A summary of some of the recently published seminal papers in neuroscience

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DiPALS Writing Committee, on behalf of the DiPALS Study Group Collaborators. Safety and efficacy of diaphragm pacing in patients with respiratory insufficiency due to amyotrophic lateral sclerosis (DiPALS): A multicentre, open-label, randomised controlled trial. Lancet Neurol 2015; 14: 883–92

Respiratory failure is the leading cause of death in patients suffering from amyotrophic lateral sclerosis (ALS). Non-invasive ventilation (NIV) improves the standard of care and extends the life of patients by an average of 7 months. The DiPALS study group evaluated the phrenic nerve stimulator. The two arms were NIV and NIV with pacing. The primary outcome of assessment was overall survival. Surprisingly, patients in NIV alone group survived 22.5 months (median) in comparison to 11 months of survival in the NIV plus pacing group. This totally unexpected outcome might be because of the post-surgical acceleration of the ALS disease progression (potential disease modifying effect); or, the direct adverse effect of pacing over already damaged motor neurons of the diaphragm (by causing excessive fatigue). The DiPALS group concluded that NIV with pacing is associated with a significantly decreased survival in patients with ALS, and hence, should be discouraged.

Contributed by Dr. Manjul Tripathi and Dr. Kanchan K. Mukherjee

Malkki H. Alcohol consumption does not seem to protect against stroke. Nat Rev Neurol 2015;11:611

This research highlight in Nature analyzes a beautiful paper by Jones SB et al., (Midlife alcohol consumption and the risk of stroke in the atherosclerosis: Risk in communities study. Stroke 2015; 46: 3124-30), which was a prospective study with a median follow up of more than 20 years. Medical personnel and media have always highlighted the protective effect of light-to-moderate alcohol consumption. These were at best based on meta-analyzed results, which have their own limitations. Their definition of one drink is equivalent to beer (12 oz), wine (4 oz) and hard liquor (1.5 oz). This work by Jones SB et al., found no protective effect of even light drinking (drinks/week). Moderate (4-17 drinks per week) to heavy (>18 drinks per week) drinking led to a significant increase in hemorrhagic stroke, and heavy drinking to an increase in ischemic stroke. They have also warned that low dose alcohol consumption might also increase the risk of hemorrhagic stroke by changing the hemostatic balance.

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The usual practice in India for neurocysticercosis (NCC) with seizure splits into two camps; antiepileptic drugs (AED) alone and AED with standard dosage of albendazole (15 mg/kg/day) for a variable duration ranging from a couple of weeks to months. This study from Peru had three arms, standard albendazole, higher dose albendazole (22.5 mg/kg/day) and a combination therapy of standard albendazole with praziquental (50 mg/kg/day) for 10 days. Enrolment was stopped after interim analysis because of the clear-cut superiority of the parasiticidal effect of combination therapy. The outcome was measured keeping three important parameters in mind; the parasiticidal effect (cyst resolution), seizure control and adverse events. It was found that the best control with no increase in adverse events was in the combination therapy in both outcome measures, provided the number of cysts were three or more.


We have slowly forgotten Hippocrates’ advise, “Cure sometimes, treat often, comfort always.” The eternal debate in evidence-based medicine is whether a clinician’s judgment is better than the currently prevalent and widely used objective scoring systems. This paper in Nature Reviews by Daniel F. Hanley Jr. reviews the article by Hwang DY et al., (Hwang DY et al. Clinician judgment vs. formal scales for predicting intracerebral hemorrhage outcomes. Neurology 2016;86:126–33.). The group has analyzed the comparative effectiveness of various scoring systems with clinical assessment in predicting the outcome of patients with intracerebral hemorrhage (ICH). Contrary to the popular belief, they have identified that clinician’s judgment is superior to clinical severity scores in the prediction of mortality and final outcome. The fundamental duty of a clinician is to predict the outcome to the relatives at the outset. Within 24 hours of admission, the clinician was asked to predict the modified Rankin Score (mRS) that the patient would be in after 3 months; and, also to indicate if they would recommend only comfort measures for the management of the patient under consideration. The ICH score and FUNC score (popular prognostic tools) were also calculated for each patient from the admission data. After three months, the actual mRS was calculated. The scoring systems predicted a bleaker outlook and the clinicians were more positive, which turned out to be right. The physicians’ clinical predictions correlated more closely with the expected outcome than the formal scoring systems. This thoughtful study has further validated the importance of the clinical judgment scoring methods including the Glasgow Coma Scale (GCS), ICH score, FUNC score, hematoma volume etc., even in patients who are assigned the extremes of the GCS scores at admission.

Tran MG, et al. Sign of the times: Be careful what you say in the operating room. Lancet 2016; 387:536

With the gradual increase in consumer rights, litigations are becoming a part and parcel of a neurosurgeon’s career. The environment inside an operation theatre and the conversation among the staff working there may be misinterpreted as derogatory or perceived in an objectionable manner. This report highlights the dynamic changes in the interpersonal trust between the patients and the caregivers, where a patient tucked a recording device inside the compression stocking. Placing such an object in ones stocking not only increases the surgical hazards but also affect the sanctity of the doctor-patient relationship endangering confidentiality. In one case, this actually led to a litigation.

Sir CV Raman got his noble prize for his discovery of the 'Raman effect,' a century ago. Most doctors are unaware of what it exactly means. Raman's spectroscopy entered clinical practice many years ago. This paper finds the “holy grail” for tumor surgery in humans. Neurosurgeons have for long tried to differentiate tumor margin from normal brain parenchyma. Intraoperative magnetic resonance imaging/ultrasonography, fluorescence guided surgery or confocal microscopies have not lived up to their expectations. This study in humans differentiates between a low grade and a high-grade tumor with its normal margin and can even subcategorize various histopathological types using stimulated Raman scattering microscopy (SRS). The chemical contrast specific to SRS microscopy enables tumor detection by revealing quantifiable alterations in tissue cellularity, axonal density, and protein/lipid ratio in tumor-infiltrated tissues. It is relatively inexpensive with near 98% sensitivity and specificity.

Contributed by Dr. Manjul Tripathi and Dr. Kanchan K. Mukherjee


With their gradual acceptance by the medical fraternity, neurosurgical procedures for refractory psychiatric illnesses are becoming more common. It is more true for deep brain stimulation (DBS). This paper shows us the way to create a consensus guideline in our own practice. The consensus document focuses on the issue that stereotactic ablative procedures such as cingulotomy and capsulotomy for depression and obsessive-compulsive disorder are considered ‘established’ in some countries. However, they still lack level I evidence. Furthermore, it is noted that deep brain stimulation of any brain target tried until now, and for any psychiatric or behavioral disorder, still remains at an investigational stage. This consensus study focuses on the ethical and scientific pursuit of psychiatric surgery and focuses on enhancing patient safety.

Contributed by Dr. Manjul Tripathi and Dr. Kanchan K. Mukherjee


This editorial on the article by Brott et al., (Long-term results of stenting versus endarterectomy for carotid-artery stenosis. N Engl J Med. DOI: 10.1056/NEJMoa1505215.) summarizes the Asymptomatic Carotid Trial termed ‘ACT1’ and Carotid Revascularization And Stenting Trial called ‘CREST’. The 5 and 10 year follow up were published in this issue concluding that both stenting and CEA were equally effective “post procedurally”. Reading between the lines, it highlights that stenting will have a significantly higher complication rate in the peri-procedural period than carotid endarterectomy (CEA). This paper warns us that many centers will perform carotid artery interventions in a majority of the “asymptomatic” patients, even though evidence suggests that most of them will undergo an unnecessary and potentially harmful procedure. It also shows us the way to the future where they propose to compare this data with the best medical management.

Contributed by Dr. Manjul Tripathi and Dr. Kanchan K. Mukherjee


This paper in Lancet highlights the fallacy and fixation of neurosurgeons to treat metastases in the form of extent of surgery, decompression, progression free survival, or imaging based end points. It proposes that quality of life, Karnofsky performance status (KPS), and neurocognition be taken as better end points in the management of such patients.

