IANCON 2018: 26th Annual National Conference of Indian Academy of Neurology

SEPTEMBER 27-30 | PANDIT DEENDAYAL UPADHYAY AUDITORIUM, SCIENCE COLLEGE CAMPUS, RAIPUR

REHABILITATION OF READING AND WRITING DEFICITS AFTER BRAIN DAMAGE

Dr Gopee Krishnan, Manipal

In the years to come, with rising literacy and technological proliferation, the clients' ability to read/write has the potential to become a major outcome measure in clinical practice of Neurology. The neurological typing of reading/writing deficits (following brain damage) is valuable in lesion localization. The cognitive (neuropsychological) models, though weak in lesion localization (despite the rigorous neuroimaging efforts), provide valuable insights on the treatment direction in these deficits. Such model-driven approaches to rehabilitation can predict the outcomes of the intervention program, and testify the models themselves, which in turn advances our understanding of the complex cognitive processes such as reading.

BREAKING BAD NEWS

Dr Roop Gursahani, Mumbai

- Communication skills are learnable and Neurologists need these skills in various situations - Delivering the diagnosis of an 'incurable' or life-limiting neurologic illness; Serious illness communication: when an existing low level neuroinflammation (LLNI) enters an advanced phase.
- Shared decision making is important in catastrophic brain injury.
- Bad news can be delivered using simple protocols (e.g., SPIKES) for organizing these conversations.

BLOCKS, INJECTIONS AND NEUROMODULATION IN REFRACTORY MIGRAINE

Dr Alok Tyagi, UK

Onabotulinum toxin A is the standard of care for chronic migraine. Although nerve-blocks are used extensively in migraine and with good effect, there is a lack of evidence-base.

Noninvasive neuromodulation is an option in migraine management. Calcitonin gene-related peptide (CGRP), a 37-amino acid neuropeptide derived from the gene encoding calcitonin exists in 2 forms in humans, and alpha-CGRP is the predominant form. In the periphery, CGRP mediates vasodilatation and centrally it mediates the transmission of pain and is also involved in regulatory mechanisms. It acts on the second order neurons in the trigemino-cervical complex.

Erenumab is the first licensed anti-CGRP monoclonal antibody for migraine prophylaxis. It is indicated for adults who have at least 4 migraine days a month. Erenumab shows efficacy in different conditions, including episodic and chronic migraines, and difficult to treat subpopulations.

FIRST AMONG EQUALS: ART OF CHOOSING THE FIRST ADD-ON IN EPILEPSY

Dr Param S Kharbanda, Chandigarh

Factors that underline the search for add-on anti-epileptic drugs (AEDs): Suboptimal efficacy and side effect profile. Many AEDs can be used as add-ons. Currently, levetiracetam, clobazam, lamotrigine, valproic acid tick most required boxes. Different groups suitable for combination are sodium channel blockers, calcium channel blockers, GABA-ergic drugs, synaptic vesicle protein 2A modulation, and carbonic anhydrase inhibitor.

Inert AEDs make better combo choices. While switching monotherapies or adding on, current AED should be held constant and new AED should be titrated gradually. If there are significant adverse effects, baseline AED must be decreased simultaneously. Multiple 2 drug combinations must be tried before adding on a third drug.

EXTENT OF CEREBRAL VENOUS THROMBOSIS ON MRV: CORRELATION WITH CLINICAL AND MRI FINDINGS

Dr VK Singh, Dr J Kalita, Dr UK Misra, Lucknow

Cerebral venous sinus thrombosis (CVST) has been reported to be a rare cause of stroke and accounts for

0.5-1% of all strokes. The clinical severity, magnetic resonance imaging (MRI) changes and outcome may be related to the extent of occlusion of venous sinuses. Papilledema is frequently encountered among patients with superficial venous system involvement and higher CVST score on magnetic resonance venography (MRV). Higher CVST score is not related to clinical severity, rapidity of symptoms and outcome. Parenchymal involvement is associated with risk of frequent seizure, focal deficit and low GCS.

