, and June 25, 2015. RESULTS: In total, 546 neonates were admitted to the NeuroNICU representing 32% of all NICU admissions. The most common admission diagnoses were congenital heart disease (30%), extreme prematurity (18%), seizures (10%), and hypoxic-ischemic encephalopathy (9%). Neuromonitoring was common, with near-infrared spectroscopy used in 69%, amplitude-integrated electroencephalography (EEG) in 45%, and continuous video EEG in 35%. Overall, 43% received neurology or neurosurgery consultation. Death prior to hospital discharge occurred in 11%. Among survivors, 87% were referred for developmental follow-up, and among those with a primary neurologic diagnosis 57% were referred for neurology or neurosurgical follow-up. CONCLUSION: The NeuroNICU-admitted newborns with or at risk of brain injury comprise a high percentage of NICU volume; 38% had primary neurologic diagnoses, whereas 62% had medical diagnoses. We found many opportunities to provide brain focused intensive care, impacting a substantial proportion of newborns in our NICU.

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17. Ann Neurol. 2018 Jun;83(6):1133-1146. doi: 10.1002/ana.25243. Epub 2018 May 16.

Somatic SLC35A2 variants in the brain are associated with intractable neocortical epilepsy.

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OBJECTIVE: Somatic variants are a recognized cause of epilepsy-associated focal malformations of cortical development (MCD). We hypothesized that somatic variants may underlie a wider range of focal epilepsy, including nonlesional focal epilepsy (NLFE). Through genetic analysis of brain tissue, we evaluated the role of somatic variation in focal epilepsy with and without MCD. METHODS: We identified somatic variants through high-depth exome and ultra-high-depth candidate gene sequencing of DNA from epilepsy surgery specimens and leukocytes from 18 individuals with NLFE and 38 with focal MCD. RESULTS: We observed somatic variants in 5 cases in SLC35A2, a gene associated with glycosylation defects and rare X-linked epileptic encephalopathies. Nonsynonymous variants in SLC35A2 were detected in resected brain, and absent from leukocytes, in 3 of 18 individuals (17%) with NLFE, 1 female and 2 males, with variant allele frequencies (VAFs) in brain-derived DNA of 2 to 14%. Pathologic evaluation revealed focal cortical dysplasia type Ia (FCD1a) in 2 of the 3 NLFE cases. In the MCD cohort, nonsynonymous variants in SCL35A2 were detected in the brains of 2 males with intractable epilepsy, developmental delay, and magnetic resonance imaging suggesting FCD, with VAFs of 19 to 53%; Evidence for FCD was not observed in either brain tissue specimen. INTERPRETATION: We report somatic variants in SLC35A2 as an explanation for a substantial fraction of NLFE, a largely unexplained condition, as well as focal MCD, previously shown to result from somatic mutation but until now only in PI3K-AKT-mTOR pathway genes. Collectively, our findings suggest a larger role than previously recognized for glycosylation defects in the intractable epilepsies. Ann Neurol 2018.

DOI: 10.1002/ana.25243 PMCID: PMC6105543 [Available on 2019-06-01] PMID: 29679388

18. Neuroimage. 2018 Feb 15;167:466-477. doi: 10.1016/j.neuroimage.2017.11.052. Epub 2017 Dec 2.

Framework for shape analysis of white matter fiber bundles.

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Diffusion imaging coupled with tractography algorithms allows researchers to image human white matter fiber bundles in-vivo. These bundles are three-dimensional structures with shapes that change over time during the course of development as well as in pathologic states. While most studies on white matter variability focus on analysis of tissue properties estimated from the diffusion data, e.g. fractional anisotropy, the shape variability of white matter fiber bundle is much less explored. In this paper, we present a set of tools for shape analysis of white matter fiber bundles, namely: (1) a concise geometric model of bundle shapes; (2) a method for bundle registration between subjects; (3) a method for deformation estimation. Our framework is useful for analysis of shape variability in white matter fiber bundles. We demonstrate our framework by applying our methods on two datasets: one consisting of data for 6 normal adults and another consisting of data for 38 normal children of age 11 days to 8.5 years. We suggest a robust and reproducible method to measure changes in the shape of white matter fiber bundles. We demonstrate how this method can be used to create a model to assess age-dependent changes in the shape of specific fiber bundles. We derive such models for an ensemble of white matter fiber bundles on our pediatric dataset and show that our results agree with normative human head and brain growth data. Creating these models for a large pediatric longitudinal dataset may improve understanding of both normal development and pathologic states and propose novel parameters for the examination of the pediatric brain.

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19. Pediatr Neurol. 2018 Jan;78:27-34. doi: 10.1016/j.pediatrneurol.2017.08.009. Epub 2017 Sep 20.

The Utility of Collaterals as a Biomarker in Pediatric Unilateral Intracranial Arteriopathy.

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BACKGROUND: Intracranial arteriopathies are frequent causes of pediatric stroke and important risk factors for stroke recurrence. Without tissue diagnosis, vascular imaging is relied upon to identify the underlying etiology and prognosis. We hypothesized that children with unilateral intracranial arteriopathy with lenticulostriate collaterals would demonstrate distinct vascular outcomes compared with children without collaterals. METHODS: We retrospectively identified children with unilateral intracranial arteriopathy from two institutions. Two blinded raters from each institution reviewed magnetic resonance or digital subtraction angiography at baseline and ≥12 months. Patients were grouped according to presence or absence of lenticulostriate collaterals. Clinical features and vascular imaging outcomes were compared using univariate analysis and multivariate logistic regression. RESULTS: Forty-four children were included: 22 males, median age 8.2 years (range two to 16.9 years), and further stratified into the collateral group (n = 20) and non-collateral group (n = 24), with median follow-up of 25.5 months and 23 months, respectively. Both groups demonstrated similar rates of progression on vascular imaging at ≥12 months, 50% in the collateral group versus 37.5% in the non-collateral group (P > 0.05). The collateral group was associated with asymptomatic clinical presentation, normal brain MRI, border zone infarcts, and either vascular stabilization or new contralateral disease. The non-collateral group demonstrated either vascular improvement or discordant progression (combination of improved and progressive lesions). Using a multivariate model, collaterals continued to be an independent predictor of vascular outcome. CONCLUSIONS: This study suggests that lenticulostriate collaterals in children with unilateral intracranial arteriopathy may serve as a useful neuroimaging biomarker that helps to stratify patients with distinct clinical features and patterns of vascular evolution.

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20. Cureus. 2017 Sep 18;9(9):e1697. doi: 10.7759/cureus.1697.

Diffusion Tensor Imaging in an Infant Undergoing Functional Hemispherectomy: A Surgical Aid.

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Hemispherectomy is a highly effective treatment option for children with severe, unilateral, medically refractory epilepsy. Many patients undergoing hemispherectomy are younger patients with dysmorphic brains, making accomplishing a complete disconnection challenging due to anatomic distortion, even with the aid of intraoperative navigation. Diffusion tensor imaging (DTI) has been proposed as a valuable imaging adjunct perioperatively to help guide surgeons intraoperatively, as well as for post-surgical evaluation and confirmation of complete hemispheric disconnection. We present a case of an infant with Otoharra syndrome and hemimegencephaly who underwent a functional hemispherectomy for treatment of severe, refractory seizures. We demonstrate how DTI was utilized both pre-, intra-, and postoperatively to help plan, guide, and confirm surgical disconnection. The application of exquisite DTI for this child led to her being seizure-free, which is a life-changing event with long-lasting benefits and will become even more critical as we now perform these disconnection procedures with a more minimally invasive approach.

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Conflict of interest statement: The authors have declared that no competing interests exist.

21. J Neurosurg Pediatr. 2018 Jan;21(1):49-53. doi: 10.3171/2017.7.PEDS17168. Epub 2017 Nov 10.

Long-term outcomes of primarily metastatic juvenile pilocytic astrocytoma in children.

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OBJECTIVE Primarily metastatic juvenile pilocytic astrocytoma (JPA) is rare, likely representing 2%-3% of all cases of JPA. Due to the rarity of primarily metastatic JPA, there is currently no standard treatment paradigm and the long-term outcomes are not fully known. The goal of this case series was to add to the current understanding of this disease process. METHODS The authors searched a comprehensive database of pediatric patients with brain and spinal cord tumors treated at Lucile Packard Children's Hospital from 1997 to 2016 and identified 5 patients with primarily metastatic JPA. A retrospective chart review was performed and details of the patients' treatment and clinical course were recorded for further analysis. RESULTS For the 5 patients with primarily metastatic JPA, the mean follow-up period was 12.3 years. All patients in our series had biopsies or subtotal resections and upfront treatment. Three patients were treated with chemotherapy alone, one was treated with chemotherapy and radiotherapy, and one was treated with radiotherapy alone. Four patients had stable disease after initial treatment, and one patient had multiple episodes of progressive disease but underwent successful salvage therapy and has had stable disease for 19 years. One patient died of an intracerebral hemorrhage 10 years following initial radiation treatment believed to be secondary to radiation vasculopathy. CONCLUSIONS Evaluation of the entire neuraxis should be performed in all instances of initial JPA diagnosis to properly assess for primarily metastatic disease. Many patients with primarily metastatic JPA will have stable disease after upfront treatment, although the higher rate of stable disease found in this series relative to other reports is likely secondary to the small sample size.