Contributed by Dr. Manjul Tripathi and Dr. Kanchan K. Mukherjee


The hunt for blood derived biomarkers for diagnosis, monitoring of growth and response to treatment in brain tumors has eluded us due to the blood brain barrier. This paper gives an overview in the new field of system biology. This includes all of components of omics i.e. genomics, transcryptomics, proteomics, phosphoproteomics, metabolomics and secretomics. Circulating tumor cells (CTC), circulating tumor DNA (ct-DNA) in plasma, extracellular vesicles (EV) containing ct-DNA, micro RNA, and protein function are extensively being studied. This can be helpful in a noninvasive histopathological diagnosis, in detection of recurrence before clinico-radiological failure occurs, in differentiating tumor relapse from radiation necrosis, and in the assessment of response to adjuvant therapy.
The neurological status was assessed systematically using the American Spinal Injury Association impairment scale (AIS) at arrival to the trauma centre and at rehabilitation discharge. Patients operated within 24 h of the trauma were compared with patients operated later than 24 h after the trauma. Potential confounders such as age, Injury Severity Score (ISS), smoking history, body mass index (BMI), Glasgow Coma Scale (GCS) score, and duration of follow-up were recorded. Fifty-three patients with complete SCI were included in the study: 33 thoracolumbar and 20 cervical SCIs. The 38 patients operated within <24 h were generally younger than the 15 patients operated ≥24 h \( (P = 0.049) \). Overall, 28\% (15/53) patients with a complete SCI had improvement in AIS; and, 34\% (13/38) who were operated in <24 h and 13\% (2/15) who were operated ≥24 h \( (P = 0.182) \) had improvement in the AIS. Sixty-four percent (9/14) of cervical complete SCI operated in <24 h had improvement in AIS as opposed to none in the subgroup of six complete cervical SCI operated ≥24 h \( (P = 0.008) \). The authors concluded that surgical decompression within 24 h in complete SCI might optimize neurological recovery, especially in patients with cervical SCI.

**Contributed by Mazda K. Turel**


It is undisputed for more than 200 years that the use of a parachute prevents major trauma when falling from a great height. Nevertheless, till date, no prospective randomized controlled trial has proven the superiority of a parachute assisted trial in preventing trauma when falling from a great height, instead of a free fall. The aim of this rather amusing, prospective randomized controlled trial was to prove the effectiveness of a parachute when falling from a great height. In this trial, a commercially acquirable rag doll was prepared for the purpose of the study design in accordance with the Declaration of Helsinki; the participation of human beings or animals in this trial was impossible. Twenty-five falls were performed with a parachute compatible with the height and weight of the doll. In the control group, another 25 falls were realized without a parachute. The total weight of the rag doll at the end of the preparation was 7.4 lb to achieve a body mass index of ~20. The main outcome measures were the rate of head injury; cervical, thoracic, lumbar, and pelvic fractures; and pneumothorax, hepatic, spleen, and bladder injuries in the control and parachute groups. An interdisciplinary team consisting of a specialized trauma surgeon, two neurosurgeons, and a coroner examined the...
rag doll for injuries. Additionally, whole-body computed tomography scans were performed to identify the injuries. All the 50 falls-25 with the use of a parachute, 25 without a parachute-were successfully performed. Head injuries, cervical trauma, thoracic trauma, lumbar trauma, pelvic trauma, and hepatic, spleen, and bladder injuries ($P < 0.001$) occurred more often in the control group. Only the pneumothorax showed no statistically significant difference between the control and parachute groups. The authors concluded that a parachute is an effective tool to prevent major trauma when falling from a great height. In general, every manuscript would end with the statement “Further prospective, randomised, controlled, double-blind studies have to be performed to confirm our findings,” but it is obvious that it is impossible to perform such a trial, and the authors believe that their study is more than sufficient to challenge such a statement.

**Contributed by Mazda K. Turel**

**Phan K. Minimally invasive versus open laminectomy for lumbar stenosis: A systematic review and meta-analysis. Spine (Phila Pa 1976) 2016;41:E91‑E100**

The authors performed a systematic review and meta-analysis to assess the relative merits of minimally invasive unilateral laminectomy for bilateral decompression (ULBD) versus an open laminectomy. They reviewed the relevant articles from six electronic databases. Satisfaction rates were significantly higher (84% vs. 75.4%; $P=0.03$), and back pain as well Visual Analog Scale scores were lower ($P<0.01$) in the minimally invasive group. In the minimally invasive laminectomy group, the operative duration was 11 minutes longer than in the open approach ($P=0.001$), however this may not have any clinical significance. There was less blood loss ($P<0.01$) and a shorter hospital stay (2.1 days; $P<0.01$) in the minimally invasive group. Dural injuries and cerebrospinal fluid leaks were comparable, but reoperation rates were lower in the minimally invasive cohort (1.6% vs. 5.8%; $P=0.02$); however, this was not significant when only randomized evidence was considered. The pooled evidence suggests ULBD may be associated with less blood loss and shorter stay, with similar complication profiles to the open approach. These findings warrant verification in large prospective registries and randomized trials.

**Contributed by Mazda K. Turel**


The authors conducted this study to determine the incidence of adjacent segment disease (ASD) after a 1- or 2-level lumbar laminectomy. The complication is commonly studied in the context of lumbar fusions, but a clinical investigation of ASD in the absence of arthrodesis has not been established. ASD was defined as clinical and/or radiographic evidence of degenerative spinal disease that required reoperation at the level above or below the index laminectomy. Of the 398 patients, the incidence of ASD requiring a reoperation was 10% over a mean follow up of 6 years. The 39 ASD cases were almost equally distributed at the L2-L3 (31%), L3-L4 (26%), and L5-S1 (31%) levels, and to a lesser extent, at the L4-L5 (15%) level. The incidence of ASD of 10% and 9% were equivalent after a 1- and 2-level laminectomy, respectively. The rostral ASD was statistically more common than the caudal ASD after both the 1- and 2-level laminectomy. Of the 39 ASD cases, 95% required a laminectomy, 26% a discectomy, and 49% a fusion. The average time to ASD was 4 years and was equivalent among the 1- and 2-level laminectomy cohorts. Although not the focus of the present study, the reasons for the relatively high occurrence of this adjacent level disease are not clearly defined but are likely multifactorial. Decompression, which typically involves removal of lamina, ligamentum flavum, interspinous ligaments, and at times, partial facetectomy, may increase motion at the adjacent levels and promote stenosis through ligamentous and facetal hypertrophy and disc degeneration. Adjacent level stenosis may also develop in part due to ongoing degenerative changes in a spine that has already demonstrated sufficient degeneration to warrant surgery. It is also likely that spinal malalignment, including scoliosis, sagittal imbalance, and pelvic incidence to lumbar lordosis mismatch, contributes to the likelihood of developing adjacent level disease.

**Contributed by Mazda K. Turel**


Lumbar paraspinal muscle (PSM) morphometry has not been analyzed in isthmic spondylolisthesis (IS). The authors of this study hypothesized that patients with IS have atrophic PSMs, and that the atrophic PSM areas in these patients have a bearing on the radiological degenerative changes in some of the spinal elements. Pedicle signal change (PSC) at the level of the pars fracture, documented to occur in many patients with IS as a function of age, has been construed
to reflect a continuum of biomechanical stresses in the spondylopathic spines. The authors postulated that thinner, and hence, weaker lumbar PSMs predispose to greater PSC in IS. In this retrospective study on 120 patients who underwent posterior lumbar interbody fusion (PLIF) for IS, cross sectional areas (CSAs) of various lumbar PSMs (psoas, P; erector spinae, ES; multifidus, MF) were calculated on the preoperative T2 weighted axial MRIs from L3 to L5 vertebral levels by two independent observers, and computed as ratios with respect to the corresponding vertebral body areas (VBAs). These values were then compared with those of 120 age- and sex-matched normative controls, and analyzed with respect to age, sex, duration of symptoms, grade of listhesis and various MRI changes at the level of the listhesis (PSC, disc degeneration and facetal arthropathy). Compared to normative controls, the mean CSA value for ES was found to be significantly higher in the study cohort ($P = 0.002$), while that of MF was significantly lower ($P = 0.009$), and this manifestation was accentuated in the patients with PSC ($P = 0.002$). MRI signal change in the pedicle was seen in half the patients, all of whom demonstrated a Type 2 change. Of the variables tested in a multivariate analysis, age independently predicted lower area values for all the 3 muscles ($P \leq 0.001$), while female sex predicted a lower mean P area value ($P < 0.001$). Decrease in the mean MF area value alone was associated with a significantly increased likelihood of the patients exhibiting PSC ($P = 0.039$). Based on these findings, the authors concluded that patients with IS suffer from selective atrophy of their MF muscle, while their ES muscle undergoes a compensatory hypertrophy. Increasing age has a detrimental effect on the areas of the lumbar PSMs, while the female gender predisposes to decreased P area. MF atrophy correlates with PSC, indicating the role of this deep stabilizer in the biomechanical stability of spondylopathic spines. This may be of clinical significance in targeted physiotherapy programs during the conservative management of IS.