VALIDATION OF BATMAN SCORE IN POSTERIOR CIRCULATION STROKE: A STUDY FROM TERTIARY CARE HOSPITAL

Dr Suresh I, Dr Muralidhar Reddy Y, Dr Subhendu Parida, Dr Shyam K Jaiswal, Dr Santosh Kumar B, Dr Lalitha P, Dr Syed Osman, Dr Murthy JMK, Telangana

Posterior circulation stroke accounts for 20-25% of all ischemic strokes. Basilar artery occlusion is associated with high morbidity and mortality rates. A link has been seen between presence of good collaterals and a significant favorable outcome in posterior circulation strokes. Basilar Artery on Computed Tomography Angiography (BATMAN) score is a novel scoring system proposed in the year 2017. It is a semi-quantitative CT angiogram based grading system to quantify the extent of basilar artery occlusion as well as the presence of collateral circulation from posterior communicating arteries. BATMAN score may be considered a useful prognostic marker of outcome in posterior circulation strokes. Subjects with BATMAN score <7 have poor outcome at 3 months.

NIPAH VIRUS ENCEPHALITIS

Dr Jayakrishnan Chellenton, Kerala

This is a highly lethal paramyxovirus infection. Mortality rates range from 70% to 80%. Its natural reservoir is large old world fruit bat. It is transmitted by coming in contact with the bat saliva, urine and stool. Human-to-human transmission can occur by droplet infection and close contact with the bodily fluids of the infected patients (respiratory secretion, urine, vomitus, blood, stool). Incubation period is 7-21 days. Symptoms include fever, headache, bodyache, vomiting and tiredness. Encephalitis is characterized by rapid onset altered sensorium and coma. Odd neurological findings like autonomic dysfunction (tachycardia, hypertensive response), profuse sweating, early brainstem dysfunction, segmental myoclonus, generalized areflexia, loss of vestibulo-ocular reflex (VOR) and ptosis are seen. Acute respiratory distress syndrome (ARDS) and myocarditis are usual in the course of illness. Laboratory investigations may show thrombocytopenia, elevated transaminases, elevated cardiac enzymes and hypoxemia. Cerebrospinal fluid examination may show elevated protein and leukocytic pleocytosis. MRI may show small discrete FLAIR hyperintensities in the neuroparenchyma. Confirmation can be made by real-time rtRNA-PCR, from serum, urine and throat swab. Virus isolation can be done only in NIV (BSL 4 lab) Pune. There are no specific antiviral medications; some trials have been done with ribavirin. Patient isolation and strict personal protection measures need to be implemented. Proper disposal and decontamination of all the bodily fluids and the fomites of the patient is a must to prevent the spread of infection. Dead patients should be cremated with utmost care, as they can be the source of infection. The disease comes under notifiable diseases (State and Central Government and WHO). Post-exposure prophylaxis trials with anti-Hendra monoclonal antibody are present (on humanitarian basis in Australia). This monoclonal antibody is not available in India.

PROTECTING BRAINS THROUGH STROKE PREVENTION STRATEGIES IN INDIA

Dr Yogeshwar Kalkonde, Maharashtra

Stroke is the fifth leading cause of disability-adjusted life years (DALYs) lost in India. In 2015, there were 7,00,000 stroke deaths in India with 55% of these occurring prematurely between 30 and 69 years of age. About 70% of stroke deaths occur in rural areas of India where access to healthcare for stroke is limited. Ten modifiable risk factors contribute to 90% risk of stroke. Two approaches - high risk and population-level - are proposed to reduce the risk of stroke. High risk approach targets people with- a) risk factors, e.g., hypertension, sedentary lifestyle, dyslipidemia, to reduce the risk of stroke; or b) higher overall cardiovascular risk determined using risk scores. Population-level preventive approaches target the entire population, e.g., reducing salt in packaged foods, promoting active transport, use of mass/social media to increase awareness, etc. Both approaches will be needed in India.

Hypertension is the most important risk factor for stroke and hypertension control is the most proven strategy to reduce strokes. Health system strengthening to improve preventive measures will be needed in addition to improved acute stroke care to prevent strokes in India.

