COMMENTARY

A summary of some of the recently published, seminal papers in neurosciences

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In this single-center trial, the authors randomly assigned 116 patients who were 18 years of age or younger with drug-resistant epilepsy to undergo brain surgery appropriate to the underlying cause of epilepsy along with appropriate medical therapy (surgery group, 57 patients) or to receive medical therapy alone (medical-therapy group, 59 patients). At 12 months, freedom from seizures occurred in 44 patients (77%) in the surgery group and in 4 (7%) in the medical-therapy group. Serious adverse events occurred in 19 patients (33%) in the surgery group, including hemiparesis in 15 (26%). The authors concluded that children and adolescents with drug-resistant epilepsy who had undergone epilepsy surgery had a significantly higher rate of freedom from seizures and better scores with respect to behavior and quality of life than did those who continued medical therapy alone at 12 months. Surgery resulted in anticipated neurologic deficits related to the region of brain resection.

Contributed by Dr. Mazda K. Turel


The authors wanted to evaluate progression of cervical ossification of the posterior longitudinal ligament (OPLL) in each motion segment using a novel system of classification. Clinical data from 34 patients (86 segments) with cervical myelopathy secondary to OPLL were evaluated retrospectively. Ossified masses were classified into four types according to the degree of disc space involvement: type 1 (no involvement); type 2 (involving disc space but not crossing it); type 3 (crossing disc space but not fused); and type 4 (complete bridging). Range of motion (ROM) for each segment was measured using dynamic radiographs. They concluded that Type 2 or 3 disc involvement and segmental ROM > 5° were risk factors for OPLL progression. They suggest that a close follow-up is warranted in cases of type 2 or 3 with greater segmental motion.

Contributed by Dr. Mazda K. Turel, Dr. Chirag K Ahuja and Dr. Kuntal Kanti Das


The aim of this study was to determine the effect of allogeneic red blood cell (RBC) transfusion on postoperative patient complication profiles and 30-day readmission rates following elective spine surgery in 160 patients. The mean pre- and postoperative hemoglobin levels were lower for the transfusion than the nontransfusion cohorts. Postoperative complication rates were 45% and 23% in the transfusion and nontransfusion cohorts, respectively. Overall, 9% of patients were re-admitted within 30 days of hospital discharge, with a three-fold higher increase in 30-day readmission rate in the transfusion cohort compared to the nontransfusion cohort (no transfusion: 5% vs. transfusion: 17%). They

concluded that allogeneic RBC transfusions may be associated with increased postoperative complications, length of hospital stay, and 30-day readmission rates.

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The authors wanted to investigate the efficacy of adding supplemental fusion or arthroplasty after cervical anterior discectomy for symptomatic single level cervical degenerative disease (radiculopathy), which has not been substantiated in controlled trials until now. A randomized controlled trial is reported with a 9-year follow-up comparing anterior cervical anterior discectomy without fusion, with fusion by cage as a stand alone procedure, or with disc prosthesis, in 142 patients. The median follow-up was 9 years. The neck disability index (NDI) at the last follow-up did not differ between the three treatment groups, nor did the secondary outcomes in pain and quality of life scores. The major improvement occurred within the first 6 weeks after surgery. Afterwards, it remained stable. Eleven patients underwent surgery for recurrent symptoms and signs due to nerve root compression at the index or adjacent level. This randomized trial could not detect a difference between the three surgical modalities for treating a single-level degenerative disc disease. Anterior cervical discectomy without implant seems to be similar to anterior cervical discectomy with fusion using a stand-alone cage or with disc prosthesis.

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Touch spray mass spectrometry using medical swabs is an ambient ionization technique (ionization of unprocessed sample in the open air) that has a potential intraoperative application in quickly identifying the diseased status of tissues and in better characterizing the resection margin. The authors studied 29 human brain tumor specimens and obtained evidence that this technique can provide diagnostic molecular information that is relevant to brain cancer. Touch spray using medical swabs involves the physical sampling of tissue using a medical swab on a spatial scale of a few mm² with subsequent ionization occurring directly from the swab tip upon addition of solvent and application of a high voltage. Oncometabolites are extracted from the tissue, incorporated into the sprayed microdroplets, vacuumed into the mass spectrometer, and characterized in the resulting mass spectra. The tumor cell load was assessed from the complex phospholipid pattern in the mass spectra and also separately by the measurement of N-acetylaspartate. Mutation status of the isocitrate dehydrogenase gene was determined via detection of the oncometabolite 2-hydroxyglutarate. The lack of sample pretreatment makes touch spray mass spectrometry using medical swabs a feasible intraoperative strategy for rapid surgical assessment.

Contributed by Dr. Mazda K. Turel


Within glioblastomas exists a subpopulation of highly plastic self-renewing cancer cells that retain the ability to expand ex vivo as tumour spheres, induce tumour growth in mice, and have been implicated in radio- and chemo-resistance. Although their identity and fate are regulated by external cues emanating from endothelial cells, the nature of such signals remains unknown. Here, the authors used a mass spectrometry proteomic approach to characterize the factors released by brain endothelial cells. They report the identification of the vasoactive peptide apelin as a central regulator for endothelial-mediated maintenance of glioblastoma patient-derived cells with stem-like properties. Targeting of apelin cognate receptor abrogates apelin and endothelial-mediated expansion of glioblastoma patient-derived cells with stem-like properties in vitro and suppresses tumour growth in vivo. Functionally, selective competitive antagonists of apelin receptor were shown to be safe and effective in reducing tumour expansion and in lengthening the survival of intracranially xenografted mice. Therefore, the apelin/apelin receptor signalling nexus may operate as a paracrine signal that sustains tumour cell expansion and progression, suggesting that apelin is a modifiable factor in the medical therapeutics of glioblastomas.