Contributed by Mazda K. Turel


Gliosarcoma (GSM) is a rare biphasic neoplasm of the central nervous system composed of a glioblastoma multiforme (GBM) admixed with a sarcomatous component. In clinical practice, a GSM is generally managed similarly to a GBM. However, there are conflicting reports regarding their clinical aggressiveness, cell line of origin and possible prognosis compared with those of a GBM. The objective of this study was to compare the clinico-pathological features in GSM patients with the GBM patients during the same study period. Out of the 518 patients with GBM treated by the authors between 2008 and 2013, 51 were GSM. In this series, the GSMs represented 9.8 % of all GBMs and included 58.8 % male patients with a median age of 44.7 years. The locations were all supratentorial, included the temporal lobe in 41.2 %, the frontal lobe in 25.5 %, the parietal lobe in 19.6 %, and the occipital lobe in 13.7 % patients. All patients underwent tumor resection followed by post-operative radiation and adjuvant chemotherapy. The methyl guanine methyl transferase (MGMT) methylation studies were significantly more frequent in the GBMs than in GSMs (80.1 % vs. 44.7 %, $P < 0.001$). The median progression free survival and overall survival for the patients with GSM were 8 and 13 months, respectively, as compared with 9 and 14 months in the GBM group (log rank test $P = 0.001$ and 0.004, respectively). The Cox proportional hazards regression model indicated that the extent of tumor resection (HR = 1.518, $P = 0.009$) and pathological types (HR = 0.608, $P = 0.002$) were the significant prognostic factors. With regard to clinical features and outcomes, GSM and GBM cannot be distinguished clinically. GSM in China may be managed similarly to GBM, with maximal safe surgical resection followed by chemo-radiotherapy. Their study adds further evidence to support GSM as a unique clinical entity with a likely worse prognosis than GBM. It would be interesting to see if an Indian cohort behaves differently.

Contributed by Mazda K. Turel


Adding temozolomide (TMZ) to radiation for patients with newly diagnosed anaplastic astrocytomas (AAs) is a common clinical practice despite the lack of prospective studies demonstrating a survival advantage. Two retrospective studies, each with methodological limitations, provide conflicting advice regarding treatment. This single-institution retrospective study was conducted to determine survival trends in patients with AA. All patients ≥18 years with newly-diagnosed AA treated from 1995 to 2012 were included. As the authors incorporated TMZ into high-grade glioma treatment regimens in 2004, the patients were divided into the pre-2004 and the post-2004 groups for analysis. The clinical, radiographic, and pathologic data were collected. The
median overall survival (OS) was calculated using Kaplan-Meier estimates. A total of 196 patients were identified; 74 from the pre-2004 and 122 from the post-2004 period; their mean age being 47 ± 15 years with 57% male patients of which 87% were white. 69% of them underwent surgical debulking. The mean RT dose was 5676 ± 746 cGy; the duration of concurrent chemoradiation was 5.8 ± 0.8 weeks; and, the mean adjuvant chemotherapy was of 4.3 ± 2.8 cycles. The baseline prognostic factors did not differ between the groups. Chemotherapy was administered to 12% of patients in the pre-2004 era (TMZ = 1, procarbazine, lomustine and vincristine = 2, carmustine wafer = 6); and, to 94% patients in the post-2004 era (TMZ in all, P < 0.001). The median overall survival (OS) was 32 months. Survival was longer in the post-2004 cohort (37 months) than in the pre-2004 cohort (27 months). A multivariate analysis controlling for age, Karnofsky performance status, and extent of resection revealed a 36% reduced risk of death in patients treated in the post-2004 period. This retrospective review found that survival in the newly diagnosed patients with AA improved with the addition of temozolomide to standard radiation. Until prospective randomized phase III data are available, these data support the practice of incorporating TMZ in the management of newly-diagnosed AA.

**Contributed by Mazda K. Turel**


Low-grade astrocytic tumors have a worse prognosis (median overall survival [OS]: 5.6 years) when compared with patients having tumors with a mixed oligo-astrocytic (6.6 years) or oligodendroglial histology (11.6 years). Acquisition of isocitrate dehydrogenase (IDH) 1 or IDH2 mutation (IDHmut) is among the earliest of the genetic events that take place in the development of most low-grade gliomas (LGGs). IDHmut has been associated with a longer overall patient survival. However, its impact on malignant transformation (MT) remains to be defined. A collection of 210-archived adult LGG previously stratified by IDHmut, Methyl guanine methyl transferase (MGMT) methylation (MGMTmet), 1p/19q combined loss of heterozygosity (1p19qloh) and TP53 immunopositivity (TP53pos) status was analysed by the authors. They used multistate models to assess MT-free survival, considering one initial, one transient (MT), and one absorbing state (death). Overall, although associated with a lower risk of death, IDHmut had a non-significant 1.8 times higher risk of MT compared to IDH wild type (IDHwt). The double combination of IDHmut and MGMTmet, and the triple combination of IDHmut, MGMTmet and 1p/19qloh, despite significantly lower hazard ratio for death (HRDEATH versus IDHwt: 0.35, P = 0.0194 and 0.15, P = 0.0008, respectively), had a non-significantly different hazard for developing a MT. Conversely, the triple combination of IDHmut/MGMTmet/TP53pos, with a non-significantly different hazard for death, had a significantly higher hazard for MT than IDHwt (HRMT versus IDHwt: 2.83; P = 0.0452). Although IDHmut status is associated with a longer overall patient survival, all IDHmut/ MGMTmet subsets consistently showed a higher risk of MT than of death, compared to IDHwt LGG. The authors conclude that this supports the findings that molecular events relevant to IDH mutations impact early glioma development prior to malignant transformation.

**Contributed by Mazda K. Turel**


The preservation of facial nerve function following vestibular schwannoma surgery is a high priority. Even those patients with normal to near-normal facial nerve function in the early postoperative period remain at risk for delayed facial palsy (DFP). The etiology of DFP remains uncertain, and is possibly either one or a combination of vascular spasm, viral reactivation, or local neural edema. The authors evaluated the incidence and prognosis of DFP and attempted to identify the risk factors for its occurrence in a retrospective study of 489 patients. DFP was defined as deterioration in the facial nerve function of at least 2 House-Brackmann (HB) grades between postoperative days 5 to 30. Only patients with a HB grade of I to III by postoperative day 5 were eligible for inclusion in the study. One hundred and twenty-one patients with HB grade IV to VI facial weakness at postoperative day 5 were excluded from analysis. Of the remaining 368 patients, 60 (16%) patients developed DFP (mean 12 days postoperatively, range: 5-25 days). All patients recovered function to HB grade I to II by a mean of 33 days (range: 7-86 days). Patients with DFP and no facial palsy did not differ significantly with regard to their gender, tumor size, operative duration, body mass index, postoperative complications, preoperative HB grade, or intraoperative facial nerve monitoring results. Patients who developed DFP had higher rates of gross total resections (83% vs 71%, P = 0.05) and retrosigmoid approaches (72% vs 52%, P < 0.01) compared to the translabyrinthine or middle fossa approach. There was no difference in the recovery time between patients who received treatment with steroids, steroids with antivirals, or no treatment at all (P = 0.530). One interesting possibility that
was raised in the article is that the introduction of bone dust into the subarachnoid space during intradural drilling of the internal auditory canal may lead to an increased inflammatory response. The authors concluded that patients with a gross total tumor resection or undergoing a retrosigmoid approach may be at higher risk of DFP. The prognosis is favorable with patients likely to recover their normal or near-normal facial function within 1 month of onset of DFP. This article will certainly prove to be useful in reassuring patients who experience this disappointing setback after surgery. It may also decrease the enthusiasm for using steroids and antiviral medication in this setting.