THE HOW AND WHY OF REFRACTORY MIGRAINE

Dr K Ravishankar, Mumbai

- There is no accepted/established definition for refractory migraine yet. A consistent nomenclature is essential. There could be a possible genetic basis, structural explanation, systems functional explanation or pharmacological explanation for refractory migraine. European Headache Federation proposed criteria for refractory chronic migraine: a) ICHD-III β chronic migraine - with no medication overuse; b) Prophylactic migraine medications in adequate dosages for at least 3 months; c) Contraindications or no effect of the following preventive medication with at least 3 drugs from the following classes: β blockers; anticonvulsants; tricyclics and others.
- Risk factors for migraine progression - *Nonmodifiable*: Female gender, age, low socioeconomic status, head trauma. *Modifiable*: Attack frequency, obesity, medication overuse, caffeine overuse, stressful life events, snoring/sleep apnea.
- Missed exacerbating factors - Risk factors for migraine progression; comorbid illness (psychiatric); medication overuse (MOH); modifiable risk factors (dietary or lifestyle factors, occupational or environmental factors, hormonal influence).
- Wrong diagnosis - Migraine may be missed or misdiagnosed - no thorough history, atypical presentations, not assessing disability levels; presence of secondary headache that mimics primary and wrong investigations.
- **Nonpharmacological treatment -** *Behavioral treatments*: Relaxation training, hypnotherapy, thermal biofeedback training, electromyographic biofeedback therapy, cognitive/behavioral management therapy. *Physical treatments*: Acupuncture, transcutaneous electrical nerve stimulation, occlusal adjustment, cervical manipulation, lifestyle changes, patient education. **Risk factor modification -** Attack frequency: prevention with pharmacologic and behavioral interventions; obesity: weight loss, exercise, behavioral intervention; stress: stress management with biobehavioral techniques, exercise; snoring: diagnose and treat sleep apnea, weight loss; allodynia: manage attack frequency and treat early; depression and anxiety: assess, treat with pharmacologic and behavioral therapies, refer when appropriate; acute drug overuse: limit acute drug use <3 days/week and be selective about which acute drugs are used; caffeine: stop.

PREVENTION OF DEMENTIA

Dr Suvarna Alladi, Bengaluru

Risk factors for Alzheimer's disease (AD): Age; genetic factors; low education; low socioeconomic status; cardiovascular risk factors; sedentary life; malnutrition; head trauma; psychological stress; pollution. Age is the most important risk factor. Vascular risk factors facilitate neuroinflammation in AD. Epigenetics plays a key role in the relationship between inflammation, life course and dementia. EWAS association studies have made it clear that epigenetic changes in response to environmental conditions like stress and pollution complement genetic mutations and contribute to the development and progression of chronic inflammation in AD. Reversible causes, especially neuroinfections and vitamin B_{12} deficiency, seem to account for 18% of all dementias. Low educational levels increase the risk of dementia. Clinical, epidemiological studies have shown protective effect of education against dementia. Education enhances cognition, brain structure and connectivity. Folic acid intake, low saturated fat consumption, high fruit and vegetable consumption, and Mediterranean diet have been associated with low risk of AD. Diet and physical exercise are being recognized as epigenetic modulators of brain plasticity and cognition. People with more companionship seem to have reduced risk of dementia and stroke. Greater emotional support is associated with reduced dementia and risk. People reporting higher levels of purpose in life exhibit better cognitive function despite brain AD pathology burden of the disease. There is a huge opportunity for prevention of dementia. This means enhancing protective factors in early, mid and later life.

UNRAVELING MRI-NEGATIVE EPILEPSIES

Dr Jayanti Mani, Mumbai

- **Why is the lesion so important?** Finding the lesion on MRI is key for successful epilepsy surgery. However, 20-40% of patients have no lesion on MRI. Localization of epileptogenic zone is difficult in MRI-negative cases. There is 2.5 times lower chance of successful surgery in MRI-negative cases. Defining the limits of the epileptogenic zone is more difficult. There is greater risk of postoperative functional deficits due to poor delineation of eloquent cortex from the epileptogenic zone.
- Magnetoencephalography (MEG): MEG measures the magnetic field generated by synchronized postsynaptic currents in cortical pyramidal cell dendrites. Current dipole maps of interictal

spikes are overlaid onto an MRI scan. Spatial and temporal resolution of MEG is superior to scalp electroencephalography (EEG) but limited to dipoles on the cortical surface and less sensitive to deeper sources.