Contributed by Dr. Mazda K. Turel


Glioblastomas are lethal cancers defined by angiogenesis and pseudo-palisading necrosis. Here, the authors demonstrate that these histological features are associated with distinct transcriptional programs, with vascular regions showing a proneural profile, and hypoxic regions showing a mesenchymal pattern. As these regions harbor glioma stem cells (GSCs), they investigated the epigenetic regulation of these two niches. Proneural, perivascular GSCs activated enhancer of zeste homolog 2 (EZH2) gene, whereas mesenchymal GSCs in hypoxic regions expressed BMI1 polycomb group protein gene, which promoted cellular survival under stress due to downregulation of the E3 ligase, ring finger protein 144 (RNF144A) gene. Using both genetic and pharmacologic inhibition, they found that proneural GSCs are preferentially sensitive to EZH2 disruption, whereas mesenchymal GSCs are more sensitive to BMI1 inhibition. Given that glioblastomas contain both proneural and mesenchymal GSCs, combined EZH2 and BMI1 targeting proved more effective than either agent alone, both in culture and in vivo, suggesting that strategies that simultaneously target multiple epigenetic regulators within glioblastomas may be effective in overcoming therapy resistance caused by intratumoral heterogeneity.

Contributed by Dr. Mazda K. Turel

Cross-talk among oncogenic signaling and metabolic pathways may create opportunities for new therapeutic strategies in cancer. The authors show that although acute inhibition of epidermal growth factor receptor (EGFR)-driven glucose metabolism induces only minimal cell death, it lowers the apoptotic threshold in a subset of patient-derived glioblastoma (GBM) cells. Mechanistic studies revealed that after attenuated glucose consumption, Bcl-xL blocks cytoplasmic p53 from triggering intrinsic apoptosis. Consequently, targeting of EGFR-driven glucose metabolism in combination with pharmacological stabilization of p53 with the brain-penetrant small molecule idasanutlin resulted in synthetic lethality in orthotopic glioblastoma xenograft models. Notably, neither the degree of EGFR-signaling inhibition nor the genetic analysis of EGFR was sufficient to predict sensitivity to this therapeutic combination. However, detection of rapid inhibitory effects on \[^{18}F\] fluorodeoxyglucose uptake, assessed through noninvasive positron emission tomography, was an effective predictive biomarker of response in vivo. Together, these studies identify a crucial link among oncogene signaling, glucose metabolism, and cytoplasmic p53, which may potentially be exploited for combination therapy in GBM and possibly other malignancies.

Contributed by Dr. Mazda K. Turel


The purpose of this study was to evaluate prognostic factors influencing the recurrence/progression and progression-free survival (PFS) rates of atypical meningiomas, particularly focused on the role of postoperative adjuvant radiotherapy. Of the 161 patients who underwent an atypical meningioma resection, 128 cases underwent surgical treatment alone and 33 cases underwent surgery and radiotherapy. The extent of resection (Simpson grade I and II) significantly influenced the risk of recurrence. There was no significant benefit for progression-free survival after adjuvant radiotherapy. Additionally, meningioma located within the anterior and posterior fossae showed a significantly longer PFS compared to other locations. Adjuvant postoperative radiotherapy had no significant impact on recurrence/progression rate or PFS. The authors concluded that the extent of resection according to Simpson grade remains the most important prognostic factor associated with lower recurrence/progression rates and longer PFS in patients with atypical meningioma.

Contributed by Dr. Mazda K. Turel


Spontaneous intracerebral hemorrhage (sICH) is a devastating disease associated with a high mortality and morbidity, and application of decompressive craniectomy (DC) in sICH is controversial. In a systematic review, the authors showed that in eligible patients, DC significantly reduced the poor outcome compared with the control group. However, in the subgroup analyses conducted only in studies published after 2010, studies using hematoma evacuation as control, and studies measuring outcome by the Glasgow Outcome Scale showed better outcomes in the DC group than in the control group. They concluded that DC effectively reduced mortality in patients with sICH. DC might improve functional outcomes in certain populations but this fact needs further verification. DC is not associated with an increased incidence of postoperative rebleeding and hydrocephalus.

Contributed by Dr. Mazda K. Turel


The authors aimed to determine the earliest possible time point for cranioplasty (CP) after decompressive craniectomy (DC) for TBI. They determined the earliest possible day for CP by reviewing the resolution of intracranial pressure on serial brain CT scan images between DC and CP. The early CP group was defined as the group within the earliest possible timing of CP; other cases constituted the late CP group. They compared complications and the Glasgow Outcome Scale (GOS) scores at six months between the groups. The mean initial Glasgow Coma Scale (GCS) score was around 8. The actual time interval between DC and CP was 94.75 ± 143.98 days. The earliest possible timing for CP was determined to be 34.60 ± 34.36 days post-DC. The incidence of complications did not differ significantly between the groups, except for ventriculomegaly, which occurred more frequently in the late CP group. Predictors of good outcome were suprisingly revision due to infection, pre-operative extradural hematoma, early cranioplasty, and ventriculomegaly following DC. They concluded that CP can be performed at around 34 days after DC for TBI. Ventriculomegaly occurred less frequently and the 6-month GOS score was better in the early CP group than in the late CP group.

Contributed by Dr. Mazda K. Turel


The purpose of this study was to determine the associations among patient factors, recurrence, and clinical outcomes of CSDH after bur hole surgery performed during an 11-year period in 756 consecutive patients. During the 6-month follow-up, 104 patients (13.8%) with recurrence after surgery for CSDH were identified. Independent risk factors for recurrence were as follows: age >75 years, obesity (body mass index ≥25.0 kg/m²), and a bilateral operation.

Contributed by Dr. Mazda K. Turel

There is no widely adopted grading system for the prediction of postoperative recurrence requiring reoperation (RrR) in patients with chronic subdural hematoma (CSDH). The authors developed a CSDH grading system to predict RrR based on predictive characteristics that can be objectively assessed at the time of first presentation and initial surgery in 107 consecutive surgical patients. The strongest predictors of RrR were isodense or hyperdense lesions and laminar or separated lesions, and a postoperative CSDH cavity volume greater than 200 mL. The moderate predictors of RrR were a postoperative CSDH cavity volume of 80 to 200 mL and a preoperative CSDH volume greater than 130 mL. According to the prognostic CSDH grading system, no patients with a score of 0 points had RrR. RrR was observed in 6% of patients with a score of 1 to 2 points, 30% of patients with a score of 3 to 4 points, and 63% of patients with a score of 5 points (that is, the maximum score). The rate of RrR increased steadily with increases in the prognostic CSDH grading score. The prognostic CSDH grading system is an applicable tool for RrR risk stratification in patients with CSDH.