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22. World Neurosurg. 2018 Feb;110:256-262. doi: 10.1016/j.wneu.2017.10.029. Epub 2017 Oct 16.

Spontaneous Intrauterine Depressed Skull Fractures: Report of 2 Cases Requiring Neurosurgical Intervention and Literature Review.

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World Neurosurg. 2018 Mar;111:421.
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BACKGROUND: Spontaneous intrauterine depressed skull fractures (IDSFs) are rare fractures that often require neurosurgical evaluation and therapy. Most of the reported congenital depressions are

secondary to maternal abdominal trauma or instrumentation during delivery. Spontaneous IDSFs occur in the setting of uneventful normal spontaneous vaginal delivery or cesarean section, without obvious predisposing risk factors. The etiology and optimal management of spontaneous IDSFs remain controversial. CASE DESCRIPTION: We describe 2 cases of spontaneous IDSF who underwent cranioplasty at our institution using an absorbable mesh, as well as review the current state of knowledge regarding the diagnosis and management of spontaneous IDSF. The 2 neonates, 1 male and 1 female, presented at Lucile Packard Children's Hospital with spontaneous IDSF after uneventful normal spontaneous vaginal deliveries. The fractures were located in the left frontal and right parietotemporal calvarium, respectively. Both patients underwent open craniotomy and elevation of their IDSFs with mesh cranioplasty. At last follow-up, both patients were normocephalic and neurologically intact. CONCLUSIONS: Neurosurgery consultation is necessary for initial evaluation of spontaneous IDSF. Surgical intervention is indicated for larger defects and/or intracranial involvement. Expectant management and negative-pressure elevation have also been shown to be effective.

DOI: 10.1016/j.wneu.2017.10.029 PMID: 29051109 [Indexed for MEDLINE]

23. Cureus. 2017 Jul 7;9(7):e1442. doi: 10.7759/cureus.1442.

Near-Fatal Gastrointestinal Hemorrhage in a Child with Medulloblastoma on High Dose Dexamethasone.

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A four-year-old female was admitted to a university-based children's hospital with a newly-diagnosed posterior fossa tumor. She was started on famotidine and high-dose dexamethasone and underwent gross total resection of a medulloblastoma. She was continued on dexamethasone and famotidine. She exhibited postoperative posterior fossa syndrome and was started on enteral feeds via the nasoduodenal tube. She had small gastrointestinal bleeds on postoperative days eight, 11, and 18, and was found to have a well-circumscribed posterior duodenal ulcer. On postoperative day 19, she suffered a massive life-threatening gastrointestinal bleed requiring aggressive resuscitation with blood products. She required an emergent laparotomy due to ongoing blood loss and she was found to have posterior duodenal wall erosion into her gastroduodenal artery. She recovered and subsequently began delayed chemotherapy. This case demonstrates a rare and life-threatening complication of high-dose dexamethasone therapy in the setting of posterior fossa pathology despite stress ulcer prophylaxis. We present a historical perspective with the review of the association between duodenal and intracranial pathology and the usage of high-dose dexamethasone in such cases.

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Conflict of interest statement: The authors have declared that no competing interests exist.

24. Mol Genet Metab. 2017 Sep;122(1-2):18-32. doi: 10.1016/j.ymgme.2017.08.006. Epub 2017 Aug 20.

Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies.

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Leukodystrophies are a broad class of genetic disorders that result in disruption or destruction of central myelination. Although the mechanisms underlying these disorders are heterogeneous, there are many common symptoms that affect patients irrespective of the genetic diagnosis. The comfort and quality of life of these children is a primary goal that can complement efforts directed at curative therapies. Contained within this report is a systems-based approach to management of complications that result from leukodystrophies. We discuss the initial evaluation, identification of common medical issues, and management options to establish a comprehensive, standardized care approach. We will also address clinical topics relevant to select leukodystrophies, such as gallbladder pathology and adrenal insufficiency. The recommendations within this review rely on existing studies and consensus opinions and underscore the need for future research on evidence-based outcomes to better treat the manifestations of this unique set of genetic disorders.

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25. Neuro Oncol. 2017 Sep 1;19(9):1279-1280. doi: 10.1093/neuonc/nox107.

Contemporary survival endpoints: an International Diffuse Intrinsic Pontine Glioma Registry study.

Cooney T(1), Lane A(1), Bartels U(1), Bouffet E(1), Goldman S(1), Leary SES(1), Foreman NK(1), Packer RJ(1), Broniscer A(1), Minturn JE(1), Shih CS(1), Chintagumpala M(1), Hassall T(1), Gottardo NG(1), Dholaria H(1), Hoffman L(1), Chaney B(1), Baugh J(1), Doughman R(1), Leach JL(1), Jones BV(1), Fouladi M(1), Warren KE(1), Monje M(1).

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DOI: 10.1093/neuonc/nox107 PMCID: PMC5570207 PMID: 28821206

26. Mol Cancer Ther. 2017 Sep;16(9):1909-1921. doi: 10.1158/1535-7163.MCT-17-0022. Epub 2017 Jun 28.

A Novel Theranostic Strategy for MMP-14-Expressing Glioblastomas Impacts Survival.

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Mol Imaging. 2017 Jan-Dec;16:1536012117730950.
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Glioblastoma (GBM) has a dismal prognosis. Evidence from preclinical tumor models and human trials indicates the role of GBM-initiating cells (GIC) in GBM drug resistance. Here, we propose a new treatment option with tumor enzyme-activatable, combined therapeutic and diagnostic (theranostic) nanoparticles, which caused specific toxicity against GBM tumor cells and GICs. The theranostic cross-linked iron oxide nanoparticles (CLIO) were conjugated to a highly potent vascular disrupting agent (ICT) and secured with a matrix-metalloproteinase (MMP-14) cleavable peptide. Treatment with CLIO-ICT disrupted tumor vasculature of MMP-14-expressing GBM, induced GIC apoptosis, and significantly impaired tumor growth. In addition, the iron core of CLIO-ICT enabled in vivo drug tracking with MR imaging. Treatment with CLIO-ICT plus temozolomide achieved tumor remission and significantly increased survival of human GBM-bearing mice by more than 2-fold compared with treatment with temozolomide alone. Thus, we present a novel therapeutic strategy with significant impact on survival and great potential for clinical translation. Mol Cancer Ther; 16(9); 1909-21. ©2017 AACR.

DOI: 10.1158/1535-7163.MCT-17-0022 PMCID: PMC5587386 PMID: 28659432 [Indexed for MEDLINE]

27. Kidney Int. 2017 Jul;92(1):47-66. doi: 10.1016/j.kint.2016.12.037. Epub 2017 Apr 20.

Current and potential imaging applications of ferumoxytol for magnetic resonance imaging.

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Contrast-enhanced magnetic resonance imaging is a commonly used diagnostic tool. Compared with standard gadolinium-based contrast agents, ferumoxytol (Feraheme, AMAG Pharmaceuticals, Waltham, MA), used as an alternative contrast medium, is feasible in patients with impaired renal function. Other attractive imaging features of i.v. ferumoxytol include a prolonged blood pool phase and delayed intracellular uptake. With its unique pharmacologic, metabolic, and imaging properties, ferumoxytol may play a crucial role in future magnetic resonance imaging of the central nervous system, various organs outside the central nervous system, and the cardiovascular system. Preclinical and clinical studies have demonstrated the overall safety and effectiveness of this novel contrast agent, with rarely occurring anaphylactoid reactions. The purpose of this review is to describe the general and organ-specific properties of ferumoxytol, as well as the advantages and potential pitfalls associated with its use in magnetic resonance imaging. To more fully demonstrate the applications of ferumoxytol throughout the body, an imaging atlas was created and is available online as supplementary material.

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28. Sci Transl Med. 2017 Mar 15;9(381). pii: eaaf2968. doi: 10.1126/scitranslmed.aaf2968.

Disrupting the CD47-SIRPα anti-phagocytic axis by a humanized anti-CD47 antibody is an efficacious treatment for malignant pediatric brain tumors.

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Morbidity and mortality associated with pediatric malignant primary brain tumors remain high in the absence of effective therapies. Macrophage-mediated phagocytosis of tumor cells via blockade of the anti-phagocytic CD47-SIRPα interaction using anti-CD47 antibodies has shown promise in preclinical xenografts of various human malignancies. We demonstrate the effect of a humanized anti-CD47 antibody, Hu5F9-G4, on five aggressive and etiologically distinct pediatric brain tumors: group 3 medulloblastoma (primary and metastatic), atypical teratoid rhabdoid tumor, primitive neuroectodermal tumor, pediatric glioblastoma, and diffuse intrinsic pontine glioma. Hu5F9-G4 demonstrated therapeutic efficacy in vitro and in vivo in patient-derived orthotopic xenograft models. Intraventricular administration of Hu5F9-G4 further enhanced its activity against disseminated medulloblastoma leptomeningeal disease. Notably, Hu5F9-G4 showed minimal activity against normal human neural cells in vitro and in vivo, a phenomenon reiterated in an immunocompetent allograft glioma model. Thus, Hu5F9-G4 is a potentially safe and effective therapeutic agent for managing multiple pediatric central nervous system malignancies.