- Magnetic source imaging (MSI) and positron emission tomography (PET): The presence of a single focal abnormality, either on MEG or PET, is associated with a good surgical outcome. However, the spatial congruence between the volume of PET or MEG abnormalities, and that of the seizure onset zone (SOZ), is far from perfect in many patients. Overall, the diagnostic accuracy of these investigations often remains insufficient to guide surgical decision without prior intracranial EEG in patients with MRI-negative epilepsy. Conversely, both investigations appear useful to guide the placement of depth or subdural electrodes, and help promote an optimal sampling of the SOZ by these electrodes.
- MSI and PET combination - Knowlton et al evaluated localizing value of association of MSI and [^{18}F]-FDG-PET in 51 patients with MRI-negative epilepsy who had achieved seizure freedom after epilepsy surgery - only 25% patients had localized abnormalities on both MSI and [^{18}F]-FDG-PET; but it was highly specific: 95% specificity for MSI + PET in comparison with 79% for MSI or PET alone.
- In MRI-negative cases, one has to rely on various functional studies. None of these are individually robust to make conclusions on epileptogenic localization. So, compare, analyze and synthesize data from multiple modalities. Integrating this information in patients' cerebral anatomy will help plan a surgical strategy. This integration mandates coregistration of these functional modalities into a common physical coordinate system.

EXPLORATORY NEUROGENETICS

Dr Mohammed Faruq, New Delhi

- Next generation sequencing has revolutionized the current field of neurogenetics and neurogenomics. It is now possible to make disease gene discovery using single patient and/or a family. In our country, we require a systematic clinical and genetic approach to decipher a variety of adult onset neurogenetic diseases, such as Parkinson disease, amyotrophic lateral sclerosis (ALS), spinocerebellar ataxias and limb-girdle muscular dystrophy (LGMD). The compendium of mutations of our population also requires a deeper exploration and systematic reporting for making genetic diagnosis feasible and cost-effective. Thousands of patients with various neurogenetic ailments have to undergo multiple rounds of hospital visits to get correct diagnosis and the time taken is so much that in the lifetime of several patients, the disease goes undetected.
- At the Council of Scientific and Industrial Research (CSIR) - Institute of Genomics and Integrative Biology (IGIB), researchers have earlier demonstrated experience in hereditary ataxia genetics in collaboration with AIIMS and other major tertiary centers. Researchers could identify genetic causality in 50% of patients who were confirmed to carry pathogenic genetic defect in one of the several genes linked to ataxias. Researchers have reported clinical and genetic account of one of the rare but unique spinocerebellar ataxia (SCA) subtype in India, SCA12 (Srivastava et al. Brain. 2015). Researchers have identified cases of Fragile X-associated tremor/ataxia syndrome (FXTAS) among the group of patients who clinically behaved as SCA12 but were negative for SCA12 mutations. Currently, to make genetic diagnosis accessible, the lab is committed to offer genetic diagnosis of various neurogenetic ailments, e.g., Huntington's disease, cerebellar ataxias, ALS, Alzheimer's, neuropathies, dystonia, etc. For details please visit, http://gomed.igib.in.

HIV NEUROLOGY: INDIAN PERSPECTIVES (OUR JOURNEY OVER THREE DECADES)

Dr P Satish Chandra, Bengaluru

- The number of people living with HIV (PLHIV) in India was estimated to be 21.17 lakhs in 2015 vs. 22.26 lakhs in 2007 (NACO report, 2016).
- There were 80,000 new infections in 2016; a decline of around 66% has been noted in infections from 2000 and 32% from 2007.
- Nervous system manifestations of HIV infections - Primary HIV virus involvement: AIDS dementia, primary HIV infection, vacuolar myelopathy, chronic sensory neuropathy; Latent phase CD4 count 200-500: Myelitis, acute inflammatory demyelinating polyneuropathy (AIDP), chronic inflammatory demyelinating polyneuropathy (CIDP), muscle disorders; Advanced phase CD4 count <200: Opportunistic infections, malignancy, lymphoma, plasmacytoma, Kaposi sarcoma, progressive multifocal leukoencephalopathy (PML),

metabolic; Due to antiretroviral therapy (ART): Peripheral neuropathy, myopathy.