Contributed by Dr. Mazda K. Turel


The authors’ objective was to conduct a prospective randomized controlled trial comparing 2 techniques for performing decompressive craniectomy (DC): With watertight duraplasty and without watertight duraplasty (rapid-closure DC). 58 patients were enrolled, 29 in each group. There were no significant differences between the groups regarding age, Glasgow Coma Scale score at the time of surgery, Glasgow outcome score, and the number of postoperative follow-up days. They concluded that rapid-closure DC without watertight duraplasty is a safe procedure. It is not associated with a higher incidence of surgical complications (cerebrospinal fluid leak, wound infection, brain abscess, or subgaleal fluid collection), and it decreased the surgical time by 31 minutes on average. There was also a hospital cost reduction of $420.00 USD (23.4% reduction) per procedure.

Contributed by Dr. Mazda K. Turel


The purpose of this study was to evaluate the effect of tranexamic acid (TXA) on hemorrhagic mass growth in traumatic brain injury (TBI) patients. In this randomized, double-blind clinical trial, 149 patients with TBI and any kind of hemorrhage visible on their computed tomography scan enrolled in the study and were randomly allocated to receive TXA or a placebo. After 24 hours, a computed tomography scan was repeated for assessing the changes in hemorrhage, and to detect areas of fresh bleeding as well as the mass effect of blood on the brain tissue. The incidence of hemorrhagic lesion growth was 20.5% in the TXA group and 22.7% in the placebo group. The difference was not significant. The frequency of deaths (2.7% vs. 4%), adverse outcome at discharge (10.8% vs. 17.3%), and 3 months later (6.8% vs. 14.7%) in the TXA group were lower than that seen in the placebo group, but the difference was not statistically significant. No side effect was observed by the administration of TXA. Hence, the authors concluded that administration of a short dose of TXA does not lead to significant prevention of growth of posttraumatic hemorrhagic lesions or in the improvement of clinical outcomes.

Contributed by Dr. Mazda K. Turel


This study reports the finding of the development of a novel method to record neural activity from the brain. The authors have designed, fabricated and tested a new silicon probe known as Neuropixel that has 384 recording channels. These large number of channels have been placed in a tiny area and can be used to study the local field potentials and neuronal spikes in both superficial and deeper brain structures. It has both excellent temporo-spatial coverage as well as significant volume cover. The authors report that using two of these probes, they recorded from 700 single neurons and had been testing the probes in the awake mouse. This technology has a potential to radically change the way the signals are recorded in patients with epilepsy, movement disorders and study the typical brain physiology.

Contributed by Dr. Ravi Yadav


The patients with chronic inflammatory demyelinating polyneuropathy (CIDP) need treatment with long-term immunotherapy, and intravenous immunoglobulin (IVIG) is one of the commonly used therapy. The use of subcutaneous immunoglobulin (SCIG) in CIDP has not been investigated in a large trial. The PATH study reports the relapse rates of treatment with SCIG versus placebo in patients with CIDP. The investigators recruited proven patients of CIDP from 69 neuromuscular centers spread across four continents. The patients had proven improvement with IVIG. They were randomized to either 0.2 g/kg or 0.4 g/kg of a 20% SCIG solution weekly versus a placebo (2% human albumin solution) for maintenance treatment for 24 weeks. The primary outcome was the relapse or withdrawal from the study due to any reason. A total of 172 patients were enrolled in a randomized,
double-blind placebo-controlled trial. Equal numbers of patients were in each arm. At the end of the study, absolute risk reductions were 25% for low-dose versus placebo, 30% for high-dose versus placebo, and 6% for high-dose versus low-dose. This study by far is the most substantial trial in CIDP showing the efficacy and safety of both low and high doses of SCIG in the maintenance treatment of CIDP.

**Contributed by Dr. Ravi Yadav**


Hereditary spastic paraplegia 5 (SPG5) is a rare type of hereditary spastic paraplegia that results in progressive degeneration of corticospinal neurons. This disease is due to an autosomal recessive mutation in the gene CYP7B1 encoding oxysterol-7α-hydroxylase. CYP7B1 deficiency causes accumulation of toxic oxysterols. In this study, 34 genetically confirmed SPG5 cases from 28 families were included from multiple centers across the world. There was a significant accumulation of CYP7B1 substrates including 27-hydroxycholesterol in the serum and cerebrospinal fluid of SPG5 patients. Based on these findings the investigators performed a randomized placebo-controlled trial using 40mg of atorvastatin. Patients were found to have significant reduction in 27-hydroxycholesterol levels in serum. There was no clinically apparent benefit seen in the short assessment of 9 weeks. This study demonstrates for the first time the treatment strategy in patients with SPG5.

**Contributed by Dr. Ravi Yadav**

**Bruurmijn MLCM, et al. Preservation of hand movement representation in the sensorimotor areas of amputees. Brain 2017; 140:3166-78.**

The authors studied an area of cortical reorganization in patients who were amputees and healthy controls using machine learning tools. It is known that there is a contraction of sensorimotor representation in the sensorimotor cortex following the amputation, but there is limited knowledge available on this subject. This is important for the development of brain-machine interface for the development of the prosthesis. The study was conducted on eight patients with above-elbow arm amputation and nine non-amputated controls who made many gestures with either of the hand. The amputees made an effort to perform gestures with their amputated hand. A 7T functional MRI was used to acquire the images. The study shows the capability to decode the tried gestures and also shows that the full hand depiction is maintained in motor cortex and nearby areas after denervation. These findings help to boost up the the sensorimotor activity patterns that may be used in brain-computer interfaces.

**Contributed by Dr. Ravi Yadav**


There are studies that show that there is an increased association of migraine with stroke. However, these studies are based on the self-reported questionnaire and not controlled for familial factors. The investigators did the study in a Swedish population-based twin cohort. In this study, 8635 twins had a migrainous headache, of which 3553 had migraine with aura, and 5082 had non-aura migraine headache (including migraine without an aura and probable migraine), and 44,769 twins had no migraine. The mean follow-up time was 11.9 years during which the authors found 1297 incident cases of stroke. Using the Cox proportions model they found that age and gender-adjusted hazard ratio was 1.27 for migraine with aura and 1.07 for migraine without aura. They performed many types of statistical methods and did not find any increased risk of stroke in patients with migraine overall but a mild increase in risk in patients of migraine without aura.