DOI: 10.1126/scitranslmed.aaf2968 PMID: 28298418 [Indexed for MEDLINE]

29. J Pediatr. 2017 Jun;185:173-180.e3. doi: 10.1016/j.jpeds.2017.01.019. Epub 2017 Feb 7.

Brain Perfusion and Diffusion Abnormalities in Children Treated for Posterior Fossa Brain Tumors.

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Comment in

J Pediatr. 2017 Jun;185:6-7.

OBJECTIVE: To compare cerebral perfusion and diffusion in survivors of childhood posterior fossa brain tumor with neurologically normal controls and correlate differences with cognitive dysfunction. STUDY DESIGN: We analyzed retrospectively arterial spin-labeled cerebral blood flow (CBF) and apparent diffusion coefficient (ADC) in 21 patients with medulloblastoma (MB), 18 patients with pilocytic astrocytoma (PA), and 64 neurologically normal children. We generated ANCOVA models to evaluate treatment effects on the cerebral cortex, thalamus, caudate, putamen, globus pallidus, hippocampus, amygdala, nucleus accumbens, and cerebral white matter at time points an average of 5.7 years after original diagnosis. A retrospective review of patient charts identified 12 patients with neurocognitive data and in whom the relationship between IQ and magnetic resonance imaging variables was assessed for each brain structure. RESULTS: Patients with MB (all treated with surgery, chemotherapy, and radiation) had significantly lower global CBF relative to controls (10%-23% lower, varying by anatomic region, all adjusted P?<?.05), whereas patients with PA (all treated with surgery alone) had normal CBF. ADC was decreased specifically in the hippocampus and amygdala of patients with MB and within the amygdala of patients with PA but otherwise remained normal after therapy. In the patients with tumor previously evaluated for IQ, regional ADC, but not CBF, correlated with IQ (R2?=?0.33-0.75). CONCLUSIONS: The treatment for MB, but not PA, was associated with globally reduced CBF. Treatment in both tumor types was associated with diffusion abnormalities of the mesial temporal lobe structures. Despite significant perfusion abnormalities in patients with MB, diffusion, but not perfusion, correlated with cognitive outcomes.

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30. Biochim Biophys Acta Mol Cell Res. 2017 Jun;1864(6):1018-1027. doi: 10.1016/j.bbamcr.2017.01.010. Epub 2017 Jan 18.

Bisacodyl and its cytotoxic activity on human glioblastoma stem-like cells. Implication of inositol 1,4,5-triphosphate receptor dependent calcium signaling.

Dong J(1), Aulestia FJ(2), Assad Kahn S(3), Zeniou M(1), Dubois LG(4), El-Habr EA(4), Daubeuf F(1), Tounsi N(1), Cheshier SH(3), Frossard N(1), Junier MP(4), Chneiweiss H(4), Néant I(2), Moreau M(2), Leclerc C(2), Haiech J(5), Kilhoffer MC(1).

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Glioblastoma is the most common malignant brain tumor. The heterogeneity at the cellular level, metabolic specificities and plasticity of the cancer cells are a challenge for glioblastoma treatment. Identification of cancer cells endowed with stem properties and able to propagate the tumor in animal xenografts has opened a new paradigm in cancer therapy. Thus, to increase efficacy and avoid tumor recurrence, therapies need to target not only the differentiated cells of the tumor mass, but also the cancer stem-like cells. These therapies need to be effective on cells present in the hypoxic, slightly acidic microenvironment found within tumors. Such a microenvironment is known to favor more aggressive undifferentiated phenotypes and a slow-growing “quiescent state” that preserves the cells from chemotherapeutic agents, which mostly target proliferating cells. Based on these considerations, we performed a differential screening of the Prestwick Chemical Library of approved drugs on both proliferating and quiescent glioblastoma stem-like cells and identified bisacodyl as a cytotoxic agent with selectivity for quiescent glioblastoma stem-like cells. In the present study we further characterize bisacodyl activity and show its efficacy in vitro on clonal macro-tumorospheres, as well as in vivo in glioblastoma mouse models. Our work further suggests that bisacodyl acts through inhibition of Ca2+ release from the InsP3 receptors.

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31. J Neurointerv Surg. 2017 Oct;9(10):1023-1026. doi: 10.1136/neurintsurg-2016-012660. Epub 2016 Oct 5.

Sclerotherapy for lymphatic malformations of the head and neck in the pediatric population.

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BACKGROUND: Sclerotherapy is one of the most commonly used minimally invasive interventions in the treatment of macrocystic lymphatic malformations (LMs). Several different sclerosing agents and injection protocols have been reported in the literature, each with varying degrees of success. The safety and efficacy of the treatments have not been evaluated comparatively in the pediatric population. METHODS: Chart review of pediatric patients with macrocystic/mixed head and neck LMs who underwent sclerotherapy using OK-432, doxycycline, or ethanolamine oleate at Lucile Packard Children's Hospital at Stanford during 2000-2014. Clinical evaluation and radiographic imaging were reviewed to assess lesion characteristics and response to sclerotherapy following each treatment session. The post-intervention clinical response was categorized as excellent, good, fair, or poor. RESULTS: Among the 41 pediatric cases reviewed, 10 patients were treated with OK-432, 19 patients

received doxycycline, and 12 patients received ethanolamine. In univariate analysis, different sclerosants had similar effectiveness after the first injection and final clinical outcome (p=0.5317). In multivariate analysis controlling for disease severity stage as well as disease characteristics (macrocystic vs mixed subtypes), different sclerosants also had similar effectiveness after the first injection (p=0.1192). Radiologic analysis indicated an 84.5% average volume reduction, with similar effectiveness between the different sclerosants (p=0.9910). CONCLUSIONS: In this series of LM cases treated at Stanford, we found that doxycycline, OK-432, and ethanolamine oleate sclerotherapy appear to have a similar safety and efficacy profile in the treatment of macrocystic and mixed LMs of the head and neck in the pediatric population.

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Conflict of interest statement: Competing interests: None declared.

32. EMBO Mol Med. 2016 May 2;8(5):511-26. doi: 10.15252/emmm.201505421. Print 2016 May.

The anti-hypertensive drug prazosin inhibits glioblastoma growth via the PKCδ-dependent inhibition of the AKT pathway.

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A variety of drugs targeting monoamine receptors are routinely used in human pharmacology. We assessed the effect of these drugs on the viability of tumor-initiating cells isolated from patients with glioblastoma. Among the drugs targeting monoamine receptors, we identified prazosin, an α1- and α2B-adrenergic receptor antagonist, as the most potent inducer of patient-derived glioblastoma-initiating cell death. Prazosin triggered apoptosis of glioblastoma-initiating cells and of their differentiated progeny, inhibited glioblastoma growth in orthotopic xenografts of patient-derived glioblastoma-initiating cells, and increased survival of glioblastoma-bearing mice. We found that prazosin acted in glioblastoma-initiating cells independently from adrenergic receptors. Its off-target activity occurred via a PKCδ-dependent inhibition of the AKT pathway, which resulted in caspase-3 activation. Blockade of PKCδ activation prevented all molecular changes observed in prazosin-treated glioblastoma-initiating cells, as well as prazosin-induced apoptosis. Based on these data, we conclude that prazosin, an FDA-approved drug for the control of hypertension, inhibits glioblastoma growth through a PKCδ-dependent mechanism. These findings open up promising prospects for the use of prazosin as an adjuvant therapy for glioblastoma patients.

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33. AJNR Am J Neuroradiol. 2016 Sep;37(9):1738-44. doi: 10.3174/ajnr.A4772. Epub 2016 Apr 21.

Gray Matter Growth Is Accompanied by Increasing Blood Flow and Decreasing Apparent Diffusion Coefficient during Childhood.

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BACKGROUND AND PURPOSE: Normal values of gray matter volume, cerebral blood flow, and water diffusion have not been established for healthy children. We sought to determine reference values for age-dependent changes of these parameters in healthy children. MATERIALS AND METHODS: We retrospectively reviewed MR imaging data from 100 healthy children. Using an atlas-based approach, age-related normal values for regional CBF, apparent diffusion coefficient, and volume were determined for the cerebral cortex, hippocampus, thalamus, caudate, putamen, globus pallidus, amygdala, and nucleus accumbens. RESULTS: All gray matter structures grew rapidly before the age of 10 years and then plateaued or slightly declined thereafter. The ADC of all structures decreased with age, with the most rapid changes occurring prior to the age of 5 years. With the exception of the globus pallidus, CBF increased rather linearly with age. CONCLUSIONS: Normal brain gray matter is characterized by rapid early volume growth and increasing CBF with concomitantly decreasing ADC. The extracted reference data that combine CBF and ADC parameters during brain growth may provide a useful resource when assessing pathologic changes in children.