Contributed by Mazda K. Turel


The natural history of unruptured intracranial aneurysms remains unclear and the management strategy is not well defined. From January 2003 to December 2012, the authors enrolled patients with aneurysm at their institution. A total of 2252 patients with 2897 aneurysms were eligible for analysis, and 1960 eligible aneurysms were conservatively managed. A precise three-dimensional evaluation was conducted using computed tomography angiography, digital subtraction angiography, or magnetic resonance angiography. They, then, assessed the risk of aneurysm rupture, mortality and morbidity associated with the aneurysm characteristics, demographics, and known health/lifestyle risk factors. The mean follow-up duration was 7388 aneurysm-years. During observation, 56 aneurysms ruptured, resulting in an overall rupture rate per year of 0.76%. The mean initial visit-to-rupture interval was 547 days. The aneurysm size, location, daughter sac, and history of subarachnoid hemorrhage were significant independent predictors for aneurysm rupture. Aneurysms that were ≥5 mm in size were associated with a significantly increased risk (12 times) of rupture when compared with 2-to 4-mm sized aneurysms. Of the 56 patients, who experienced a haemorrhage, 29 (52%) died or were rendered severely disabled. Of the patients who had a large or giant aneurysm, none recovered without deficits, and the mortality rate after rupture was 69%. For aneurysms sized <5 mm, the mortality rate was 18%.

Contributed by Mazda K. Turel


Giant intracranial arteriovenous malformations (AVMs) are rare cerebrovascular lesions that pose a management challenge. The authors performed a retrospective review to further clarify outcomes in patients with giant cerebral AVMs managed with conservative or interventional therapies at their institution from 1990 to 2013. Patients with a single intracranial AVM ≥6 cm in size were included. The patients were divided into 2 groups: Conservative management or intervention (microsurgery, radiosurgery, or embolization). The functional outcome was assessed with the modified Rankin Scale (mRS) and compared between the 2 groups. A total of 55 patients with giant AVMs were included, and 35 patients (63.6%) had a clinical follow-up with a mean duration of 11.8 years. The Spetzler-Martin grades were as follows: Grade III, n = 2 (3.6%); grade IV, n = 15 (27.3%); and grade V, n = 38 (69.1%). Twenty-four patients (43.6%) were conservatively managed. The patients in the conservatively managed group had larger AVMs with more frequent involvement of the temporal lobe. Five patients (26.3%) in the conservatively managed group and 5 (31.3%) in the intervention group experienced haemorrhage during the follow-up period, translating to an annualized risk of 2.7% and 4.1%, respectively. No significant difference in the risk of first subsequent haemorrhage was observed between the two groups. Despite comparable mRS scores at presentation, the authors observed a trend toward a better outcome (mRS <2) in patients undergoing conservative management (P = 0.06) compared with the intervention group at the last available follow-up. They conclude that interventions for giant AVMs should be considered cautiously because the risk of haemorrhage is similar regardless of the management strategy; and, functional outcome is likely to be the same or even better in the conservatively managed population.

Contributed by Mazda K. Turel


Current clinical practice calls for a noncontrast computed tomography (CT) of the brain followed by a lumbar puncture (LP) if the CT scan is negative to exclude the presence of subarachnoid hemorrhage (SAH). Emerging evidence demonstrating the high sensitivity of early brain CT brings into question the necessity of always performing a LP after a negative CT scan in the diagnosis of spontaneous SAH. The authors performed a systematic review meta-analysis to determine the sensitivity of brain CT using modern scanners (16-slice technology or greater).
when performed within 6 hours of headache onset to exclude SAH in neurologically intact patients. A total of 882 titles were reviewed and 5 articles met the inclusion criteria. The review included an estimated 8907 patients. Thirteen patients had a missed SAH (incidence 1.46 per 1000) on brain CT scans within 6 hours. The overall sensitivity of the CT scan was 0.987 (95% confidence intervals, 0.971-0.994) and the specificity was 0.999 (95% confidence intervals, 0.993-1.0). The pooled likelihood ratio of a negative CT scan was 0.010 (95% confidence intervals, 0.003-0.034). The authors concluded that in patients presenting with thunderclap headache and normal neurological examination, a normal brain CT within 6 hours of headache is extremely sensitive in ruling out aneurysmal SAH. The sensitivity decreases as time from onset to CT elapses because the blood in the subarachnoid spaces is progressively diluted by the normal flow of cerebrospinal fluid. The study would have been more interesting if the time frames of 24 and 48 hours were also considered since a majority of patients undergo a CT scan within that time frame. It would also be worthwhile to know the sensitivity and specificity of CT scan in a pooled analysis.

Contributed by Mazda K. Turel


There is no consensus regarding the optimal timing for surgery for poor-grade (World Federation of Neurosurgical Societies [WFNS] IV/V) aneurysmal subarachnoid hemorrhage (SAH). The authors retrospectively evaluated variations in the patient characteristics and outcomes between early (<72 hrs of ictus) and delayed surgery (>72 hrs) groups. The mean follow-up duration was 12.5 ± 3.4 months. Of the 118 patients included in the study, 80 (68%) underwent early surgery and 38 (32%) underwent delayed surgery. Patients with brain herniation (P < 0.001) and a lower Fisher grade (P = 0.02) more often underwent early surgery. Patients in the early group more often underwent decompressive craniectomy (P < 0.001). Postoperative complications (91% vs 84%) and length of hospital stay (23.8 vs 20.6 days) did not differ, and outcomes were similar between the 2 groups (mRS 0-1; 36% vs 28%). The multivariate analysis showed a slight trend towards an excellent outcome in the early surgery group.

Contributed by Mazda K. Turel


Atherosclerotic vertebrobasilar (VB) occlusive disease is a significant etiology of posterior circulation stroke, with regional hypoperfusion as an important potential contributor to the stroke risk. The authors conducted this prospective, blinded, longitudinal cohort study at 5 academic hospital-based centres in the United States and Canada (n = 82; 69 patients had a minimum 1 year follow up). The hypothesis was that, among patients with symptomatic VB stenosis or occlusion, those with a distal blood flow compromise, as measured by the large-vessel quantitative magnetic resonance angiography (QMRA), are at a higher risk of developing a subsequent posterior circulation stroke. Participants with a recent VB transient ischemic attack or stroke, and 50% or more atherosclerotic stenosis or occlusion in the vertebral and/or basilar arteries underwent large-vessel flow measurements in the VB territory using QMRA. The primary outcome was VB-territory stroke. The distal flow status was low in 25% of the patients, and was significantly associated with a higher risk of a subsequent VB stroke (P = 0.04), with the 12- and 24-month event-free survival rates being 78% and 70%, respectively, in the low-flow group vs 96% and 87%, respectively, in the normal-flow group. The hazard ratio, adjusted for age and stroke risk factors, in the low distal flow status group was 11.55 (95% CI, 1.88-71.00; P = 0.008). The distal flow status remained significantly associated with the risk of stroke even when controlling for the degree of stenosis and location. The authors concluded that the distal flow status determined using a non-invasive and practical imaging tool is robustly able to determine the risk for the development of a subsequent stroke in patients with symptomatic atherosclerotic VB occlusive disease. Identification of high-risk patients has important implications for future investigations as well as for more aggressive interventional treatments such as revascularization of the posterior fossa or medical therapies. Furthermore, the data indicates that patients with a normal distal flow, who
cells. Each of them individually contributes to cancer
tumors composed of neoplastic and non-neoplastic

There is a growing recognition that gliomas are complex

Hambardzumyan D, et al. The role of microglia
and macrophages in glioma maintenance and

Evans SM, et al. Initial evidence that blood-borne
microvesicles are biomarkers for recurrence and
survival in newly diagnosed glioblastoma patients.
J Neurooncol 2016; 127:391-400

The purpose of this pilot study was to determine if blood-borne
microvesicles from newly diagnosed glioblastoma patients
could be used as biomarkers. The authors collected 2.8 mL
blood from 16 post-operative patients at the time that they
were being prepared for radiation with concurrent
temozolomide. Two additional samples were collected during
the chemoradiation therapy and a final sample was collected
at the end of the chemoradiation therapy. Patients continued
with the therapy suggested by their physicians based on tumor
conference consensus and were followed for recurrence and
overall survival. Microvesicles were isolated using serial
centrifugation and stained for surface markers (Annexin V
for phosphotidyl serine, CD41 for platelets, anti-EGFR for
tumor cells, and CD235 for red blood cells). Flow cytometry
analysis was performed. The findings provide the initial
evidence that increases in Annexin V positive microvesicle
levels during chemoradiation therapy are associated with
earlier recurrence and shorter overall survival in newly
diagnosed glioblastoma patients. The effect is dramatic,
with over a four-fold increase in the hazard ratio for an
individual at the 75th versus the 25th percentile. Moreover,
the pattern of increase of Annexin V positive microvesicles
remains significant after adjustment for confounding clinical
variables that have previously been shown to be prognostic
for recurrence and survival. Inclusion of neutrophil levels at
the start of chemoradiation therapy in the model yielded
the largest attenuation of the observed association. Further
studies will be needed to verify and further investigate the
association between these two entities.