- Opportunistic infections of nervous system associated with HIV/AIDS - Virus: Cytomegalovirus, herpes simplex virus, varicella-zoster virus, JC virus; Bacteria: *Mycobacterium tuberculosis*, atypical mycobacteria, *Bartonella, Nocardia*; Fungi: Cryptococci, Coccidioidomycosis, Histoplasmosis, Blastomycosis, Aspergillosis, *Candida albicans*, Mucormycosis, Sporotrichosis; Parasites: CNS Toxoplasmosis, *Acanthamoeba*, *Trypanosoma*, *Strongyloides stercoralis*, Cysticercosis. There has been an upsurge in TB due to HIV infection.
- India has been declared as 'hotzone' for MDR TB. New-onset seizures are frequent manifestations among HIV seropositive patients. Common causes include mass lesions, meningitis, and HIV encephalopathy. Long-term AEDs should be given, even for single seizure among HIV seropositive patients.
- According to a 2005 study in 500 HIV seropositive patients with neurological manifestations, seizures were noted in 99 patients, and were absent in 401 patients. About one-fifth of HIV-infected drug naïve patients with neurological disorders had new-onset acute symptomatic seizures, mainly secondary to opportunistic neuroinfections. Of the 99 HIV-infected patients with new-onset acute symptomatic seizures, 20 patients (4.0%) presented with seizure as the initial manifestation.
- In a retrospective study conducted at National Institute of Mental Health and Neurosciences (NIMHANS), 335 HIV-seropositive patients with cryptococcal meningitis were analyzed. Overall, 96% of the patients had headache as their predominant clinical manifestation. Headache was associated with fever in 79% of the patients.
- Toxoplasmosis and seizures - According to study conducted at NIMHANS, 35% patients presented with seizures as the initial manifestation. In all, 22 patients had seizure as their initial manifestation of cerebral toxoplasmosis.
- Gupta et al used standardized neuropsychological tests to assess cognitive functioning in a sample of 119 adults infected with Clade C HIV-1 who were not on antiretroviral medications. Among the seropositive subjects, 60.5% had mild-to-moderate cognitive deficits. None of the subjects had severe cognitive deficits.
- The Frascati criteria is more sensitive to neurological progression in highly active antiretroviral therapy (HAART) experienced HIV-infected individuals. The progression of HIV-dementia is variable. Few patients remain cognitively stable till death. Those with CD4 counts <100 tend to progress more quickly. Neuropsychological features of HIV-dementia reflect the predominance of subcortical involvement. Incidence of peripheral neuropathy is less common with HIV-1 Clade C unlike the West (Clade B).
- Demyelination is more prominent than axonal pathology in asymptomatic cases. Cytomegalovirus remaining latent in nerve may be the forerunner for development of symptomatic peripheral neuropathy.
- Special features of Neuro AIDS in India: In spite of heavy burden of HIV/AIDS - HIV-associated neoplasia are infrequent, including primary lymphoma; HIV-associated dementia and HIV encephalitis are less common; spinal pathology including vacuolar myelopathy is rare; Kaposi sarcoma has not been reported. There seems to be a low prevalence of PML in India and Africa.

IN CONVERSATION WITH DR BHUPENDRA CHAUDHARY

Dr Bhupendra Chaudhary, Meerut, UP

What are the current therapeutic options and unmet medical need in epilepsy?

The following AEDs have been approved by the US Food and Drug Administration (FDA): Carbamazepine, clonazepam, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, topiramate, valproate, vigabatrin and zonisamide. About 60% of people living with epilepsy have partial-onset seizures and one-third remain uncontrolled, despite trying treatment with a range of AEDs.

What is the mechanism of action of lacosamide compared to other AEDs?

Lacosamide enhances slow inactivation phase of sodium channels without affecting fast inactivation. It acts in the following ways:

- By enhancing the number of sodium channels entering the slow inactivation, it reduces the long-term availability of sodium channels for activation.
- Targets activity occurring during sustained high-frequency neuronal firing or prolonged

depolarization, as seen in epilepsy. It does not affect activity mediated by fast inactivation.