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34. PLoS One. 2016 Apr 19;11(4):e0153550. doi: 10.1371/journal.pone.0153550. eCollection 2016.

Anti-CD47 Treatment Stimulates Phagocytosis of Glioblastoma by M1 and M2 Polarized Macrophages and Promotes M1 Polarized Macrophages In Vivo.

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Tumor-associated macrophages (TAMs) represent an important cellular subset within the glioblastoma (WHO grade IV) microenvironment and are a potential therapeutic target. TAMs display a continuum of different polarization states between antitumorigenic M1 and protumorigenic M2 phenotypes, with a lower M1/M2 ratio correlating with worse prognosis. Here, we investigated the effect of macrophage polarization on anti-CD47 antibody-mediated phagocytosis of human glioblastoma cells in vitro, as well as the effect of anti-CD47 on the distribution of M1 versus M2 macrophages within human glioblastoma cells grown in mouse xenografts. Bone marrow-derived mouse macrophages and peripheral blood-derived human macrophages were polarized in vitro toward M1 or M2 phenotypes and verified by flow cytometry. Primary human glioblastoma cell lines were offered as targets to mouse and human M1 or M2 polarized macrophages in vitro. The addition of an anti-CD47 monoclonal antibody led to enhanced tumor-cell phagocytosis by mouse and human M1 and M2 macrophages. In both cases, the anti-CD47-induced phagocytosis by M1 was more prominent than that for M2. Dissected tumors from human glioblastoma xenografted within NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ mice and treated with anti-CD47 showed a significant increase of M1 macrophages within the tumor. These data show that anti-CD47 treatment leads to enhanced tumor cell phagocytosis by both M1 and M2 macrophage subtypes with a higher phagocytosis rate by M1 macrophages. Furthermore, these data demonstrate that anti-CD47 treatment alone can shift the phenotype of macrophages toward the M1 subtype in vivo.

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35. Neuron. 2016 Jan 6;89(1):37-53. doi: 10.1016/j.neuron.2015.11.013. Epub 2015 Dec 10.

Purification and Characterization of Progenitor and Mature Human Astrocytes Reveals Transcriptional and Functional Differences with Mouse.

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Neuron. 2016 Jan 6;89(1):1-2.
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The functional and molecular similarities and distinctions between human and murine astrocytes are poorly understood. Here, we report the development of an immunopanning method to acutely purify astrocytes from fetal, juvenile, and adult human brains and to maintain these cells in serum-free cultures. We found that human astrocytes have abilities similar to those of murine astrocytes in promoting neuronal survival, inducing functional synapse formation, and engulfing synaptosomes. In contrast to existing observations in mice, we found that mature human astrocytes respond robustly to glutamate. Next, we performed RNA sequencing of healthy human astrocytes along with astrocytes from epileptic and tumor foci and compared these to human neurons, oligodendrocytes, microglia, and endothelial cells (available at http://www.brainrnaseq.org). With these profiles, we identified novel human-specific astrocyte genes and discovered a transcriptome-wide transformation between astrocyte precursor cells and mature post-mitotic astrocytes. These data represent some of the first cell-type-specific molecular profiles of the healthy and diseased human brain.

DOI: 10.1016/j.neuron.2015.11.013 PMCID: PMC4707064 PMID: 26687838 [Indexed for MEDLINE]

36. Invest Radiol. 2016 Apr;51(4):221-227. doi: 10.1097/RLI.0000000000000230.

Safety Report of Ferumoxytol for Magnetic Resonance Imaging in Children and Young Adults.

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OBJECTIVE: The aim of this study was to assess the safety profile of ferumoxytol as an intravenous magnetic resonance imaging contrast agent in children. MATERIALS AND METHODS: We prospectively evaluated the safety of ferumoxytol administrations as an “off-label” contrast agent for magnetic resonance imaging in nonrandomized phase 4 clinical trials at 2 centers. From September 2009 to February 2015, 49 pediatric patients (21 female and 28 male, 5-18 years) and 19 young adults (8 female and 11 male, 18-25 years) were reported under an investigator-initiated investigational new drug investigation with institutional review board approval, in health insurance portability and accountability act compliance, and after written informed consent of the child's legal representative or the competent adult patient was obtained. Patients received either a single dose (5 mg Fe/kg) or up to 4 doses of ferumoxytol (0.7-4 mg Fe/kg) intravenously, which were approximately equivalent to one third of the dose for anemia treatment. We monitored vital signs and adverse events directly for up to 1 hour after injection. In addition, we examined weekly vitals, hematologic, renal, and liver

serum panels for 1 month after injection in over 20 pediatric patients. At fixed time points before and after ferumoxytol injection, data were evaluated for significant differences by a repeated measures linear mixed model. RESULTS: Four mild adverse events, thought to be related to ferumoxytol, were observed within 1 hour of 85 ferumoxytol injections: 2 episodes of mild hypotension and 1 case of nausea in 65 injections in pediatric patients without related clinical symptoms. One young adult patient developed warmness and erythema at the injection site. All adverse events were self-resolving. No spontaneous serious adverse events were reported. At a dose of 5 mg Fe/kg or lower, intravenous ferumoxytol injection had no clinical relevance or statistically significant effect ($P > 0.05$) on vital signs, hematological parameters, kidney function, or liver enzymes within 1 month of the injection. CONCLUSIONS: Ferumoxytol was overall well tolerated among 49 pediatric and 19 young adult patients experiencing various tumors or kidney transplants without major adverse events or signs of hematologic and kidney impairment or liver toxicity. Larger studies are needed to determine the incidence of anaphylactic reactions.

DOI: 10.1097/RLI.0000000000000230 PMCID: PMC4783197 PMID: 26656202 [Indexed for MEDLINE]

37. J Child Neurol. 2016 Oct;31(12):1354-66. doi: 10.1177/0883073815610428. Epub 2015 Oct 26.

Pediatric Ependymoma.

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Over the past 150 years since Virchow's initial characterization of ependymoma, incredible efforts have been made in the classification of these tumors and in the care of pediatric patients with this disease. While the advent of modern neurosurgery and the optimization of radiation have provided significant gains, a more complex but incomplete picture of pediatric ependymomas has begun to form through a combination of international collaborations and detailed genetic and histologic characterizations. This review includes and synthesizes the clinical understanding of pediatric ependymoma and their developing molecular insight into what is truly a family of malignancies in which distinct members require different surgical approaches, radiation plans, and targeted therapies.

DOI: 10.1177/0883073815610428 PMID: 26503805 [Indexed for MEDLINE]

38. Neuropsychopharmacology. 2016 Apr;41(5):1191-8. doi: 10.1038/npp.2015.282. Epub 2015 Sep 11.

Randomized Placebo-Controlled Trial of Methylphenidate or Galantamine for Persistent Emotional and Cognitive Symptoms Associated with PTSD and/or Traumatic Brain Injury.

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We report findings from a 12-week randomized double-blinded placebo-controlled trial of methylphenidate or galantamine to treat emotional and cognitive complaints in individuals (n=32) with a history of PTSD, TBI, or both conditions. In this small pilot study, methylphenidate treatment was associated with clinically meaningful and statistically significant improvement compared with placebo on the primary outcome, a measure of cognitive complaints (Ruff Neurobehavioral Inventory-Postmorbid Cognitive Scale), as well as on the secondary outcomes reflecting post-concussive (Rivermead Post Concussive Symptom Questionnaire) and post-traumatic stress symptoms (Posttraumatic Stress Disorder Checklist). Treatment was well tolerated. These results suggest the need for a larger RCT to replicate and confirm these findings. Design considerations for such a trial should include the need for multiple sites to facilitate adequate recruitment and extension of the treatment and follow-up periods.

DOI: 10.1038/npp.2015.282 PMCID: PMC4793116 PMID: 26361060 [Indexed for MEDLINE]

39. Neurosurgery. 2015 Nov;77(5):794-802; discussion 802. doi: 10.1227/NEU.0000000000000918.

Neural Placode Tissue Derived From Myelomeningocele Repair Serves as a Viable Source of Oligodendrocyte Progenitor Cells.

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BACKGROUND: The presence, characteristics, and potential clinical relevance of neural progenitor populations within the neural placodes of myelomeningocele patients remain to be studied. Neural stem cells are known to reside adjacent to ependyma-lined surfaces along the central nervous system axis. OBJECTIVE: Given such neuroanatomic correlation and regenerative capacity in fetal development, we assessed myelomeningocele-derived neural placode tissue as a potentially novel source of neural stem and progenitor cells. METHODS: Nonfunctional neural placode tissue was harvested from infants during the surgical repair of myelomeningocele and subsequently further analyzed by in vitro studies, flow cytometry, and immunofluorescence. To assess lineage potential, neural placode-derived neurospheres were subjected to differential media conditions. Through assessment of platelet-derived growth factor receptor α (PDGFRα) and CD15 cell marker expression, Sox2+Olig2+ putative oligodendrocyte progenitor cells were successfully isolated. RESULTS: PDGFRαCD15 cell populations demonstrated the highest rate of self-renewal capacity and

multipotency of cell progeny. Immunofluorescence of neural placode-derived neurospheres demonstrated preferential expression of the oligodendrocyte progenitor marker, CNPase, whereas differentiation to neurons and astrocytes was also noted, albeit to a limited degree. CONCLUSION: Neural placode tissue contains multipotent progenitors that are preferentially biased toward oligodendrocyte progenitor cell differentiation and presents a novel source of such cells for use in the treatment of a variety of pediatric and adult neurological disease, including spinal cord injury, multiple sclerosis, and metabolic leukoencephalopathies.