Contributed by Mazda K. Turel

Hambardzumyan D, et al. The role of microglia
and macrophages in glioma maintenance and

There is a growing recognition that gliomas are complex
tumors composed of neoplastic and non-neoplastic
cells. Each of them individually contributes to cancer
formation, progression and response to treatment. The
majority of the non-neoplastic cells are tumor-associated
macrophages (TAMs), either of peripheral origin or
representing brain-intrinsic microglia, that create a supportive
stroma for neoplastic cell expansion and invasion. TAMs are
recruited to the glioma environment, have immune functions,
and can release a wide array of growth factors and cytokines
in response to those factors produced by cancer cells. In this
manner, TAMs facilitate tumor proliferation, survival and
migration. Through such iterative interactions, a unique
tumor ecosystem is established. It is now evident that TAMs
home to the evolving glioma and interact in a complex fashion
with the tumor environment to promote glioma growth in
mouse models and in human patients. However, there are still
many unanswered questions. The factors truly responsible
for mediating the interaction between glioma cells and
microglia and macrophages are still not clear. In this respect,
we do not know how microglia and macrophages interact in
the tumor, and whether they acquire distinct properties and
execute distinct functions. Whether or not TAMs acquire
different functional phenotypes depending on individual
glioma types (low-grade versus high-grade, glioblastoma
molecular subtypes) also remains an open question. Similarly,
even in a given tumor, TAMs might interact differently with
different neoplastic cell types (gliosarcomas, differentiated
astrocytoma cells, etc). Nonetheless, after decades of applying
treatments specifically against the tumor cells directly, TAMs
have emerged as exciting targets for therapeutic intervention.
Further investigation into the mechanisms and interactions
between TAM populations and the variety of neoplastic and
non-neoplastic cells in these tumors may one day yield new
glioma treatment strategies.

Contributed by Mazda K. Turel

Shao L, et al. Hypertonic saline for brain relaxation
and intracranial pressure in patients undergoing
neurosurgical procedures: A meta-analysis of
randomized controlled trials. PLoS One
2015;10:e0117314. doi: 10.1371/journal.pone.0117314

A wealth of evidence from randomized controlled trials (RCTs)
has indicated that hypertonic saline (HS) is at least as
effective as, if not better than, mannitol in the treatment of
increased intracranial pressure (ICP). However, there is little
known evidence about the effects of HS in patients during
neurosurgery. Thus, this meta-analysis was performed to
compare the intraoperative effects of HS with mannitol
in patients undergoing craniotomy. Seven RCTs with 468
participants were included. The quality of the included
trials was acceptable. The main findings were as follows: (1) HS could significantly increase the odds of a satisfactory intraoperative brain relaxation and decrease the mean difference of maximal ICP before opening the dura in comparison withmannitol. (2) Compared with HS, mannitol had a more prominent diuretic effect. However, there was no significant difference in the total volume of intravenous fluid required between the groups, which were associated with a statistically significant heterogeneity. (3) The hemodynamic parameters such as mean arterial pressure and central venous pressure during surgery were similar in both the groups treated with HS or mannitol. (4) Patients treated with HS had a significantly higher serum sodium than the mannitol-treated patients without differences in serum osmolality between the groups. Considering that robust outcome measures are absent because brain relaxation and ICP can be influenced by several other factors apart for the hyperosmotic agents, the results of present meta-analysis should be interpreted with caution. Well-designed RCTs in the future are needed to further test the present results, identify the impact of HS on the clinically relevant outcomes and explore the potential mechanisms of HS.

**Contributed by Mazda K. Turel**


Localization of the epileptogenic zone is the centre point of all pre/per operative investigations in epilepsy surgery. In this regard, stereo-electroencephalography (SEEG) has emerged as an alternative to the conventional intraoperative invasive EEG. SEEG has intrinsic high precision electrode placement features. Thus, large craniotomies and a relatively high morbidity has seen invasive conventional EEG recordings gradually being superseded by SEEG. The authors intended to analyse the complication profile of SEEG using a systematic literature review and meta-analysis. Their aim was to determine the incidence of various surgical complications associated with SEEG electrode implantation quoted in the literature. Such an estimate, the authors felt, could allow physicians to accurately counsel their patients about the potential complications related to this method of extra operative invasive monitoring.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was utilized to conduct the interview. The authors reviewed 1901 citations on SEEG using MEDLINE, Scopus, and Web of Science database searches. A fixed-effects model with inverse variance weighting was used to analyse the complications. The principal summary measures were the effect summary value and 95% confidence intervals (CIs). Out of the 1901 citations reviewed, 787 articles were duplicates leaving 1116 publications for screening. The authors further excluded 1057 articles for either not meeting the inclusion criteria or in failing to address the key question, that is, the complications of SEEG. Hence, only 57 articles were finally scrutinized to complete the meta-analysis. The meta-analysis revealed 121 surgical complications related to SEEG insertion and monitoring (pooled prevalence 1.3%, 95% CI 0.9–1.7%). The most common complications were hemorrhagic (pooled prevalence 1.0%, 95% confidence interval [CI] 0.6–1.4%) or infectious (pooled prevalence 0.8%, 95% CI 0.3–1.2%). Five mortalities were identified (pooled prevalence 0.3%, 95% CI −0.1–0.6%). The authors thus concluded that SEEG is associated with a very low complication rate compared to other methods of extra-operative invasive monitoring. They stated that SEEG had the desired precision, and the fear of complication that often crosses the mind of the physician is almost negligible.

**Contributed by Kuntal Kanti Das**


The authors intended to evaluate the role of reoperation for recurrent glioblastomas (GBM), a situation that still remains a grey zone as far as the management of glioblastomas is concerned. The authors utilized the prospective patient cohort from the DIRECTOR trial, a prospective randomized multicenter trial comparing the 2 dose-intensified temozolomide regimens at recurrence of GBM.

Clinical and imaging data of 105 patients were analysed from the DIRECTOR cohort. The authors carried out a volumetric analysis of the tumor on gadolinium contrast-enhanced MRI as well as on the fluid attenuated inversion recovery/T2 MRI. The extent of excision derived from the volumetric analysis was correlated with the progression free survival (PFS) after initial progression (PFS1) and the post-recurrence survival (PRS). The EORTC QLQ-C30 and QLQ-BN20 questionnaires assessed the quality of life at 8-week intervals.

A total of 71 patients received surgery at the first recurrence. Prognostic factors, including age, MGMT promoter methylation, and Karnofsky performance score, were comparable between the patients with and without
reoperation. The outcome in patients with versus without surgery at recurrence was similar for PFS (2.0 mo vs 1.9 mo, \( P = 0.360 \)) and PRS (11.4 mo vs 9.8 mo, \( P = 0.633 \)). Among re-operated patients, post-surgery imaging was available in 59 cases. In these patients, complete resection of contrast-enhancing tumor (N = 40) versus residual detection of contrast enhancement (N = 19) was associated with improved PRS (12.9 mo [95% CI: 11.5–18.2] vs 6.5 mo [95% CI: 3.6–9.9], \( P < 0.001 \)) and better quality of life.Incomplete tumor resection was associated with inferior PRS compared with patients who did not undergo surgery (6.5 vs 9.8 mo., \( P = 0.052 \)). The quality of life was similar in these 2 groups. Thus, the authors concluded that complete resection of the enhancing part at the first recurrence does improve the survival outcome in GBM.

Contributed by Kuntal Kanti Das


Although the practice guidelines for deformity correction in patients with adolescent idiopathic scoliosis (AIS) are well established, the same cannot be said about another common type of scoliosis, the syringomyelia-associated scoliosis (SMS). There was also lack of any scientific study to directly compare the results of surgical treatment between these two groups of patients. This led the authors to perform a comparative study between patients with right-thoracic SMS and those with right-thoracic AIS to evaluate the radiographic and clinical outcomes following posterior spinal fusion.