**Contributed by Dr. Ravi Yadav**


Febrile seizures are the most common seizures in the pediatric population (one month to five years age group). In India, the incidence ranges from 5-10%. A seizure in this age group leads to anxiety among the parents. Among clinicians, there is significant variation regarding the routine use of an electroencephalogram (EEG) and the prolonged use of antiepileptic drugs. There is no definitive evidence of the value of an EEG for prognostication of simple and complex febrile seizures and the prolonged daily use of oral antiepileptic drugs for its prevention. In this Cochrane database review, Shah et al., have tried to identify the role of EEG in prognostication. They evaluated 41 studies from the Cochrane Epilepsy group. With this detailed analysis, it was concluded that there is no conclusive evidence to support or refute the use of EEG and its timing after the occurrence of a complex partial febrile seizure. The authors also recommend the urgent need of well designed randomized control trials to address this very common but bothering paediatric emergency.

**Contributed by Dr. Manjul Tripathi**


Routine surveillance MRI, increased life expectancy, more effective therapies to control extra-cranial disease, and brain being a sanctuary has lead to a high incidence of brain metastases among those with primary malignant tumors. Majority of these patients have limited brain metastases (1-4). This guideline serves as the best level of evidence in favour of stereotactic radiosurgery (SRS) for limited brain metastases. There are four key points derived from this study; first, there is no detriment to survival by withholding whole brain radiation (WBRT) in the upfront management of brain metastases with SRS. Second, while SRS on its own provides a high rate of local control (L.C),
The guidelines strictly recommend that men drink no more than one to two drinks per day and that women drink no more than one drink per day. In addition, people who do not currently drink alcohol should not start drinking it for any reason.

Contributed by Dr. Manjul Tripathi


The Lancet Neurology Commission has made a concerted effort to define global health burden posed by traumatic brain injury (TBI). This detailed report elaborates the current problem, the variability in the presentation, the deficiencies in the management, and the research undertaken to address the huge social and economic burden of TBI. By now, it is evident that there cannot be a uniform policy that fits all approaches and targets the needs of the individual patients. The majority of TBI in high income countries are secondary to a fall, while in the middle and low income countries, they occur due to road traffic accidents. In large countries such as China and India, the problem starts with the insufficient recording of the injuries that leads to a significant underestimation of the trauma sustained by the patient. TBI is a multidimensional care, which needs concerted efforts right from the identification of the patient to the rehabilitation, which extends for many years. This extensive but comprehensive report can be a good guide for framing new policies and to learn from the mistakes that occurred in the past. This report is especially valuable for low and middle income countries where TBI is the leading cause of morbidity and mortality in the productive age group of the population.

Contributed by Dr. Manjul Tripathi


Famous American confederate general Stonewall Jackson once quoted, “I am more afraid of alcohol than of all the bullets of the enemy.” Alcohol drinking has been established as a social norm in nearly all the societies. Though it has been recognized as an established risk factor for several malignancies, the leading oncology group, American Society of Clinical Oncology (ASCO), only recently decided to issue a public statement regarding the significant health hazards and mutagenic potential of alcohol even with casual drinking habits. Approximately 3.3 million deaths worldwide result from the harmful use of alcohol per year. Alcohol and its metabolite, acetaldehyde, are considered as group 1 carcinogens. There is established relation between alcohol consumption and aerodigestive tract cancer, colorectal cancer, and estrogen receptor positive breast cancer. The previously published and widely publicized report of light alcohol use, especially that of red wine and its cardioprotective value, is questionable. The results obtained may simply be the result of an abstainer bias. The report also highlights how the low physician knowledge of alcohol use and cancer risk is another barrier for effectively addressing alcohol abuse in the patients. The guidelines strictly recommend that men drink no more than one to two drinks per day and that women drink no more than one drink per day. In addition, people who do not currently drink alcohol should not start drinking it for any reason.

Contributed by Dr. Manjul Tripathi


A patent foramen ovale (PFO) increases the chance of ischemic stroke. While some advocate medical management with prophylactic antiplatelets or anticoagulation to prevent stroke, others believe surgical closure is better. This randomized, multicenter, open-label trial of surgical closure of the PFO (PFO closure group) versus medical therapy alone (aspirin, warfarin, clopidogrel, or aspirin combined with extended-release dipyridamole; medical-therapy group) aimed to compare the two management strategies. Analysis of data of 980 adult patients at 69 sites revealed rates of recurrent ischemic strokes of 0.58 events per 100 patient-years and 1.07 events per 100 patient-years in the PFO closure group and medical therapy group, respectively. Surgical closure definitely led to better results in terms of reduced recurrent ischemic strokes during the extended follow-up period than the results obtained in their medically managed counterparts.

Contributed by Dr. Chirag K Ahuja and Dr. Srijithesh PR


Contributed by Dr. Manjul Tripathi

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Lumbar puncture in children is associated with its own set of morbidities. The authors have attempted to identify whether the prevalence of bacterial meningitis and herpes simplex virus meningoencephalitis (HSV-ME) in children with a complex febrile seizure is significant so as to warrant lumbar puncture in all patients presenting with such complaints. This was a large French multicenter retrospective study conducted in 7 pediatric emergency departments (EDs) where they evaluated the visits of patients below 5 years of age due to the occurrence of a complex febrile seizure over a 6 year period. A subgroup was identified whose clinical examination result was not suggestive of meningitis or encephalitis. From a total of 1,183,487 visits of 839 patients who presented with a complex febrile seizure, 31% had a lumbar puncture. In these, bacterial meningitis was detected in 5 (0.7%) patients and no case of HSV-ME was identified. It can, thus, be reasonably concluded that it is an unlikely event that children with a complex febrile seizure, in whom the clinical examination is not suggestive of meningitis or encephalitis, will have a cerebrospinal fluid proven bacterial meningitis or HSV-ME.