DOI: 10.1227/NEU.0000000000000918 PMID: 26225855 [Indexed for MEDLINE]

40. Neurooncol Pract. 2014 Dec;1(4):158-165. Epub 2014 Sep 1.

Sports and childhood brain tumors: Can I play?

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BACKGROUND: It is unknown whether children with brain tumors have a higher risk of complications while participating in sports. We sought to estimate the prevalence of such events by conducting a systematic review of the literature, and we surveyed providers involved with pediatric central nervous system (CNS) tumor patients. METHODS: A systematic review of the literature in the PubMed, Scopus, and Cochrane databases was conducted for original articles addressing sport-related complications in the brain-tumor population. An online questionnaire was created to survey providers involved with pediatric CNS tumor patients about their current recommendations and experience regarding sports and brain tumors. RESULTS: We retrieved 32 subjects, including 19 pediatric cases from the literature. Most lesions associated with sport complications were arachnoid cysts (n = 21), followed by glioma (n = 5). The sports in which symptom onset most commonly occurred were soccer (n = 7), football (n = 5), and running (n = 5). We surveyed 111 pediatric neuro-oncology providers. Sport restriction varied greatly from none to 14 sports. Time to return to play in sports with contact also varied considerably between providers. Rationales for limiting sports activities were partly related to subspecialty. Responders reported 9 sport-related adverse events in patients with brain tumor. CONCLUSIONS: Sport-related complications are uncommon in children with brain tumors. Patients might not be at a significantly higher risk and should not need to be excluded from most sports activities.

DOI: 10.1093/nop/npu020 PMCID: PMC4369718 PMID: 26034627

41. Glycobiology. 2015 Aug;25(8):836-44. doi: 10.1093/glycob/cwv024. Epub 2015 Apr 21.

A congenital disorder of deglycosylation: Biochemical characterization of N-glycanase 1 deficiency in patient fibroblasts.

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N-Glycanase 1, encoded by NGLY1, catalyzes the deglycosylation of misfolded N-linked glycoproteins retrotranslocated into the cytosol. We identified nine cases with mutations in NGLY1. The patients show developmental delay, seizures, peripheral neuropathy, abnormal liver function and alacrima (absence of tears). The mutations in NGLY1 resulted in the absence of N-glycanase 1 protein in patient-derived fibroblasts. Applying a recently established cellular deglycosylation-dependent Venus fluorescence assay, we found that patient fibroblasts had dramatically reduced fluorescence, indicating a pronounced reduction in N-glycanase enzymatic activity. Using this assay, we could find no evidence of other related activities. Our findings reveal that NGLY1 mutations destroy both N-glycanase 1 protein and enzymatic activity.

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42. Mol Genet Metab. 2015 Apr;114(4):527-36. doi: 10.1016/j.ymgme.2015.01.014. Epub 2015 Feb 7.

Disease specific therapies in leukodystrophies and leukoencephalopathies.

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Leukodystrophies are a heterogeneous, often progressive group of disorders manifesting a wide range of symptoms and complications. Most of these disorders have historically had no etiologic or disease specific therapeutic approaches. Recently, a greater understanding of the pathologic mechanisms associated with leukodystrophies has allowed clinicians and researchers to prioritize treatment strategies and advance research in therapies for specific disorders, some of which are on the verge of pilot or Phase I/II clinical trials. This shifts the care of leukodystrophy patients from the management of the complex array of symptoms and sequelae alone to targeted therapeutics. The unmet needs of leukodystrophy patients still remain an overwhelming burden. While the overwhelming consensus is that these disorders collectively are symptomatically treatable, leukodystrophy patients are in need of advanced therapies and if possible, a cure.

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43. J Neurooncol. 2015 Jul;123(3):449-57. doi: 10.1007/s11060-015-1729-x. Epub 2015 Feb 15.

Glioblastoma stem cells and stem cell-targeting immunotherapies.

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Advancements in immunotherapeutics promise new possibilities for the creation of glioblastoma (GBM) treatment options. Ongoing work in cancer stem cell biology has progressively elucidated the role of this tumor sub-population in oncogenesis and has distinguished them as prime therapeutic targets. Current clinical trials take a multifaceted approach with the intention of harnessing the intrinsic cytotoxic capabilities of the immune system to directly target glioblastoma cancer stem cells (gCSC) or indirectly disrupt their stromal microenvironment. Monoclonal antibodies (mAbs), dendritic cell (DC) vaccines, and chimeric antigen receptor (CAR) T cell therapies have emerged as the most common approaches, with particular iterations incorporating cancer stem cell antigenic markers in their treatment designs. Ongoing work to determine the comprehensive antigenic profile of the gCSC in conjunction with efforts to counter the immunosuppressive tumor microenvironment holds much promise in future immunotherapeutic strategies against GBM. Given recent advancements in these

fields, we believe there is tremendous potential to improve outcomes of GBM patients in the continuing evolution of immunotherapies targeted to cancer stem cell populations in GBM.

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44. BMC Genomics. 2015 Jan 22;16:11. doi: 10.1186/s12864-014-1211-8.

Joint eQTL assessment of whole blood and dura mater tissue from individuals with Chiari type I malformation.

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BACKGROUND: Expression quantitative trait loci (eQTL) play an important role in the regulation of gene expression. Gene expression levels and eQTLs are expected to vary from tissue to tissue, and therefore multi-tissue analyses are necessary to fully understand complex genetic conditions in humans. Dura mater tissue likely interacts with cranial bone growth and thus may play a role in the etiology of Chiari Type I Malformation (CMI) and related conditions, but it is often inaccessible and its gene expression has not been well studied. A genetic basis to CMI has been established; however, the specific genetic risk factors are not well characterized. RESULTS: We present an assessment of eQTLs for whole blood and dura mater tissue from individuals with CMI. A joint-tissue analysis identified 239 eQTLs in either dura or blood, with 79% of these eQTLs shared by both tissues. Several identified eQTLs were novel and these implicate genes involved in bone development (IPO8, XYLT1, and PRKAR1A), and ribosomal pathways related to marrow and bone dysfunction, as potential candidates in the development of CMI. CONCLUSIONS: Despite strong overall heterogeneity in expression levels between blood and dura, the majority of cis-eQTLs are shared by both tissues. The power to detect shared eQTLs was improved by using an integrative statistical approach. The identified tissue-specific and shared eQTLs provide new insight into the genetic basis for CMI and related conditions.

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45. Mol Genet Metab. 2015 Apr;114(4):516-26. doi: 10.1016/j.ymgme.2014.12.433. Epub 2014 Dec 27.

Consensus statement on preventive and symptomatic care of leukodystrophy patients.

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Leukodystrophies are inherited disorders whose primary pathophysiology consists of abnormal deposition or progressive disruption of brain myelin. Leukodystrophy patients manifest many of the same symptoms and medical complications despite the wide spectrum of genetic origins. Although no definitive cures exist, all of these conditions are treatable. This report provides the first expert consensus on the recognition and treatment of medical and psychosocial complications associated with leukodystrophies. We include a discussion of serious and potentially preventable medical complications and propose several preventive care strategies. We also outline the need for future research to prioritize clinical needs and subsequently develop, validate, and optimize specific care strategies.

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46. Oncogene. 2015 Jul;34(29):3770-9. doi: 10.1038/onc.2014.304. Epub 2014 Sep 22.

Survivin as a therapeutic target in Sonic hedgehog-driven medulloblastoma.

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Medulloblastoma (MB) is a highly malignant brain tumor that occurs primarily in children. Although surgery, radiation and high-dose chemotherapy have led to increased survival, many MB patients still die from their disease, and patients who survive suffer severe long-term side effects as a consequence of treatment. Thus, more effective and less toxic therapies for MB are critically important. Development of such therapies depends in part on identification of genes that are necessary for growth and survival of tumor cells. Survivin is an inhibitor of apoptosis protein that regulates cell cycle progression and resistance to apoptosis, is frequently expressed in human MB and when expressed at high levels predicts poor clinical outcome. Therefore, we hypothesized that Survivin may have a critical role in growth and survival of MB cells and that targeting it may enhance MB therapy. Here we show that Survivin is overexpressed in tumors from patched (Ptch) mutant mice, a model of Sonic hedgehog (SHH)-driven MB. Genetic deletion of survivin in Ptch mutant tumor cells significantly inhibits proliferation and causes cell cycle arrest. Treatment with small-molecule antagonists of Survivin impairs proliferation and survival of both murine and human MB cells. Finally, Survivin antagonists impede growth of MB cells in vivo. These studies highlight the importance of Survivin in SHH-driven MB, and suggest that it may represent a novel therapeutic target in patients with this disease.