Sixty-nine adolescents with SMS were matched with patients with AIS for sex, age, and curve magnitude. The patients were evaluated before surgery, immediately after surgery, and at the latest follow-up examination for changes in curve correction, global coronal balance, and scores on the Scoliosis Research Society (SRS)-22 questionnaire. The authors noted that the preoperative primary curve magnitude was similar between the two groups, but a trend toward less flexibility was observed in the SMS group. The amount of correction of the thoracic Cobb angles obtained surgically (68% compared with 71%) and the ratio of percent correction to flexibility (1.80 compared with 1.76) were similar in the SMS and AIS groups. At the latest evaluation, eight patients with SMS and five with AIS had lost >10° of thoracic spine correction (\( P = 0.382 \)). The postoperative coronal decompensation averaged 13% and 6%, respectively, in the SMS and AIS groups (\( P = 0.243 \)). No intergroup differences were noted with respect to the sagittal vertical axis or proximal junctional change, with preservation of global sagittal balance in both the groups during follow-up. There were no neurologic or other major complications related to surgery in either group.

The authors concluded that despite the differences in the preoperative status, adolescents with idiopathic right thoracic scoliosis and those with syringomyelia-associated right thoracic scoliosis had comparable clinical and radiographic outcomes of pedicle-screw-based posterior spinal fusion, without neurologic complications.

Contributed by Kuntal Kanti Das


In this study, the authors analysed the risks and benefits of re-operation following an initial resective surgery in drug-resistant epilepsy. This group of patients represents a very challenging and complicated subset of surgically treatable epilepsy patients.

The authors retrospectively analysed the clinical data, long-term seizure outcome (International League Against Epilepsy grade), neuropsychological outcome and postoperative complications of patients who had undergone a second resective epilepsy surgery from 1989 to 2009 at their center.

A total of 66 patients with a median follow-up of 10.3 years were included in the study. Out of these 66 patients, majority (\( n = 51,77% \)) had their first surgery for temporal lobe epilepsy while the remaining 15 cases (23%) were operated for extra-temporal lobe epilepsies. The most frequent histological findings of the first surgery were tumours (\( n = 33, 50% \)), followed by dysplasia, gliosis (\( n = 11, 17% \) each) and hippocampal sclerosis (\( n = 9 \)). The main reason for seizure recurrence was incomplete resection (59.1%) of the putative epileptogenic lesion. After reoperation, 69.7% (n = 46) of the patients were completely seizure-free at the last available follow-up. The neuropsychological evaluation following the re-surgery demonstrated that repeated losses in the same cognitive domain, that is, successive changes from better to worse performance categories, were rare and that those losses after the first surgery were followed by improvement rather than decline. However, the authors noted that reoperations were
associated with an increased rate of permanent neurological deficits (9%), overall surgical complications (9%) and visual field deficits (67%).

Thus, the authors concluded that reoperation after failed resective epilepsy surgery led to approximately 70% long-time seizure freedom and a reasonable neuropsychological outcome. They stressed on the appropriate counselling of the patients regarding the heightened chances of permanent complications following the relook surgery.

*Contributed by Kuntal Kanti Das*


The authors conducted a prospective phase III trial to confirm the results of a preliminary pilot study that showed a beneficial effect on facial and cochlear nerve preservation following vestibular schwannoma (VS) surgery with prophylactic treatment using nimodipine and hydroxyethyl starch.

In this open-label, 2-arm, randomized parallel group and multicenter Phase III trial with blinded expert review, 112 patients who underwent VS surgery between January 2010 and February 2013 at 7 departments of neurosurgery were included to investigate the efficacy and safety of the prophylactic treatment. These patients preoperatively underwent an online randomization into a treatment (n = 56) and a control group (n = 56). The treatment group received parenteral nimodipine (1–2 mg/hr) and hydroxyethyl starch (hematocrit 30%–35%) from the day before surgery until the 7th postoperative day. The control group was not treated prophylactically.

They performed an intent-to-treat analysis which showed no statistically significant effects of the treatment on either preservation of facial nerve function (35 [67.3%] of 52 [treatment group] patients compared with 34 [72.3%] of 47 [control group]) patients (P = 0.745) or hearing preservation (11 [23.4%] of 47 [treatment group] patients compared with 15 [31.2%] of 48 [control group]) patients (P = 0.530) at 12 months after surgery. Due to the fact that the tumor sizes were significantly larger in the treatment group than in the control group, the authors performed a logistic regression analysis to determine the odd’s ratio. The risk for deterioration of facial nerve function was adjusted nearly the same in both groups (OR 1.07 [95% CI 0.34–3.43], P = 0.91). In contrast, the risk for postoperative hearing loss was adjusted 2 times lower in the treatment group compared with the control group (OR 0.49 [95% CI 0.18–1.30], P = 0.15). Apart from dose-dependent hypotension (P < 0.001), no clinically relevant adverse reactions were observed with the medications in the treatment arm.

The authors, thus, concluded that the prophylactic treatment did not have any statistically significant effects. They, however, conceded that despite the width of the confidence intervals, the odds ratios suggested but did not prove, a clinically relevant effect of the medication on the preservation of cochlear nerve function after VS surgery. They stressed on the need for further studies before prophylactic nimodipine could be recommended in VS surgery.

*Contributed by Dr. Kuntal Kanti Das*


Flow diverters (FDs) have been used successfully in anterior circulation aneurysms, particularly in internal carotid artery (ICA) aneurysms. For posterior circulation aneurysms (PCAs), however, their role is still controversial mainly because of their association with higher rates of ischemic stroke and perforator infarction. There are several studies which have reported the efficacy of flow diverter treatment for PCAs but have not systematically evaluated the mortality rate, aneurysmal occlusion, and procedure related complications.

The main aim of this meta-analysis was a systematic review to provide an insight into the treatment of PCAs using flow diverters. This meta-analysis included all studies on the treatment of PCAs with FDs which were in English, had a minimum 5 patients and were published between July 2005 and July 2015. A total of 14 studies were included in this analysis including seven prospective single-arm cohort studies and seven retrospective case series. This meta-analysis included a total of 220 patients with 225 PCAs, of which 16% were ruptured and 84% were unruptured aneurysms. Size-wise, 29% of the aneurysms were classed as small (<10mm), 48% as large (10-25mm), and 23% as giant aneurysms(>25mm). Thirty four percent were saccular aneurysms, and 66% were not; 26% of the patients with aneurysms received FD treatment as a retreatment.

The procedure-related good outcome rate was 79%, with significantly lower rates among patients with ruptured aneurysms.
aneurysms and basilar artery aneurysms. The aneurysm size, aneurysm type, preoperative symptoms, and prior treatment were not significantly associated with the rate of procedure-related good outcome. The procedure-related mortality rate was 15%, with significantly higher rates among patients with giant aneurysms and basilar artery aneurysms. The rate of complete occlusion of aneurysms when assessed with a DSA at 6 months was 84%. Patients with basilar artery aneurysms had a a higher mortality rate as basilar artery has many perforator arteries, most of which supply the cerebellum, brain stem, and other important structures. Effective vascular compensatory mechanisms are lacking which lead to a relatively higher perforator infarction rate when FDs were placed in the vascular lumen. The association between the location of the aneurysms and the rate of perforator infarction during the follow-up was not analysed because many of the studies lacked this vital information. This meta-analysis provided more representative data on the mortality rate, with a significantly higher rate among patients with giant and basilar artery aneurysms.

When results of this study were compared with another meta-analysis done for all intracranial aneurysms which were treated with FDs, and the total mortality rate of intracranial aneurysms was 4%, which was significantly lower than that in the patients with PCAs reported in the present study (i.e. 15%).

The main complications of FDs were ischemic stroke (11%), perforator infarction (7%), postoperative subarachnoid haemorrhage (3%), and intraparenchymal hemorrhage (4%).

Among these complications, ischemic stroke and perforator infarction were apparently higher than those reported for flow diverter treatment of intracranial aneurysms (which were 6 and 3% respectively). A higher ischemic complication rate may relate to the lack of optimal platelet inhibition. Therefore, platelet function tests should be performed in all the patients prior to the FD procedure to make sure that the level of platelet inhibition is adequate (>30%). It has been also highlighted that adverse event rates drop significantly with experience, and that they are more among patients with a large/giant aneurysm which may be due to the longer procedure time.

Several limitations may have affected this meta-analysis as it included articles published in English only, had more number of smaller studies (which generally report more adverse events), and most of the studies were retrospective.

This meta analysis concluded that FD treatment of PCAs should be conducted in carefully selected patients with a poor natural history and no optimal treatment strategy. For ruptured and giant basilar artery aneurysms, further research is required for establishing a better and a more viable treatment option.