Contributed by Dr. Chirag K Ahuja


The evolution of any first demyelinating event to multiple sclerosis (MS) is a matter of debate. Minocycline administration has shown to reduce this conversion in few preliminary studies. A randomized, controlled trial was conducted over a period of four and a half years to determine whether minocycline actually reduces the risk of conversion from a first demyelinating event (clinically isolated syndrome, CIS) to multiple sclerosis. 142 patients with CIS were randomized into two groups of 72 and 70 patients and assigned to the minocycline administered and the placebo administered cohorts. The primary outcome was conversion to multiple sclerosis within 6 months after randomization, while the secondary outcome measures were conversion to multiple sclerosis within 24 months and changes on MRI at 6 months and 24 months. There was significant difference in the risk of conversion to multiple sclerosis within 6 months between the two groups with minocycline proving to be beneficial. These results, however, did not last until 24 months. All secondary MRI outcomes favored the administration of minocycline over the placebo at 6 months but not at 24 months. The adverse effects were more common among participants who received minocycline. It was eventually realized that the risk of conversion from a clinically isolated syndrome to multiple sclerosis was significantly lower with minocycline than with placebo over 6 months, a beneficial effect which is neutralized at 24 months.

Contributed by Dr. Chirag K Ahuja


It has been claimed that hydrogel coils produce better aneurysm occlusion with lower recurrence rates on follow-up. Two cohorts from PRET (Patients Prone to Recurrence After Endovascular Treatment) 1 and 2 trials were taken to investigate whether the use of hydrogel coils improved efficacy outcomes compared with bare platinum coils. After appropriate randomization, the outcome measures (composite of a residual/recurrent aneurysm, retreatment, intracranial bleeding, mass effect, mortality, morbidity, etc.) were evaluated during the 18-month follow-up period. A poor outcome occurred in 44.4% of those in PRET-1 allocated to platinum compared with 52.5% allocated to hydrogel, and in 49.0% in PRET-2 allocated to platinum compared with 42.1% allocated to hydrogel. The adverse events and morbidity were similar. The use of hydrogel coiling did not significantly change the recurrence rates over platinum coils.

Contributed by Dr. Chirag K Ahuja


While it is recognized that intermittent hypoxia may often go undetected in the first few days after acute stroke, the definite status of the use of oxygen supplementation after acute stroke remains partly unexplored. The stroke oxygen study was a single blind randomized clinical trial that assigned patients with acute stroke within 24 hours of admission to 3 days of continuous oxygen, nocturnal oxygen, or control. The main aim was to assess whether routine prophylactic low dose oxygen therapy was more effective than control oxygen administration in reducing death or disability at 90 days, and if so, whether nocturnal oxygen administration was more effective (keeping in account the probable frequent hypoxic spells at night). 8003 participants from 136 centers in the United Kingdom were enrolled and Modified Rankin Scale score was assessed at 90 days as primary outcome. Primary outcome was available for 7677 patients. No reduction of death or disability at 3 months was noted with the use of prophylactic low dose oxygen supplementation. No subgroup could be identified that benefitted from oxygen. The findings of this trial did not support the use of prophylactic low dose oxygen in non-hypoxic patients with acute stroke.

Contributed by Dr. Aastha Takkar


Even after introduction of many newer oral anticoagulants, the controversy of which anticoagulation is to be used after stroke following the occurrence of atrial fibrillation (AF) prevails. The optimal oral anticoagulation strategy remains unclear. This randomized, multicenter, open label, blinded, comparative phase 2 trial was conducted in 14 academic medical centers in South Korea among patients with mild AF related stroke within the previous 5 years. The aim of the trial was to test whether rivaroxaban or warfarin is safe and more effective for preventing early recurrent strokes in patients with AF related acute ischemic stroke. Participants were randomized to receive
rivaroxaban, 10mg/d for 5 days followed by 15/20 mg/d, or warfarin with a target international normalised ratio (INR) of 2.0-3.0, for 4 weeks. The primary end point was the composite of new lesions or new intracranial hemorrhage seen on MRI done at 4 weeks. Key secondary end points included length of hospitalization in addition. Of the 195 patients randomized, 183 completed MRI imaging follow up and were included in the primary end point analysis. Neither the rivaroxaban group nor the warfarin group showed any statistically significant difference in the primary end point or in any of its individual components (that included the occurrence of new ischemic lesion/new intracranial hemorrhage). Hospitalization length was reduced with rivaroxaban compared with warfarin. The authors concluded that in mild AF-related acute stroke both these anticoagulants had comparable safety and efficacy.

Contributed by Dr. Aastha Takkar


Benign essential blepharospasm (BEB) is a common disabling cranio-facial movement disorder. Life long therapy with periocular botulinum toxin injections is commonly resorted to but this therapy provides transient alleviations often leading to non-compliance. This was a retrospective chart review of patients certified for medical cannabis use for BEB from September 2015 to May 2016. The objective of this study was to observe the effect of medical cannabis in BEB as an adjunct to botulinum toxin. Details of patient demographics, responses, cannabis history, and severity indices were noted. Ten patients were certified for medical cannabis use. Patients with a diagnosis of BEB receiving standard botulinum toxin treatment who had started medical cannabis treatment by a registered distributor, and were contactable by phone were included. The study finally included only four patients for the final analysis. Three out of four patients (75%) reported symptomatic improvement. Medical cannabis has made huge strides as a therapeutic agent in various disorders like muscle spasms in multiple sclerosis and other muscle spastic disorders. The authors conclude that this observational case series may provide a backdrop to exploring prospective, double-masked studies to determine the therapeutic effect of cannabis for patients suffering from BEB.

Contributed by Dr. Aastha Takkar


Pituitary tumors are notorious to cause progressive vision loss. Compression by presence/increase in the size of pituitary tumors is often blamed upon. Definite and objective radiological predictors of visual outcome in these patients are not adequately described in literature. Another ongoing challenge in the management of pituitary tumors is the cost, availability, and reliability of the current neuro-radiological techniques to capture clinically significant as well as incremental tumor growth. This study was aimed at evaluating the various MRI-based analyses and to explore the relationship between measures of structure and function in the afferent visual pathway of patients with pituitary tumors. A critical review of literature on MRI-based structural analyses of pituitary adenomas using PubMed, Embase, Cochrane Library, and Google Scholar was performed. In addition, preoperative structural characteristics of the anterior visual pathway (optic apparatus, optic nerve compression, and optic chiasm) was examined in 18 patients from October 2010 to January 2014. A total of 443 citations were obtained from the search strategy followed. Eight of these studies met the inclusion/exclusion criteria and were retrieved for critical review. Of the 8 included studies, only 2 studies examined the relationship between MRI-based structural measurements and postoperative visual recovery. MRI analysis of chiasm elevation, severity of optic nerve compression, chiasm position, height of chiasm, tumor height, and tumor volume failed to differentiate patients with postoperative visual dysfunction vs those with visual recovery. The authors concluded that though MRI-based structural analysis is an important and a useful tool for managing patients with pituitary tumors, there are only limited objective measures that prove to be predictive of postoperative visual recovery.