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47. Neuro Oncol. 2015 Mar;17(3):440-7. doi: 10.1093/neuonc/nou162. Epub 2014 Aug 13.

Clinical course and progression-free survival of adult intracranial and spinal ependymoma patients.

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BACKGROUND: Ependymomas are rare CNS tumors. Previous studies describing the clinical course of ependymoma patients were restricted to small sample sizes, often with patients at a specific institution. METHODS: Clinically annotated ependymoma tissue samples from 19 institutions were centrally reviewed. Patients were all adults aged 18 years or older at the time of diagnosis. Potential prognostic clinical factors identified on univariate analysis were included in a multivariate Cox proportional hazards model with backwards selection to model progression-free survival. RESULTS: The 282 adult ependymoma patients were equally male and female with a mean age of 43 years (range, 18-80y) at diagnosis. The majority were grade II (78%) with the tumor grade for 20 cases being reclassified on central review (half to higher grade). Tumor locations were spine (46%), infratentorial (35%), and supratentorial (19%). Tumor recurrence occurred in 26% (n = 74) of patients with a median time to progression of 14 years. A multivariate Cox proportional hazards model identified supratentorial location (P < .01), grade III (anaplastic; P < .01), and subtotal resection, followed or not by radiation (P < .01), as significantly increasing risk of early progression. CONCLUSIONS: We report findings from an ongoing, multicenter collaboration from a collection of clinically annotated adult ependymoma tumor samples demonstrating distinct predictors of progression-free survival. This unique resource provides the opportunity to better define the clinical course of ependymoma for clinical and translational studies.

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48. Childs Nerv Syst. 2014 Oct;30(10):1625-43. doi: 10.1007/s00381-014-2502-8. Epub 2014 Aug 1.

Ventricular endoscopy in the pediatric population: review of indications.

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INTRODUCTION: Neuroendoscopy has greatly impacted pediatric neurosurgery over the past few decades. Improved optics and microsurgical tools have allowed neuroendoscopes to be used for a multitude of neurosurgical procedures. DISCUSSION: In this review article, we present the breadth of intraventricular neuroendoscopic procedures for the treatment of conditions ranging from hydrocephalus and brain tumors to congenital cysts and other pathologies. We critically discuss treatment indications and reported success rates for neuroendoscopic procedures. We also present novel approaches, technical nuances, and variations from recently published literature and as

practiced in the authors' institution.

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49. J Neurol Surg B Skull Base. 2014 Apr;75(2):96-103. doi: 10.1055/s-0033-1358374. Epub 2014 Feb 10.

The transpalatal approach to repair of congenital Basal skull base cephaloceles.

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Basal skull base herniations, including meningoceles and encephaloceles, are rare and may present with characteristic facial and neurologic features. The traditional craniotomy approach has known morbidity, and nasal endoscopy may not allow for control of large posterior basal defects, especially in newborns. We present two cases of successful repair of basal transsphenoidal meningoceles using an oral-transpalatal approach. The first patient with an intact palate presented with respiratory distress, and a palatectomy was performed for access to the skull base. The second patient had a large basal herniation that was reduced through a congenital midline cleft palate, and a calvarial bone graft was used to repair the defect. A literature search revealed 10 previous successful cases using the transpalatal repair, which allows for excellent access, low morbidity, and a team-oriented method to skull base surgery.

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50. Hum Mol Genet. 2014 Dec 15;23(24):6616-33. doi: 10.1093/hmg/ddu363. Epub 2014 Jul 15.

Imputation and subset-based association analysis across different cancer types identifies multiple independent risk loci in the TERT-CLPTM1L region on chromosome 5p15.33.

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Genome-wide association studies (GWAS) have mapped risk alleles for at least 10 distinct cancers to a small region of 63 000 bp on chromosome 5p15.33. This region harbors the TERT and CLPTM1L genes; the former encodes the catalytic subunit of telomerase reverse transcriptase and the latter may play a role in apoptosis. To investigate further the genetic architecture of common susceptibility alleles in this region, we conducted an agnostic subset-based meta-analysis (association analysis based on subsets) across six distinct cancers in 34 248 cases and 45 036 controls. Based on sequential conditional analysis, we identified as many as six independent risk loci marked by common single-nucleotide polymorphisms: five in the TERT gene (Region 1: rs7726159, P = 2.10 × 10(-39); Region 3: rs2853677, P = 3.30 × 10(-36) and PConditional = 2.36 × 10(-8); Region 4: rs2736098, P = 3.87 × 10(-12) and PConditional = 5.19 × 10(-6), Region 5: rs13172201, P = 0.041 and PConditional = 2.04 × 10(-6); and Region 6: rs10069690, P = 7.49 × 10(-15) and PConditional = 5.35 × 10(-7)) and one in the neighboring CLPTM1L gene (Region 2: rs451360; P = 1.90 × 10(-18) and PConditional = 7.06 × 10(-16)). Between three and five cancers mapped to each independent locus with both risk-enhancing and protective effects. Allele-specific effects on DNA methylation were seen for a subset of risk loci, indicating that methylation and subsequent effects on gene expression may contribute to the biology of risk variants on 5p15.33. Our results provide strong support for extensive pleiotropy across

this region of 5p15.33, to an extent not previously observed in other cancer susceptibility loci.

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51. AJNR Am J Neuroradiol. 2014 Jul;35(7):1263-9. doi: 10.3174/ajnr.A3990. Epub 2014 May 15.

MRI surrogates for molecular subgroups of medulloblastoma.

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BACKGROUND AND PURPOSE: Recently identified molecular subgroups of medulloblastoma have shown potential for improved risk stratification. We hypothesized that distinct MR imaging features can predict these subgroups. MATERIALS AND METHODS: All patients with a diagnosis of medulloblastoma at one institution, with both pretherapy MR imaging and surgical tissue, served as the discovery cohort (n = 47). MR imaging features were assessed by 3 blinded neuroradiologists. NanoString-based assay of tumor tissues was conducted to classify the tumors into the 4 established molecular subgroups (wingless, sonic hedgehog, group 3, and group 4). A second pediatric medulloblastoma cohort (n = 52) from an independent institution was used for validation of the MR imaging features predictive of the molecular subtypes. RESULTS: Logistic regression analysis within the discovery cohort revealed tumor location (P < .001) and enhancement pattern (P = .001) to be significant predictors of medulloblastoma subgroups. Stereospecific computational analyses confirmed that group 3 and 4 tumors predominated within the midline fourth ventricle (100%, P = .007), wingless tumors were localized to the cerebellar peduncle/cerebellopontine angle cistern with a positive predictive value of 100% (95% CI, 30%-100%), and sonic hedgehog tumors arose in the cerebellar hemispheres with a positive predictive value of 100% (95% CI, 59%-100%). Midline group 4 tumors presented with minimal/no enhancement with a positive predictive value of 91% (95% CI, 59%-98%). When we used the MR imaging feature-based regression model, 66% of medulloblastomas were correctly predicted in the discovery cohort, and 65%, in the validation cohort. CONCLUSIONS: Tumor location and enhancement pattern were predictive of molecular subgroups of pediatric medulloblastoma and may potentially serve as a surrogate for genomic testing.

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52. AJNR Am J Neuroradiol. 2014 Jul;35(7):1433-9. doi: 10.3174/ajnr.A3891. Epub 2014 Mar 20.

Hydrocephalus decreases arterial spin-labeled cerebral perfusion.

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BACKGROUND AND PURPOSE: Reduced cerebral perfusion has been observed with elevated intracranial pressure. We hypothesized that arterial spin-labeled CBF can be used as a marker for symptomatic hydrocephalus. MATERIALS AND METHODS: We compared baseline arterial spin-labeled CBF in 19 children (median age, 6.5 years; range, 1-17 years) with new posterior fossa brain tumors and clinical signs of intracranial hypertension with arterial spin-labeled CBF in 16 age-matched controls and 4 patients with posterior fossa tumors without ventriculomegaly or signs of intracranial hypertension. Measurements were recorded in the cerebrum at the vertex, deep gray nuclei, and periventricular white matter and were assessed for a relationship to ventricular size. In 16 symptomatic patients, we compared cerebral perfusion before and after alleviation of hydrocephalus. RESULTS: Patients with uncompensated hydrocephalus had lower arterial spin-labeled CBF than healthy controls for all brain regions interrogated ($P < .001$). No perfusion difference was seen between asymptomatic patients with posterior fossa tumors and healthy controls ($P = 1.000$). The median arterial spin-labeled CBF increased after alleviation of obstructive hydrocephalus ($P < .002$). The distance between the frontal horns inversely correlated with arterial spin-labeled CBF of the cerebrum ($P = .036$) but not the putamen ($P = .156$), thalamus ($P = .111$), or periventricular white matter ($P = .121$). CONCLUSIONS: Arterial spin-labeled-CBF was reduced in children with uncompensated hydrocephalus and restored after its alleviation. Arterial spin-labeled-CBF perfusion MR imaging may serve a future role in the neurosurgical evaluation of hydrocephalus, as a potential noninvasive method to follow changes of intracranial pressure with time.