- Since slow inactivation of sodium channels is an endogenous mechanism by which neurons reduce ectopic hyperactivity, this modulation represents an effective mechanism to selectively reduce pathophysiological hyperactivity, while leaving physiological activity intact.

Lacosamide has a dual mode of action and both mechanisms are unique and not shared by any other AED.

What is the efficacy of lacosamide for the seizure or the epilepsy syndrome?

Lacosamide has shown greater reduction in seizure frequency. It has an early-onset of action. It has shown effectiveness with the broadest range of AEDs, including second- and first-generation agents. In studies it is seen that lacosamide provides more seizure free days along with long-term retention rate.

What are the benefits of lacosamide over other antiepileptics?

Sodium channel inhibition by lacosamide was compared to other anticonvulsants in neuroblastoma cells. Lacosamide exhibited far better enhancement of slow inactivation compared to other AEDs.

What is known about the tolerability of lacosamide?

A pooled tolerability data of 3 clinical studies (n = 1,308 patients) suggests that it is a well-tolerated molecule in patients with partial-onset seizures. The overall incidences of treatment-emergent adverse events occurring during the treatment phase (titration plus maintenance) were 65% in placebo recipients and 70% and 82% in recipients of the recommended dosages of lacosamide 200 and 400 mg/day. The most common treatment-emergent adverse events included dizziness, headache, nausea and diplopia. Overall, the incidence of nervous system (especially dizziness) and gastrointestinal adverse events were dose related. Lacosamide does not have tendency to prolong the QT/QTc interval or QRS duration.

What is known about the safety of lacosamide?

As observed, lacosamide has low rate of somnolence comparable to placebo. There is low rate of cognitive impairment and behavioral abnormalities similar to placebo. The incidence of rash and edema is low, similar to placebo. It has weight-neutral results. The small increase in mean PR interval is not of clinical significance.

CURRENT DIAGNOSIS AND TREATMENT OF VERTIGO AND DIZZINESS

Dr Michael Strupp, Munich, Germany

- Vertigo and dizziness are among the most frequent symptoms with an annual incidence of 11%. The keys to the diagnosis are: Systematic patient history with four key questions: time course, type, modulating factors, accompanying symptoms and combined clinical examination of the - Vestibular system with four aspects: nystagmus, head impulse test, positioning maneuvers, Romberg test with the eyes open and closed and Ocular motor system to differentiate peripheral from central vertigo with five clinical signs: skews deviation, central fixation nystagmus, gaze-evoked nystagmus, normal head-impulse test, patient not able to stand unaided.
- The most frequent forms are benign paroxysmal positional vertigo (BPPV), functional dizziness, central vertigo, in particular cerebellar dizziness, vestibular migraine, Menière's disease, acute unilateral vestibulopathy (vestibular neuritis) and bilateral vestibulopathy.
- Depending on the specific diagnosis, the treatment is based on physiotherapy, pharmacotherapy, psychotherapy and rarely surgery.
- Treatment of - *BPPV:* liberatory maneuvers; *Functional dizziness*: psychoeducational therapy and selective serotonin reuptake inhibitor; *Vestibular migraine*: prophylactic treatment with a β-blocker; *Menière's disease*: titrate the attacks with betahistine; *Acute unilateral vestibulopathy*: betahistine, steroids, physiotherapy; *Bilateral vestibulopathy*: balance training.

A DIALOGUE WITH DR SUBHASH KAUL

Dr Subhash Kaul, Hyderabad

What are conventional and newer anticoagulants?

Oral anticoagulants block the coagulation cascade either by an indirect mechanism (e.g., vitamin K antagonists [VKAs]) or by a direct one (e.g., the novel oral anticoagulants [NOACs]). VKAs are widely used as treatment of venous thromboembolism and for stroke prevention in patients with atrial fibrillation (AF). Although low-molecular-weight heparin remains the first-line in venous thromboembolism prophylaxis, more recently, the NOACs such as dabigatran, rivaroxaban and apixaban were approved for stroke prevention in patients with AF after showing at least noninferiority to warfarin in RE-LY, ROCKET-AF and ARISTOTLE

trials, with dabigatran (110 or 150 mg twice-daily), rivaroxaban (20 or 15 mg once-daily) and apixaban (5 mg twice-daily), respectively. While awaiting long-term safety data, the choice among all these available therapies should be based on patient preferences, compliance and ease of administration, as well as on local factors affecting cost-effectiveness.[1]

What are the concerns and benefits associated with anticoagulant therapy?