Contributed by Dr. Aastha Takkar


Caffeine is an adenosine antagonist and is considered neuroprotective against development of Parkinson’s disease (PD) based on various epidemiological studies. This multicentre parallel group randomized trial studied the symptomatic effects of caffeine in Parkinson’s disease. 60 patients received caffeine and 61 received a placebo and both the groups were followed up for a period of 6 months. There was no improvement in motor parkinsonism and no change in motor signs or motor symptoms at 6 months on the Movement Disorder Society Unified Parkinson’s Disease Rating Scale (MDS UPDRS). There was a slight increase in dyskinesia and worse cognitive testing scores in the caffeine treated patients. This study suggests that drinking coffee does not provide any symptomatic benefit on motor symptoms in PD patients.

Contributed by Dr. Sahil Mehta


West syndrome is an age dependent epileptic syndrome comprising of infantile spasms, neurodevelopmental regression and hypersrrhythmia on electroencephalogram. The drugs, which can be used for control of infantile spasms include adrenocorticotropic hormone (ACTH), prednisolone andvigabatrin. The investigators in this trial randomized half of the 97 infants with untreated West syndrome to intramuscular long-acting synthetic ACTH (40 to 60 IU every other day) and half to 14 days of oral prednisolone (40 to 60 mg/day). The children were evaluated at three, six and 12 months. Control of
spasms was significantly better at 3 months for the prednisolone group. There was no significant difference at 6 and 12 months but the trend was in favour of prednisolone. The study provided evidence that high dose prednisolone may be superior to ACTH for short-term control of spasms. This is important as ACTH is quite costly compared to oral prednisolone.

**Contributed by Dr. Sahil Mehta**


Focused ultrasound ventral intermediate thalamotomy was recently approved by US Food and Drug Administration (FDA) for essential tremor. Tremor predominant Parkinson’s disease occurs in around 70-80% cases and is distinct from akinetic rigid or postural instability and gait dysfunction (PIGD) variant. Tremor in PD can be resistant to dopamine replacement therapy in quite a high proportion of cases. This two centre double blind sham controlled pilot randomized clinical trial consisted of 27 patients with medication refractory tremor predominant PD. Twenty patients were in the thalamotomy group and seven were in the sham group. The authors find significant difference in the clinical rating tremor score in the thalamotomy group compared to the sham group at 3 months. Two cases of transient hemiparesis occurred owing to heating of internal capsule. Preliminary results regarding efficacy of focused ultrasound thalamotomy for PD tremor are encouraging but further studies on a large sample size over a long-term follow-up are needed.

**Contributed by Dr. Sahil Mehta**


Adrenoleukodystrophy is an x-linked disorder caused by mutation in ABCD1 gene characterized by demyelination and neurodegeneration. Allogenic hematopoietic transplantation is the only effective therapy to halt its progression, if performed early in the disease. The authors of this open label trial enrolled 17 boys aged 4-13 years with early stage disease and gadolinium enhancement on MRI. The patients received Lenti D gene therapy, which involved infusion of autologous CD34 + cells transduced with the elivaldogene tavalentivec lentiviral vector. At a median follow up of 29.4 months, 88% patients were alive and free from major functional disability. No treatment related death or graft versus host disease occurred. The authors found that a higher National Institutes of Health Stroke Scale (NIHSS) score, a lower baseline Alberta Stroke Program Early CT score (ASPECTS) and no or poor collateral blood vessel status were associated with ASPECTS decay (from > 6 to < 6). It is prudent from this study that patients with poor collateral flow are not good candidates for being transferred to a thrombectomy capable stroke centre, where doing an intervention may be futile in such a setting.

**Contributed by Dr. Sahil Mehta**


The association between atrial fibrillation (AF) and dementia is well known. Imaging studies have shown that structural cerebral changes are common in patients with atrial fibrillation even in the presence of infarction. This retrospective registry based study of over half a million patients found lower risk of dementia in AF patients on anticoagulation compared to those without anticoagulation. Absence of oral anticoagulant treatment was an independent risk factor for dementia along with age, Parkinson’s disease, alcohol abuse and earlier stroke. Moreover, the benefit with oral anticoagulant treatment was more pronounced with early initiation of treatment. The study suggests the importance of early diagnosis and initiation of anticoagulation in patients with atrial fibrillation to preserve cognitive function.

**Contributed by Dr. Sahil Mehta**


Alzheimer’s disease (AD) is the most common dementia. AD pathology initiates years before the onset of clinical dementia. Approximately 30-50% of individuals harbour AD pathology but do not develop AD. The authors of this study compared dendritic spines in pyramidal layers II and III in 12 age-matched pathology-free controls, 8 controls with AD pathology (CAD) and 21 AD cases. Spine density was similar among controls and CAD but reduced significantly in AD cases. The authors hypothesized that dendritic spine plasticity is a mechanism of cognitive resilience that protects older individuals with AD pathology from developing clinical dementia.

**Contributed by Dr. Sahil Mehta**
Prodromal Alzheimer’s disease (AD) is defined as mild but noticeable cognitive and functional impairment. Diet is an important modifiable risk factor for dementia. Fortasyn Connect contains docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), uridine monophosphate, choline, vitamins B12, B6, C, E, folic acid, phospholipids and selenium. This 24-month randomised controlled trial studied patients with prodromal Alzheimer’s disease defined according to the International Working Group criteria. 1,311 patients were randomised to receive the active product (Fortasyn connect) or were assigned to the control group. No significant difference was found between the two groups in clinical conversion to dementia at 2 years. More clinical trials are needed to establish the role of diet in preventing or slowing the progression of prodromal AD to frank dementia.