DOI: 10.3174/ajnr.A3891 PMID: 24651817 [Indexed for MEDLINE]

53. J Neurooncol. 2014 Mar;117(1):175-82. doi: 10.1007/s11060-014-1375-8. Epub 2014 Feb 13.

Diffusion-weighted MRI derived apparent diffusion coefficient identifies prognostically distinct subgroups of pediatric diffuse intrinsic pontine glioma.

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While pediatric diffuse intrinsic pontine gliomas (DIPG) remain fatal, recent data have shown subgroups with distinct molecular biology and clinical behavior. We hypothesized that diffusion-weighted MRI can be used as a prognostic marker to stratify DIPG subsets with distinct clinical behavior. Apparent diffusion coefficient (ADC) values derived from diffusion-weighted MRI were computed in 20 consecutive children with treatment-naïve DIPG tumors. The median ADC for the cohort was used to stratify the tumors into low and high ADC groups. Survival, gender, therapy, and potential steroid effects were compared between the ADC groups. Median age at diagnosis was 6.6 (range 2.3-13.2) years, with median follow-up seven (range 1-36) months. There were 14 boys and six

girls. Seventeen patients received radiotherapy, five received chemotherapy, and six underwent cerebrospinal fluid diversion. The median ADC of 1,295 × 10(-6) mm(2)/s for the cohort partitioned tumors into low or high diffusion groups, which had distinct median survivals of 3 and 13 months, respectively (log-rank $p < 0.001$). Low ADC tumors were found only in boys, whereas high ADC tumors were found in both boys and girls. Available tissue specimens in three low ADC tumors demonstrated high-grade histology, whereas one high ADC tumor demonstrated low-grade histology with a histone H3.1 K27M mutation and high-grade metastatic lesion at autopsy. ADC derived from diffusion-weighted MRI may identify prognostically distinct subgroups of pediatric DIPG.

DOI: 10.1007/s11060-014-1375-8 PMID: 24522717 [Indexed for MEDLINE]

54. Cureus. 2014;6(9). pii: e207. doi: 10.7759/cureus.207. Epub 2014 Sep 17.

A Bioengineered Peptide that Localizes to and Illuminates Medulloblastoma: A New Tool with Potential for Fluorescence-Guided Surgical Resection.

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Tumors of the central nervous system are challenging to treat due to the limited effectiveness and associated toxicities of chemotherapy and radiation therapy. For tumors that can be removed surgically, extent of malignant tissue resection has been shown to correlate with disease progression, recurrence, and survival. Thus, improved technologies for real-time brain tumor imaging are critically needed as tools for guided surgical resection. We previously engineered a novel peptide that binds with high affinity and unique specificity to αVβ3, αVβ5, and α5β1 integrins, which are present on tumor cells, and the vasculature of many cancers, including brain tumors. In the current study, we conjugated this engineered peptide to a near infrared fluorescent dye (Alexa Fluor 680), and used the resulting molecular probe for non-invasive whole body imaging of patient-derived medulloblastoma xenograft tumors implanted in the cerebellum of mice. The engineered peptide exhibited robust targeting and illumination of intracranial medulloblastoma following both intravenous and intraperitoneal injection routes. In contrast, a variant of the engineered peptide containing a scrambled integrin-binding sequence did not localize to brain tumors, demonstrating that tumor-targeting is driven by specific integrin interactions. Ex vivo imaging was used to confirm the presence of tumor and molecular probe localization to the cerebellar region. These results warrant further clinical development of the engineered peptide as a tool for image-guided resection of central nervous system tumors.

DOI: 10.7759/cureus.207 PMCID: PMC5515084 PMID: 28729960

55. Neurosurgery. 2014 Mar;10 Suppl 1:1-14. doi: 10.1227/NEU.0000000000000119.

Less invasive pedicled omental-cranial transposition in pediatric patients with moyamoya disease and failed prior revascularization.

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BACKGROUND: Patients with moyamoya disease and progressive neurological deterioration despite previous revascularization pose a major treatment challenge. Many have exhausted typical sources for bypass or have ischemia in areas that are difficult to reach with an indirect pedicled flap. Omental-cranial transposition has been an effective, but sparingly used technique because of its associated morbidity. OBJECTIVE: We have refined a laparoscopic method of harvesting an omental flap that preserves its gastroepiploic arterial supply. METHODS: The pedicled omentum can be lengthened as needed by dividing it between the vascular arcades. It is transposed to the brain via skip incisions. The flap can be trimmed or stretched to cover ischemic areas of the brain. The cranial exposure is performed in parallel with pediatric surgeons. We performed this technique in 3 pediatric patients with moyamoya disease (aged 5-12 years) with previous superficial temporal artery to middle cerebral artery bypasses and progressive ischemic symptoms. In 1 patient, we transposed omentum to both hemispheres. RESULTS: Blood loss ranged from 75 to 250 mL. After surgery, patients immediately tolerated a diet and were discharged in 3 to 5 days. The ischemic symptoms of all 3 children resolved within 3 months postoperatively. Magnetic resonance imaging at 1 year showed improved perfusion and no new infarcts. Angiography showed excellent revascularization of targeted areas and patency of the donor gastroepiploic artery. CONCLUSION: Laparoscopic omental harvest for cranial-omental transposition can be performed efficiently and safely. Patients with moyamoya disease appear to tolerate this technique much better than laparotomy. With this method, we can achieve excellent angiographic revascularization and resolution of ischemic symptoms.

DOI: 10.1227/NEU.0000000000000119 PMID: 23921707 [Indexed for MEDLINE]

56. Brain Sci. 2013 Nov 26;3(4):1597-614. doi: 10.3390/brainsci3041597.

Reorganization and stability for motor and language areas using cortical stimulation: case example and review of the literature.

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The cerebral organization of language in epilepsy patients has been studied with invasive procedures such as Wada testing and electrical cortical stimulation mapping and more recently with noninvasive neuroimaging techniques, such as functional MRI. In the setting of a chronic seizure disorder, clinical variables have been shown to contribute to cerebral language reorganization underscoring the need for language lateralization and localization procedures. We present a 14-year-old pediatric patient with a refractory epilepsy disorder who underwent two neurosurgical resections of a left frontal epileptic focus separated by a year. He was mapped extraoperatively through a subdural grid using cortical stimulation to preserve motor and language functions. The clinical history and extensive workup prior to surgery is discussed as well as the opportunity to compare the cortical maps for language, motor, and sensory function before each resection. Reorganization in cortical tongue sensory areas was seen concomitant with a new zone of ictal and interictal activity in the previous tongue sensory area. Detailed neuropsychological data is presented before and after any surgical intervention to hypothesize about the extent of reorganization between epochs. We conclude that intrahemispheric cortical plasticity does occur following frontal lobe resective surgery in a teenager with medically refractory seizures.

DOI: 10.3390/brainsci3041597 PMCID: PMC4061887 PMID: 24961623

57. J Neurosurg Pediatr. 2013 Mar;11(3):302-6. doi: 10.3171/2012.10.PEDS11159. Epub 2012 Dec 21.

Use of the NeuroBalloon catheter for endoscopic third ventriculostomy.

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Endoscopic third ventriculostomy (ETV) has become the procedure of choice for treatment of obstructive hydrocephalus. While patient selection is the most critical factor in determining the success of an ETV procedure, the technical challenge lies in the proper site of fenestration and the successful creation of a patent stoma. Positioning of a single balloon catheter at the level or below the floor of the third ventricle to achieve an optimal ventriculostomy can at times be challenging. Here, the authors describe the use of a double-barrel balloon catheter (NeuroBalloon catheter), which facilitates positioning across, as well as dilation of, the floor of the third ventricle. The surgical technique and nuances of using the NeuroBalloon catheter and the experience in more than 1000 cases are described. The occurrence of vascular injury was less than 0.1%, and the risk of balloon rupture was less than 2%. The authors found that the placement and deployment of this balloon catheter facilitate the creation of an adequate ventriculostomy in a few simple steps.

DOI: 10.3171/2012.10.PEDS11159 PMID: 23259463 [Indexed for MEDLINE]

58. Childs Nerv Syst. 2013 Feb;29(2):297-301. doi: 10.1007/s00381-012-1938-y. Epub 2012 Oct 26.

Using bioabsorbable fixation systems in the treatment of pediatric skull deformities leads to good outcomes and low morbidity.