Anticoagulants are the cornerstone of stroke prophylaxis in patients with AF, a condition that disproportionately affects individuals as they age. Since, older age is a risk factor for bleeding as well as thrombosis, weighing the risks and benefits of anticoagulants—which increase bleeding risk—is essential.[2] NOACs have emerged as alternatives to VKAs, but are "underused" in the elderly because of concerns about high frequency of renal failure, low body mass index and body composition of muscle and fatty tissue in the elderly. Comorbidities and polypharmacy, often present in the elderly, are additional factors that raise these concerns.[3] Downside to the use of NOACs is the lack of a quick reversal agent, except idarucizumab, which is approved for reversal of dabigatran's anticoagulant effects. Take-home message is that the NOACs are preferred and effective in patients without renal failure.

Can oral anticoagulants be used in patients on dialysis?

AF facilitates the development or progression of chronic kidney disease (CKD), and the prevalence and incidence of AF increases with decreasing renal function. Patients with AF and CKD have increased morbidity and mortality due to excessive risk for both thromboembolic and severe bleeding events. The efficacy and safety of NOACs in patients with end-stage renal dysfunction and on dialysis is unclear. The routine use of NOACs in patient with severe renal dysfunction (CrCl <15 mL/min) as well as in patients on dialysis is best avoided. Additionally, there is lack of evidence for VKA in this patient population. Thus, the decision to anticoagulate should be individualized based on a multidisciplinary approach considering patients' preferences.[4]

Can dabigatran be used in patients with hepatic impairment?

No change in dabigatran exposure is reported in patients with moderate hepatic insufficiency. However, the use of dabigatran is not studied in patients with severe hepatic impairment.

When switching from VKA to NOAC, what should be considered?

When switching between different anticoagulant therapies, it is important to ensure the continuation of anticoagulant therapy while minimizing the risk for bleeding. Switching from VKA to NOAC can be done immediately once the INR is ≤2.0. If the INR is 2.0-2.5, NOACs can be started immediately or (better) the next day.[4]

How can we switch between NOACs?

The alternative NOAC can be initiated when the next dose of the initial NOAC is due, except in situations where higher than therapeutic plasma concentrations are expected (e.g., in a patient with impaired renal function). In such situations, a longer interval may be foreseen.

References: [1]Gallego P, et al. Am J Respir Crit Care Med. 2013;188(4):413-21. [2]Quinn GR, et al. Cleve Clin J Med. 2016;83(5):345-8. [3]Karamichalakis N, et al. J Geriatr Cardiol. 2013;13:718-23. [4]Steffel J, et al. Eur Heart J. 2018;39(16):1330-93.

IMPROVING OUTCOMES IN CHILDHOOD EPILEPSY

Prof J Helen Cross, London

Prof Cross has been awarded the Order of the British Empire (OBE) in 2015 for services to children with epilepsy.

- Early-onset epilepsy is associated with a poor prognosis for long-term seizure remission and neurodevelopmental outcome. Epileptic activity itself contributes to cognitive and behavioral impairments beyond that expected from the underlying pathology alone (e.g., cortical malformation).
- There is a major impact from etiology, compounded by seizures. Accurate diagnosis, with appropriate interventions, is likely to have greatest impact on outcome.
- Treatment choices in infantile spasms - Vigabatrin (1996); steroids may be preferred over vigabatrin (UKISS Lux et al, 2004); vigabatrin + steroids therapy is more effective than steroids alone (ICISS O'Callaghan et al, 2017).
- Dravet syndrome accounts for 1% of the epilepsy population. Effective AEDs for Dravet syndrome include valproate, clobazam, topiramate, levetiracetam and ketogenic diet.
- Devinsky et al have shown in a 2017 study that in patients with Dravet syndrome, cannabidiol

resulted in a greater reduction in convulsive-seizure frequency than placebo and was associated with higher rates of adverse events. Ceulemans et al demonstrated success with the use of fenfluramine as an add-on treatment for Dravet syndrome in 12 patients aged 3-35 years at last evaluation. Exposure duration to fenfluramine ranged from 1 to 19 years. Seven patients who were still receiving treatment at the time of the last visit had been seizure-free for at least 1 year.