Contributed by Dr. Sahil Mehta


In this retrospective study, the authors evaluated the occurrence of neuronal autoantibodies in elderly patients (>60 years) with no inflammatory changes on MRI and in the CSF. The study used rat brain immunohistochemistry and cell based assay on HEK-293 cell. The antibodies tested were against LGI1, CASPR2, IgLON5, DPPX, mGlur5, NMDAR, AMPAR, GABAb receptor, or GABAa receptor. Among the 155 patients above 60 years of age with neurologic syndromes related to antibodies against neuronal surface antigens, 35 (22.6%) did not have any MRI or CSF evidence of inflammation. The most common antibody detected was LGI1, while the antibody most frequently associated with the development of a clinical syndrome without evidence of CNS inflammation was IgLON5 (95%). Being a retrospective study, it was detected that all the recruited patient had shown improvement to empirical immunotherapy. The IgLON5 antibody associated clinical phenotype was characterized by bulbar symptoms, gait instability and sleep disturbance including insomnia, rapid eye movement (REM) sleep stage behavioral disorder (RBD), and sleep apnea. The non-inflammatory profiles of autoimmune CNS syndromes were more frequent in younger patients compared to the elderly (25% vs 3%) ones.

This paper disproves the ‘essentiality’ of two components of the clinical criteria for making a diagnosis of CNS autoimmune syndrome: the CSF pleocytosis and MRI signal changes. The insidious onset and slow progressive nature of the clinical phenotype of IgLON2 defy the other component of the criteria (subacute onset and rapid progression of symptoms). This report underlines the importance of making independent and prospective validation of clinical criteria from multiple population subsets. Also, as most of the clinical criteria are derived from retrospective data sets of a few central laboratories, with the phenotype defined based on what is already recorded (rather than prospectively verified), the risk of bias in the resultant conclusions is very high. This paper validates this general rule.

Contributed by Dr. Srijithesh PR


The authors report a systematic review of population-based cross-sectional and prospective studies evaluating the association of sleep-disordered breathing (SDB) and cognitive decline in elderly persons. Studies with at least 200 participants with a mean participant age of 40 years or older were included. Fourteen studies with 6 prospective studies covering 4,288,419 patients were included. Two studies with a combined population sample of 208,483 patients used clinical diagnosis alone, while other studies estimated the apnea-hypopnea index. The studies had significant heterogeneity. Within this limitation, the meta-analysis indicated that patients with SDB were 26% more likely to develop cognitive impairment (risk ratio, 1.29; 95% confidence interval, 1.05-1.5). The cross-sectional studies indicated that patients with SDB had slightly worse executive function, although global cognition and memory were not affected. The study indicates that SDB may be a modifiable risk factor for cognitive impairment in elderly patients. However, its clinical relevance with respect to actual effect modification has to be evaluated in control trials.

Contributed by Dr. Srijithesh PR


This paper is a retrospective analysis of the ‘Finding atrial fibrillation in stroke - randomised evaluation of enhanced and prolonged Holter-ECG (Find-AF)’ trial, that evaluated the role of 7-day Holter ECG monitoring versus standard-of-care procedures for detection of atrial fibrillation/atrial flutter (AF) in stroke patients aged 60 years and above. In the present report the significance of supraventricular tachycardia lasting <30 sec was examined over a follow-up period of 3 years. The study also examined whether or not the paroxysmal atrial fibrillation detected after cerebral ischemia is a temporal or a persisting phenomenon. Of the 280 patients enrolled in the Find-AF trial, 254 patients were included for the analysis. Four groups of patients were identified: patients with AF detected at admission AF-adm group, the paroxysmal AF group (pAF), the supraventricular run group (SV run group), and the control group with no AF detected. After a mean 3.7 years of follow-up, recurrent stroke occurred in 15.4% of all patients: 29% in the AF-adm group, 12.5% in the pAF group, 20.1% in the SV run group, and 8.8% in the control group. Six of 8 patients with pAF had evidence of ongoing AF on follow-up.

The study shows that pAF and SV-run groups have a higher risk of recurrent strokes than the control group. However, the question on whether or not the latter group needs oral anticoagulation to prevent recurrent strokes can only be
that although the progression free survival was better in the combination group, there was no survival advantage of the combination over monotherapy with lomustine.

Contributed by Dr. Anant Mehrotra


Medical records of 750 patients of newly diagnosed glioma, 44 cases of vestibular schwannoma, 271 cases of meningioma, 102 cases of nonlesional epilepsy and 682 healthy controls from 3 hospitals were retrospectively collected and analysed. Values of preoperative inflammatory markers, including neutrophil/lymphocyte ratio (NLR), derived NLR (dNLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), and prognostic nutritional index (PNI) were noted. Compared with healthy controls and patients with vestibular schwannoma, meningioma, or nonlesional epilepsy, the patients with glioma had higher values of preoperative NLR and dNLR as well as lower values of LMR and PNI, whereas PLR was higher in glioma patients than in healthy controls and in patients with nonlesional epilepsy. There was a positive correlation between NLR, dNLR, PLR, and tumor grade but a negative correlation between LMR, PNI, and tumor grade in patients of glioma. The combination of NLR + LMR and dNLR + LMR had the best diagnostic performance. NLR, dNLR, PLR, LMR and PNI had a significant predictive value for diagnosing a glioblastoma when compared with the healthy group and other diseases. The authors concluded that the combination of NLR along with LMR is a noninvasive marker with a high sensitivity and specificity for the diagnosis of glioma.

Contributed by Dr. Anant Mehrotra


Twenty five consecutive patients, in whom operculoinsular cortectomy was undertaken as the form of epilepsy surgery with a minimum of 1 year follow up, were included in the study. Cases of vascular malformations and tumor were excluded from the study. The mean age at surgery was 35 years. The mean duration of symptoms was 19 years with the majority being female patients; and, the mean follow up was 4.7 years. In 72% of cases, the MRI of the operculoinsular region was either normal or had nonspecific findings. Dominant side surgery was performed in 7 patients; and, an opercular resection was performed in all cases except in 2 cases where only insular resection was performed. Engel class I seizure control was achieved in 80% of patients. Postoperative neurological deficits (paresis, dysphasia, alteration of taste, smell, hearing, pain, and thermal perceptions) were frequent (75%) but always transient, except in a patient in whom mild alteration of thermal and pain perception persisted. The authors concluded that the surgical treatment of operculoinsular epilepsy is effective in seizure control with an acceptable long-term complication rate.