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BACKGROUND: Bioabsorbable fixation systems have been widely employed in pediatric patients for cranial reconstruction, obviating the complications of hardware migration and imaging artifact occurring with metallic implants. Recent concern over complications unique to bioabsorbable materials, such as inflammatory reaction and incomplete resorption, necessitates additional conclusive studies to further validate their use in pediatric neurosurgery and craniofacial surgery. Likewise, long-term follow-up in this clinical cohort has not previously been described. METHODS: We included consecutive pediatric patients under the age of 2, from Lucile Packard Children's Hospital, who underwent cranial vault reconstruction with the use of a bioabsorbable fixation system between 2003 and 2010. Hospital records were queried for patient characteristics, intraoperative data, and postoperative complications. RESULTS: Ninety-five patients with the following preoperative pathologies were analyzed: craniosynostosis (87), cloverleaf skull (5), frontonasal dysplasia (1), and frontonasal encephalocele (2). Median age was 6 months (range 1-24 months). Average case duration was 204 minutes (range 40-392 min), with median of 154 mL blood loss (range 30-500 mL). Ninety-three percent of patients had 1-4 plates implanted with 48% receiving three plates. The median number of screws used was 59 (range 0-130). The median length of hospital stay was 4 days (range 2-127 days) with an average follow-up of 22 months (five postoperative visits). The complications related to hardware implantation included swelling (1%) and broken hardware (1%), the latter of which required reoperation. DISCUSSION: The bioabsorbable fixation systems for cranial vault reconstruction in children less than 2 years of age is safe with tolerable morbidity rates.

DOI: 10.1007/s00381-012-1938-y PMID: 23099613 [Indexed for MEDLINE]

59. J Pediatr. 2012 Oct;161(4):734. doi: 10.1016/j.jpeds.2012.05.019.

50 years ago in The Journal of Pediatrics: the surgical management of meningoceles and meningomyeloceles.

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DOI: 10.1016/j.jpeds.2012.05.019 PMID: 22999580 [Indexed for MEDLINE]

60. Pediatr Neurosurg. 2012;48(1):13-20. doi: 10.1159/000337876. Epub 2012 Jul 21.

Ventricular access devices are safe and effective in the treatment of posthemorrhagic ventricular dilatation prior to shunt placement.

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Intraventricular hemorrhage of prematurity (IVH) is a diagnosis that has become more frequent in recent years. Advances in medical care have led to survival of increasingly premature infants, as well as infants with more complex medical conditions. Treatment with a ventricular access device (VAD) was reported almost 3 decades ago; however, it is unclear how effective this treatment is in the current population of premature infants. At our institution (from 2004 to present), we treat posthemorrhagic hydrocephalus (PHH) with a VAD. In order to look at safety and efficacy, we retrospectively combed the medical records of premature children, admitted to Lucile Packard

Children's Hospital from January 2005 to December 2009, and identified 310 premature children with IVH. Of these, 28 children required treatment for PHH with a VAD. There were no infections associated with placement of these devices and a very low rate of other complications, such as need for repositioning (7.41%) or replacement (3.75%). Our data show that treatment with a VAD is very safe, with few complications and can be used to treat PHH in this very complex infant population.

DOI: 10.1159/000337876 PMID: 22832699 [Indexed for MEDLINE]

61. Transl Stroke Res. 2011 Sep;2(3):250-65. doi: 10.1007/s12975-011-0093-1. Epub 2011 Aug 4.

Intravascular stem cell transplantation for stroke.

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Stroke is the third leading cause of death and the leading cause of adult disability in North America. Emphasis has been placed on developing treatments that reduce the devastating long-term impacts of this disease, and preclinical research on stem cell therapy has demonstrated promising results. However, questions about the optimal cell delivery method and timing of cell transplantation are not fully answered. Recent findings suggest that intravascular stem cell delivery is a safe and efficacious alternative to stereotactic cell injections. It also offers advantages should repeat treatments prove beneficial. Recent reports further suggest that intra-arterial injection results in a wider distribution of cells throughout the stroked hemisphere with a significantly greater cell engraftment compared to intravenous injection. In this review, we describe the benefits and potential risks associated with intravascular stem cell delivery and compare intra-arterial to intravenous cell transplantation methods. We discuss the importance of cell biodistribution and timing of transplantation in driving cell survival. We examine current proposed mechanisms involved in cell migration and functional recovery and discuss future directions for intravascular stem cell therapy research.

DOI: 10.1007/s12975-011-0093-1 PMID: 24323647

62. Neurosurgery. 2011 Mar;68(1 Suppl Operative):68-74. doi: 10.1227/NEU.0b013e31820780cd.

Fronto-orbital advancement using an en bloc frontal bone craniectomy.

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BACKGROUND: Fronto-orbital advancement is a procedure commonly performed in craniofacial centers for coronal and metopic suture synostosis. Several variations of the technique have been reported. OBJECTIVE: To describe our modifications to the anterior cranioplasty procedure and the results of our surgical series. METHODS: Using our craniofacial database, we retrospectively analyzed the records of all patients undergoing fronto-orbital advancement for craniosynostosis. The same team of neurosurgeons and plastic surgeons performed all procedures. Demographic data, operative time, blood loss, length of stay, and clinical outcome were analyzed. RESULTS: Of 248 patients treated for craniosynostosis, a total of 70 patients underwent fronto-orbital advancement. Nineteen

presented with metopic, 26 with unilateral coronal, 17 with bilateral coronal, and 8 with multiple synostosis. Median age at surgery was 6.5 months. Mean operative time was 210 minutes; mean blood loss was 167 mL; and length of stay was 4.5 days. A positive correlation was found between operative time and blood loss ($r = 0.1$, $P < .01$) and age at surgery and blood loss ($r = 0.3$, $P < .0001$). There was a minor morbidity rate of 2.9%. A good reconstruction was obtained in all patients using our en bloc fronto-orbital advancement without any midline osteotomies at a mean follow-up of 15 months. CONCLUSION: A team approach and the application of a standardized surgical technique should make it safer to operate in young children, shorten the surgical time, and lead to a reduction in blood loss. Reconstructing the frontal bone as an entire unit yielded excellent correction for coronal and metopic synostosis.

DOI: 10.1227/NEU.0b013e31820780cd PMID: 21206324 [Indexed for MEDLINE]

63. J Neurosurg Pediatr. 2010 Oct;6(4):393-7. doi: 10.3171/2010.7.PEDS10149.

Langerhans cell histiocytosis in a 5-month-old presenting with biparietal masses.

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Langerhans cell histiocytosis (LCH) is a rare proliferative disorder that occurs most commonly in the pediatric population as a result of pathological clonal proliferation of Langerhans cells with subsequent damage and destruction to surrounding tissue. Clinically, LCH presents in a variety of ways, which often results in prolonged time to diagnosis and subsequently poorer outcomes. In this case report, the authors describe an unusually early presentation of multisystem LCH in a patient at birth, which resulted in a 5-month delay to diagnosis and treatment. This patient presented both atypically young and with an uncommon initial manifestation of multisystem disease with multiple soft-tissue swellings rather than early skin involvement. Additionally, this patient had an unusual radiographic appearance with biparietal skull destruction on initial skull radiographs and biparietal soft-tissue lesions on CT resembling cephalohematoma at 3 months of age. The clinical and radiological evaluation, pathology, and treatment strategies are discussed, with particular attention paid to the importance of further workup of atypical nonresolving cephalohematomas to prevent disease progression and poorer outcomes.

DOI: 10.3171/2010.7.PEDS10149 PMID: 20887116 [Indexed for MEDLINE]

64. Neurosurg Clin N Am. 2010 Jul;21(3):565-73. doi: 10.1016/j.nec.2010.03.013.

Direct bypass techniques for the treatment of pediatric moyamoya disease.

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Moyamoya is an increasingly recognized cause of stroke in children and adults. Identification of the disease early in its course with prompt institution of therapy is critical to providing the best outcome for patients. Revascularization surgery seems to be effective in preventing stroke in moyamoya, with

direct techniques providing durable protection when performed at experienced centers.

DOI: 10.1016/j.nec.2010.03.013 PMID: 20561504 [Indexed for MEDLINE]

65. Neurosurg Focus. 2009 Nov;27(5):E8. doi: 10.3171/2009.8.FOCUS09168.

Vein of Galen malformation.

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A vein of Galen malformation is a rare intracranial vascular lesion affecting the pediatric population. Its poor prognosis has been significantly improved with the development of endovascular embolization. In this paper the authors review the developmental mechanisms, clinical pathophysiology, and the available data on the management and outcome of the disease.

DOI: 10.3171/2009.8.FOCUS09168 PMID: 19877798 [Indexed for MEDLINE]

66. J Neurosurg Pediatr. 2009 Sep;4(3):266-9. doi: 10.3171/2009.4.PEDS09126.

Successful treatment of severe cerebral vasospasm following hemorrhage of an arteriovenous malformation. Case report.

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The authors describe the case of a 13-year-old boy who presented with an intraventricular hemorrhage caused by a left trigonal arteriovenous malformation. After an initial recovery, the patient experienced complete right-sided paresis on posthemorrhage Day 6. Severe cerebral vasospasm was found on MR angiography and confirmed on conventional cerebral angiography. Intraarterial nicardipine injection and balloon angioplasty were successfully performed with improved vasospasm and subsequent neurological recovery. Cerebral vasospasm should be considered in the differential diagnosis for neurological deterioration following an arteriovenous malformation hemorrhage, and aggressive treatment can be administered to prevent ischemia and further neurological deficits.

DOI: 10.3171/2009.4.PEDS09126 PMID: 19772412 [Indexed for MEDLINE]