*Contributed by Dr. Vivek Singh*


Diabetes is associated with cognitive dysfunction and an increased risk of dementia. Earlier studies have shown global brain atrophy in patients with type 2 adult onset diabetes. MRI brain is done frequently to find the underlying cause of cognitive dysfunction in diabetes. Generalized brain atrophy along with microvascular changes present in diabetes type 2, occur in the context of aging and often also in relation to an adverse vascular risk factor profile. Advanced imaging techniques detect microstructural lesions in the cerebral grey and white matter of patients with diabetes that affect the structural and functional connectivity. Challenges are to further unravel the etiology of these cerebral complications by integrating findings from different imaging modalities and detailed clinical phenotyping and by linking structural MRI abnormalities to histology. This study was done to demonstrate diffusion tensor imaging (DTI) changes in the white matter (WM) and their association with cognitive decline in patients with type 2 diabetes mellitus. This can be used to complement the neuropsychological test scores in identifying patients with mild cognitive impairment. This study was done on forty-two patients with type 2 diabetes mellitus who were divided into two groups, one with mild cognitive impairment \((n = 20)\), and the other with normal cognition \((n = 22)\). Age-, sex-, and education-matched healthy controls \((n = 26)\) were also recruited for the study. This study was done on a 3Tesla MRI where DTI was followed by tract-based spatial statistical analysis to investigate the differences in fractional anisotropy, mean diffusivity, axial diffusivity and radial diffusivity among the groups. A receiver operating characteristic analysis assessed the performance of DTI parameters in separating the 2 groups with type 2 diabetes mellitus.

The analysis of whole-brain tract-based spatial statistics revealed that there was a considerable difference in the fractional anisotropy (7.3%) and mean diffusivity (24.9%) of WM between the diabetes mellitus patients with cognitive decline and those without cognitive decline. When these parameters were compared between the patients with diabetes mellitus with mild cognitive impairment and the...
healthy control groups, the former showed considerable alterations in the larger WM regions with fractional anisotropy (36.6%) and mean diffusivity (58.8%) changes. There was an elevated radial diffusivity which was responsible for these changes in patients with diabetes mellitus with mild cognitive impairment, while subtle changes in the radial diffusivity between the diabetes mellitus with normal cognition and the healthy control groups were noticed. Brain regions responsible for cognitive function showed fractional anisotropy reduction and elevated mean diffusivity.

The receiver operating characteristic analysis of the right cingulum (hippocampus) showed that fractional anisotropy produced a larger area under the curve (0.832) than mean diffusivity (0.753) for separating the mild cognitive impairment from normal cognition among patients with type 2 diabetes mellitus. When fractional anisotropy was combined with mean diffusivity, the area under the curve further improved to 0.857. The authors of this study concluded that DTI parameters showed a substantial difference between patients with type 2 diabetes mellitus and without mild cognitive impairment. Thus, these DTI findings have a potential use as an imaging marker for detecting cognitive decline in patients with type 2 diabetes mellitus. DTI can pick up these changes before the patients can be diagnosed clinically. These DTI parameter changes are because of a compromise in the myelin sheaths and axonal damage. However, the exact mechanism explaining how hyperglycemia is responsible for these changes is still unclear and needs further study.

Contributed by Dr. Vivek Singh


Use of stent retrievers in endovascular recanalization of large vessel occlusion is a well established therapy for acute stroke. Recent randomized trials have established the supremacy of endovascular treatment in combination with medical management over medical management alone. These trials were confined to large proximal vessels supplying the brain. The vessel size for which stent retrievers were approved was between 2–9mm in diameter. Sometimes, occlusion of small sized (less than 2mm) vessel occlusion is encountered, which may either reflect the extension of the thrombus or its spread via fragmentation during the procedure performed for the large thrombus extraction. There is limited information available regarding the safety and efficacy of these procedures in small vessels. Recently, some studies have demonstrated the feasibility and safety of thrombectomy of small vessels including the M2 segment of middle cerebral artery and the anterior cerebral branch occlusion. The successful recanalization was associated with an improved clinical outcome and a smaller infarct size in a recent study. However, all these studies have used the regular sized stent retrievers, which may be potentially harmful when used in the affected vessels of small diameter.

Retrievers with a reduced radial force and an appropriate diameter that fits the small calibre microcatheters may increase the spectrum of potentially treatable vessel occlusions. pRESET LITE 4–20 and 3–20 were designed and approved to meet these demands. This article report the first hand experience with pRESET LITE (phenox GmbH, Bochum, Germany) in performing the thrombectomy of vessels ≤2 mm in diameter. From a prospectively maintained institutional database, they selected consecutive patients treated with pRESET LITE in target vessels of ≤2 mm diameter between August 2013 and March 2015. Recanalization success was measured by applying the modified Thrombolysis in Cerebral Infarction (mTICI) score. To assess for safety, the authors recorded the device-related procedural complications which included the presence of hemorrhage even on follow up imaging. Assessment of infarcts in the dependent territory served as a measure for the efficacy of the procedure. Of the 536 patients treated between August 2013 and March 2015, 76 met the inclusion criteria of vessel less than 2 mm and supplying the eloquent cortex. pRESET LITE was used in 90 branches with an average diameter of 1.6 mm (1.3–2.0 mm). Out of the 90 branches, 63 were involved in primary thrombotic occlusions, 14 were occluded due to emboli into the already affected territory, 12 were occluded due to the presence of emboli in a new territory, and one had an undetermined occlusion. An mTICI score ≥2b was achieved in 70% patients. The procedural events consisted of significant vasospasm in 5.6%, suspected dissections in 2.2%, downstream emboli in 2.2%, and self-limiting extravagations in 1.1% patients. On posttreatment imaging, 2.2% patients developed parenchymal hemorrhages and 13.3%, a focal subarachnoid hemorrhage (SAH) that were potentially device related, but all of these events remained asymptomatic. A hemorrhage was classified as possibly device related if it was anatomically related to the target branch and no other cause was identifiable. A device-related adverse event or hemorrhage was regarded as symptomatic if the National Institutes of Health Stroke Scale (NIHSS) increased by ≥4 points, and the adverse event or hemorrhage was the most likely cause for the clinical deterioration. The follow-up imaging was
also evaluated and assessed for the development of new infarcts in the territory of the target branch and the findings were categorized into no infarction, partial infarction, and complete infarction.

After successful recanalization, 33.3% patients developed no ischemia in the dependent territory, while 41.7% developed a partial infarct and 25% developed a complete infarct. Successful recanalization significantly increased the chance of developing either no infarct or only a partial infarct compared with a complete infarction ($P = 0.003$, $P = 0.013$). The authors concluded that thrombectomy of small vessels with pRESET LITE is feasible with a good recanalization rate and reasonable safety margins. Successful recanalization significantly reduces the risk of infarction in the dependent territory, but its impact on the overall clinical outcome needs further large follow up studies.

Contributed by Dr. Vivek Singh


Inadequate guidelines exist regarding the establishment of diagnosis of atlanto-occipital dislocation (AOD). The authors conducted a study to identify the normal occipital condyle–C1 interval (CCI) in healthy adults and compare it with the CCI in adults with AOD to establish a highly sensitive and specific cutoff value for the diagnosis of AOD. A total of 81 patients, 59 without AOD and 22 with AOD, were included in this study. Measurements obtained from thin-slice CT scans of the craniovertebral joint were utilized to assess the atlantooccipital dislocation.

The mean CCI for non-AOD patients was $0.89 \pm 0.12$ mm while the mean CCI in AOD patients was $3.35 \pm 0.18$ mm (range 1.5 mm–6.4 mm). The cutoff values for AOD were set at 1.5 mm for the CCI and 3.0 mm for the condylar sum (sum of bilateral distances between the midpoint of occipital condyle and atlantal condylar fossae), both with a sensitivity of 1 and a false-negative rate of 0. Sensitivity for the Powers, Wholey, Harris, Sun, Wackenheim, and Lee criteria were determined to be 0.55, 0.46, 0.27, 0.23, 0.41, and 0.41, respectively.