The authors conducted a retrospective study of 161 patients of aneurysmal subarachnoid haemorrhage (aSAH). The patients were divided into two groups, namely, patients who underwent stent-assisted coiling or placement of flow diverters requiring dual antiplatelet therapy (DAPT; the DAPT group), and patients who underwent coiling only without DAPT (the control group). There were 85 patients in the DAPT group and 76 patients in the control group. The risk of clinical vasospasm was significantly lower in the DAPT group as compared to the control group. Haemorrhagic complications associated with placement of external ventricular drain or ventriculo-peritoneal shunt were similar in both the groups.

Contributed by Dr. Anant Mehrotra


The authors conducted a retrospective analysis on 9523 resected brain specimens from patients who underwent surgery for drug resistant epilepsy in 36 centres from 12 European countries over a 25 year period. In 75.9% of the cases, the onset of seizure was before the age of 18 years, and 72.5% of patients underwent surgery as adults. 20.1 years and 5.3 years was the mean duration of epilepsy before surgery was undertaken in adults and children, respectively. In 71.9% of surgeries, the temporal lobe was involved. Hippocampal sclerosis was the most common histopathological diagnosis (36.4%), followed by tumours (mainly gangliogioma; 23.6%) and malformations of cortical development (19.8%). No histopathological diagnosis could be established in 7.7% of cases. The authors concluded that in patients who underwent surgery for drug resistant epilepsy, hippocampal sclerosis was the most common histopathological diagnosis in adults, and focal cortical dysplasia was the most common histopathological diagnosis in children.

Contributed by Dr. Anant Mehrotra


This interesting study provides a mathematical algorithm and a scoring system to estimate the risk of rapid tumor growth in small, asymptomatic meningiomas. Such a scoring system is intended to help in treatment decision making between some form of upfront treatment versus a conservative approach of wait and watch. The authors analyzed 232 patients with a radiologically suspected intracranial meningioma who had been offered conservative treatment with serial radiographic follow-ups between 1997 and 2013. They defined rapid tumor growth as increase in tumor volume ≥2 cm³/year which was observed in 25.4% of their patients (n = 59). Applying a logistic regression model, the authors found out that the tumor size (odds ratio [OR] per cm³ 1.07, P = 0.000), absence of calcification (OR 3.87, P = 0.004), peritumoral edema (OR 2.74, P = 0.025), and hyperintense or isointense signal on T2-weighted MRI (OR 3.76, P = 0.049) were predictors of tumor growth rate. Each of these four MRI parameters were given scores and then the sum scores were calculated for each patient. The risk of rapid tumor growth was estimated to be <10% when the total score was 0–2, 10%–50% when the total score was 3–6, and ≥50% when the total score was 7–11. The area under the receiver operating characteristic curve was 0.86 indicating a high positive predictive value of this scoring system.

Contributed by Dr. Kuntal Kanti Das


It has been long known that recurrent seizures lead to severe neurocognitive disturbances in the affected patients. Thus, irrespective of the site of origin of the seizures, the neocortical structures seem to get affected in these patients suggesting a role of disturbed circuitry. In this prospective case-control study, the author intended to analyze, using functional MRI studies, the abnormal connection between subcortical structures like the ascending reticular activating system (ARAS) and several neocortical areas in patients with intractable epilepsy of temporal lobe origin. The authors noted that the connectivity between ARAS and other cortical/subcortical structures in the controls (n = 27) was highest for limbic system, thalamus and certain other neocortical regions. The ARAS connectivity was, however, significantly lower in patients with TLE than in controls (P < 0.05, paired t-test), particularly to the neocortical regions like insular, lateral frontal, posterior temporal and opercular cortex. When these connectivities were correlated with disease and neuropsychological parameters, poor connectivity correlated with an increased frequency of consciousness-impairing seizures (P < 0.01, Pearson’s correlation) and impairments in neuropsychological scores (P < 0.05) respectively. Therefore, this study objectively proves the role of disturbed circuitry between brainstem structures and certain neocortical/subcortical areas as the possible underlying reason of neurocognitive decline in patients with recurrent temporal lobe epilepsy.

Contributed by Dr. Kuntal Kanti Das


As clinicians, we always tend to prefer fresh blood transfusion over transfusion of relatively old and stored blood. However, such an understanding has not been evaluated and substantiated by prospective randomized trials. This international,
multicenter, randomized, double-blind study, focusing on the critically ill patients, attempted to clarify this clinically relevant issue. For this purpose, 4919 patients were studied over 4 years after randomizing them into two groups. The group ($n=2457$) which received relatively fresh blood transfusion (mean storage duration 11.8 days) and the long term storage group ($n=2462$, mean storage time 22.4 days) were compared with respect to the primary outcome measure of 90-day mortality. On analysis, it was found that the primary outcome was reached in 24.8% ($n=610$) patients in the short storage group compared to 24.1% in the long term storage group. This difference was not statistically significant (95% confidence interval [CI], $-1.7$ to $3.1$; $P=0.57$). The significance level remained unchanged even after 180 days (95% CI, $-2.1$ to $3.0$; $P=0.75$). Thus, as of now, this trial puts an end to this common clinical dilemma and convincingly clarifies that the age of the transfused blood is not an important factor in determining outcome in critically ill patients and there is no need for any concern on the part of the clinicians.

Contributed by Dr. Kuntal Kanti Das

Zorrilla-Vaca A A, et al. Comparison of regional versus general anesthesia for lumbar spine surgery:


This meta-analysis intended to provide some data on the feasibility of regional anesthesia (RA) in lumbar spine surgery compared to the commonly used practice of general anesthesia (GA). The study specifically enquired into the intraoperative events, incidence of postoperative complications, and recovery time of patients between these two modalities of anesthesia. The authors identified 15 randomized clinical trials comprising 961 patients dealing with this subject and available on major databases. They noted that the use of RA for lumbar spine surgery was significantly associated with lower incidence of postoperative nausea and vomiting at 24 hours (OR = 0.42; 95% confidence interval [CI] = 0.23-0.77, $P=0.005$), as well as lower length of stay (standardized mean difference [SMD]=−0.73; 95% CI=−1.17 to −0.29, $P=0.001$) and intraoperative blood loss (SMD=−1.24; 95% CI=−2.27 to −0.21, $P=0.02$). However, the pain scores, incidence of urinary retention or analgesic requirement were not significantly different between the two groups. Thus, RA seems to be a reasonable alternative to GA in these patients, particularly in patients deemed to be at high risk from a medical point of view.

Contributed by Dr. Kuntal Kanti Das