- Ketogenic diet is a high fat diet designed to mimic the metabolic effects of starvation. It is used in the treatment of epilepsy. Jung et al have suggested that ketogenic diet should be considered as an additional option even in patients with focal malformation of cortical development, and long-term seizure-free outcome can be expected for patients who become seizure-free 3 months after the diet.
- New ways of thinking with regard to treatment, related to etiology, are likely to have further impact in other epilepsies.

STATINS FOR PRIMARY PREVENTION OF CEREBROVASCULAR EVENTS

Dr L Sankaranarayanan, Chennai

Elevated lipid levels have been linked with an increase in ischemic stroke, while low lipid levels may increase the risk of hemorrhagic stroke. Lipid-lowering treatment with statins has been shown to reduce the incidence of ischemic stroke without increasing the frequency of hemorrhagic stroke. These benefits could be attributed to a combination of mechanisms. Statins decrease cholesterol levels and reduce the progression of atherosclerotic plaque formation in carotid arteries, and the incidence of emboli from cardiac, aortic and carotid sites. Statins also yield cholesterol-independent effects such as improvement in cerebral blood flow and reduction in inflammation and oxidative stress, which seem to have a role in limiting the size of an ischemic lesion. Statins have potential benefits in reducing the incidence and improving the prognosis of stroke.[1]

A meta-analysis revealed that treatment with statins in the primary prevention of major cardiovascular and cerebrovascular events led to a significant relative risk (RR) reduction in the first-time occurrence of major cardiovascular or cerebrovascular events (RR 0.75), fatal/nonfatal stroke (RR 0.69) and fatal/nonfatal myocardial infarction (RR 0.70).[2]

In another meta-analysis, for primary prevention in patients without established cardiovascular disease, statins helped reduce the cardiovascular and cerebrovascular events. Statins were associated with a significant reduction in the incidence of major adverse cardiovascular and cerebrovascular events (MACCE) and the risk of stroke and coronary revascularization were reduced 29% and 26%.[3] Statins have been shown to reduce the risk of stroke as well as transient ischemic attack (TIA). Statin use reduced the incidence of carotid bruits and cerebrovascular events as well as new-onset or worsening of angina pectoris and intermittent claudication.[4]

Each 1 mmol/L (39 mg/dL) decrease in low-density lipoprotein (LDL) cholesterol corresponds to a reduction in RR for stroke of 21.1%. Statins are recommended for primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events. Additionally, statins reduce the risk of stroke recurrence by 12-16% and are recommended for patients with ischemic stroke or TIA that has an atherosclerotic origin or associated with other comorbid atherosclerotic cardiovascular disease.[5]

Recently, a study revealed that statin treatment is an effective and safe therapy for cerebral small vessel disease (CSVD) in older hypertensive patients. The increase in white matter hyperintensities (WMH) volume was significantly lower in the rosuvastatin group than in the placebo group.[6]

In patients undergoing thoracic endovascular aortic repair (TEVAR), chronic statin use has been found to be associated with reduced 30-day MACCEs (myocardial infarction, stroke, arrhythmia, cardiovascular death or cerebrovascular death) in nonacute aortic syndrome patients.[7]

Therefore, statins seem to have potential effects in preventing cerebrovascular events.

References: [1]Di Napoli M. Curr Opin Investig Drugs. 2004;5(3):295-305. [2]de Vries FM, et al. Drugs. 2012;72(18):2365-73. [3]Chen YH, et al. Exp Clin Endocrinol Diabetes. 2012;120(2):116-20. [4]Pedersen TR, et al. Am J Cardiol. 1998;81(3):333-5. [5]Castilla-Guerra L, et al. Curr Pharm Des. 2016;22(30):4638-44. [6]Ji T, et al. J Am Med Dir Assoc. 2018 Jul 10. [Epub ahead of print] [7]Ham SY, et al. J Cardiovasc Surg (Torino). 2018 Apr 3. [Epub ahead of print]

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