Contributed by Dr. K Sridhar


Previous clinical trials have suggested that carotid-artery stenting with a device to capture and remove emboli (“embolic protection”) is an effective alternative to carotid endarterectomy in patients at an average or a high risk for developing surgical complications. The authors compared carotid-artery stenting with embolic protection and carotid endarterectomy in patients 79 years of age or younger who had severe carotid stenosis and were asymptomatic (i.e., had not had a stroke, transient ischemic attack, or amaurosis fugax in the 180 days before enrolment) and were not considered to be at a high risk for surgical complications. The trial was halted early, after 1453 patients underwent randomization, because of the slow enrolment. The authors concluded that stenting was noninferior to endarterectomy with regard to the rate of the primary composite end point at 1 year. In analyses that included up to 5 years of follow-up, there were no significant differences between the study groups in the rates of non–procedure-related stroke, all strokes, and survival.

Contributed by Dr. K Sridhar


The N-terminal pro B-type natriuretic peptide (NT-proBNP) has a well-documented prognostic value for cardiovascular diseases (CVD) and higher levels are associated with cognitive-dysfunction in patients with CVD. However, how NT-proBNP relates to incidental dementia and cognitive-decline in community-dwelling persons is unknown. Between 1997 and 2001, the serum NT-proBNP was measured in 6040 participants (mean age 69 years, 57% women) from the Rotterdam study, who were free of heart-failure and dementia. The participants were continuously followed-up for incident dementia until the year 2012.

Higher levels of NT-proBNP were associated with a higher risk of dementia, even after excluding patients with CVD and adjusting for cardiovascular risk factors. Associations were particularly strong for vascular dementia, but also for Alzheimer’s disease. Patients with a higher level of NT-proBNP were cross-sectionally associated with a poorer performance in multiple cognitive tests but longitudinally only in Letter-Digit-Substitution-task.

The authors concluded that NT-proBNP can be a useful marker of imminent cognitive-decline and dementia in the absence of clinical CVD.
Contributed by Dr. K Sridhar


In the patients of multiple sclerosis (MS) who had at least one eye without optic neuritis, the authors conducted a multi-centre cohort study to assess the role of peripapillary retinal nerve fibre layer (pRNFL) thickness and macular volume in the eyes which were not involved in optic neuritis (ON) as a marker of disability worsening (as assessed by the Expanded Disability Status Scale (EDSS)). 879 patients suffering from MS (74 with the clinically isolated syndrome, 664 with relapsing–remitting MS and 141 with progressive MS) were included in the primary analyses. The pRNFL and macular volume were assessed once at the study entry by optical coherence tomography (OCT) and was calculated as the mean of both eyes if neither eye was previously affected by ON, or of the unaffected eye if one eye was previously affected by ON. The researchers who performed the OCT and who assessed the EDSS were blinded from each other. Proportional hazards models that included OCT metrics and age, disease duration, disability, presence of previous unilateral optic neuritis, and use of disease-modifying therapies as covariates were used to estimate the association of pRNFL thickness and macular volume with the risk of subsequent disability worsening. After a median follow up of 2 years (range: 0.5–5 years), the disability worsening occurred in 252 (29%) of 879 patients. Patients with a pRNFL of less than or equal to 87 μm, or less than or equal to 88 μm (measured with Spectralis or Cirrus OCT devices), had double the risk of disability worsening at any time after the first and up to the third year of follow-up (hazard ratio 2.06, 95% CI 1.36–3.11; P = 0.002), and the risk was increased by nearly four times after the third and up to the fifth year of follow-up (3.81, 1.63–8.91; P = 0.002). There was however, no significant association of disability worsening with macular volume. The authors concluded that monitoring of pRNFL thickness for predicting disability worsening with time is a useful tool.

Contributed by Dr. Anant Mehrotra


One of the independent risk factors of poor outcome in the cases of ischaemic stroke is hyperglycemia at admission. Various strategies to control hyperglycemia like using insulin have failed to show any significant improvement in post stroke outcome. However, glucagon-like peptide 1 receptor agonists (exendin-4), which modulate blood glucose levels by stimulating secretion of insulin have been shown to exert cytoprotective effects by inhibiting inflammation and oxidative stress. The authors conducted the study to evaluate whether exendin-4 could reduce glucose levels and has any protective effects after acute focal ischaemia in rats with hyperglycemia. Dextrose was injected intraperitoneally 15 minutes prior to transient middle cerebral artery occlusion for 60 minutes. Four groups were formed namely those with (1) normal glucose (vehicle control), (2) induced hyperglycemia, (3) induced hyperglycemia with insulin treatment, and (4) induced hyperglycemia with exendin-4 treatment. 24-hours and 7-days post ischaemia, the injury to the brain was assessed in each group. The infarct

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The authors conducted a randomized, multicenter, double blind, placebo-controlled study to assess the safety and efficacy of repeated administrations of botulinum toxin A in patients with neuropathic pain. Patients in the range of 18-85 years of age were randomly assigned to receive two subcutaneous administrations of botulinum toxin A (up to 300 units) or a placebo, 12 weeks apart. Based upon the change from the baseline in self reported mean weekly pain intensity over the course of 24 weeks from the first administration, the primary outcome of efficacy of botulinum toxin A versus the placebo was measured. 152 patients were enrolled, of whom 68 were randomly assigned (34 per group), and 66 (37 [56%] men) were included in the primary analysis (34 in the botulinum toxin A group and 32 in the placebo group). Over a 24 week period, botulinum toxin A was able to reduce the pain intensity as compared to the placebo (adjusted effect estimate −0.77, 95% CI −0.95 to −0.59; P < 0.0001). The only adverse event encountered was pain on injection, which occurred in 19 patients of the botulinum group and 17 in the placebo group. The authors concluded that two administrations of botulinum toxin A, each of which comprised several injections, have a sustained analgesic effect against peripheral neuropathic pain.
volume (36.3 ± 1.20 versus 26.9 ± 1.28; \( P < 0.001 \)), brain edema (\( P < 0.05 \)), and hemorrhagic transformation were significantly increased by hyperglycemia. Increased blood brain barrier disruption and matrix metalloproteinase-9 activation was associated with the increased infarct volume. Exendin-4 attenuated matrix metalloproteinase-9 activation, tumor necrosis factor-\( \alpha \) release, and biomarkers of oxidative stress and showed significant inhibition of infarct growth at 24 hours as compared to insulin (23.6 ± 0.97 versus 36.3 ± 1.20; \( P < 0.001 \)); and, at 7 days after ischemia (21.0 ± 0.92 versus 29.3 ± 1.41; \( P < 0.001 \)). The authors concluded that treatment with exendin-4 could be potentially useful in cases of focal ischemia.

**Contributed by Dr. Anant Mehrotra**


Caveolins (a group of proteins) are said to play an important role in the blood brain barrier (BBB) permeability but its role during ischaemic injury is yet not identified. The authors conducted the study on mice in which they measured the Cav-1 expression by immunoblotting after photothermotic ischemia. A direct functional role of Cav-1 in cerebral edema and BBB permeability during cerebral ischemia was investigated by genetic manipulation (gene disruption and re-expression) of Cav-1 protein expression in mice. The authors found a significant correlation between the Cav-1 expression and the extent of BBB disruption. In mice which were Cav-1 deficient, the extent of BBB disruption (postcerebral ischaemia) was increased as compared to that seen in the wild type mice. In mice in which lentiviral-mediated re-expression of Cav-1 was done, the increase in cerebral edema volume was ameliorated. Cav-1 deficient mice had a significantly higher proteolytic activity of matrix metalloproteinase and degradation of tight junction proteins as compared to the wild type mice. On reexpression of Cav-1 in Cav-1 deficient mice, there was restoration of the tight junction protein expression and reduction of matrix metalloproteinase proteolytic activity. The authors have concluded that Cav-1 is an important determinant of BBB permeability and treatment options that regulate Cav-1 might help in controlling the BBB disruption and subsequent neurological deterioration during cerebral ischemia.

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In a small number of patients with chromosome 22q11.2 deletion syndrome, Parkinson’s disease has been reported. The authors have analyzed the data from four separate case control Parkinson’s disease studies which were independent of the original reports reporting on the chromosomal deletion. Using the Fisher’s exact test, the authors performed a case-control association analysis to compare the proportion of the deletion and with the help of Mantel–Hanzel test, they performed the meta-analysis. Out of a total of 9387 patients of Parkinson’s disease, 8 had the 22q11.2 deletion while out of 13863 controls, none had this deletion (\( P = 0.00082 \)). The age of onset of Parkinson’s disease was lower in those patients who had the 22q11.2 deletion (median age 37 years, 95% CI 32.0-55.5; mean 42.1 years +/- 11.9) as compared to those who did not have the deletion (median 61 years, CI 60.5-61; mean 60.3 years +/- 12.8; \( P < 0.0001 \)).

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