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HEALTH MANAGEMENT FOR NEUROLOGISTS

Dr Pravar Passi, Indore

- Doctors are ignoring their own health. The burnout, depression and suicide rate amongst doctors continues to rise.
- In the last decade or so, the complexity of medicine has increased several-fold. The options are more than ever before. The patients are more demanding, at times unreasonably so. Doctors remain constrained for time and continue to ignore their health.
- Emphasis should be given to positive health.

THERAPEUTICS - GOALS, CURRENT AND EMERGING THERAPY IN MULTIPLE SCLEROSIS

Dr Nishita Singh, New Delhi

- Among clinically isolated syndrome (CIS) patients, conversion rates to clinically definite multiple sclerosis (CDMS) have been found to be 10-65% in those with optic neuritis, 41-61% in those with spinal cord syndrome and 53-60% in those with brainstem syndrome.
- As per the AAN 2018 guidelines, one should prescribe disease-modifying therapy (DMT) to people with a single clinical demyelinating event and two or more brain lesions characteristic of multiple sclerosis (MS) after discussing risks and benefits of therapy with the patient. According to the ECTRIMS EAN guidelines 2018, offer interferon or glatiramer acetate to patients with CIS and an abnormal MRI with lesions suggestive of MS who do not fulfil criteria for MS.
- Therapeutic options in aggressive relapsing-remitting multiple sclerosis (RRMS): Induction therapy with second-line agent; drug treatment options - natalizumab, mitoxantrone, fingolimod, alemtuzumab, ocrelizumab, rituximab, cyclophosphamide and autologous hematopoietic stem cell transplantation (aHSCT). As per the AAN guidelines 2018, there is level B evidence to prescribe alemtuzumab, fingolimod or natalizumab for people with highly active MS.
- Patients most likely to benefit from aHSCT: Relatively young, i.e., <50 years of age; relatively short disease duration, i.e., 5 years or less; have active RRMS and accumulating disability but ambulatory; have ongoing disease activity despite DMT.
- Reasons to stop treatment: Adverse effects, planned pregnancy, logistics, noncompliance.
- According to the AAN guidelines, discontinuation of DMT may be advised in people with secondary progressive multiple sclerosis (SPMS) who do not have ongoing relapses (or gadolinium-enhanced lesions on MRI activity) and have not been ambulatory (Expanded Disability Status Scale score 7 or greater) for at least 2 years.

DEVELOPMENT OF NEUROLOGY SERVICES IN THE SULTANATE OF OMAN

Dr Abdullah Al-Asmi, Oman

- The College of Medical and Health Sciences Sultan Qaboos University (SQUH) was established in September 1986.
- Adult/pediatric neurology units at SQUH include general neurology clinic, epilepsy clinic, VNS clinic, movement disorder clinic, botox clinic, memory clinic, vascular neurology clinic, MS clinic, sleep clinic, neurodevelopmental clinic and neurogenetics clinic.
- MOH work force involves Khoula Hospital, Royal Hospital, Salalah Hospital, Nizwa Hospital, Sohar Hospital.
- In Khoula Hospital neurology department, digital neurophysiological equipment, 1.5 T MRI, vascular lab and neuropathology lab are available.
- Neurologists in private are available only in Muscat and approximately 75% of them are Indians.

NEUROLOGICAL SERVICES WITHIN A FREE PUBLIC HEALTHCARE SYSTEM

Dr Harsha Gunasekara, Sri Lanka

- Achievements and challenges of free public healthcare system (PHS):

- Primary preventive care has helped to achieve excellent public health indices.
- In the curative sector, health system has concentrated mostly on tertiary care and to some extent on secondary care.
- What we need is to develop the primary curative care in terms of both quality and quantity.

- Development of Essential Health Service Package (SLESP) with WHO:
  - It aims at universal care at PHC level - to improve and expand the PHC preventive system and develop and re-structure the PHC curative network.
  - Strengthen the referral system for complete and comprehensive care.
  - Develop human resource needs based on workload rather than cadres.
- Future role of the Association of Sri Lankan Neurologists (ASN):
  - Advice health authorities on rational expansion of neurological services on - cadre projections based on population and specialized services; provision of facilities for neurology units and specialized services.
  - Promote research through collaboration, research grants.
  - Establishment of an independent Board of Study to maintain standards of training and to develop subspecialty training.

NEWER THROMBOLYTICS IN STROKE MANAGEMENT

Dr S Meenakshi-Sundaram, Madurai

- Neurologists have only 2 children - Alteplase and tenecteplase. Alteplase vs. tenecteplase fight is preferred over thrombolysis or no thrombolysis fight.
- Alteplase has procoagulant effects and neurotoxicity effects. Another issue with alteplase - Can compromise integrity of the blood-brain barrier; destructive effects on extracellular matrix and endothelial basal lamina; proteolytic activity of alteplase.
- Alternative formulations of recombinant tissue plasminogen activator (rtPA), in the absence of arginine, would provide new insight into rtPA neurotoxicity, and have the potential to offer more efficacious thrombolytic therapy for ischemic stroke.
- Tenecteplase has been shown to be associated with significantly better early major neurological improvement compared to alteplase. Tenecteplase has been associated with better reperfusion, recanalization and NIH Stroke Scale change at 24 hours, with no safety concerns.
- In acute ischemic stroke, tenecteplase 0.25 mg/kg has been found to be superior to alteplase for efficacy outcomes at 24 hours and 90 days.
- Additional thrombectomy procedures are averted with tenecteplase.
- A 2018 study revealed that intravenous tenecteplase 0.2 mg/kg administered within 3 hours of symptom onset was well-tolerated and effective in acute ischemic stroke.
- Tenecteplase bolus allows reducing time between stroke onset and thrombectomy.
- Molecules in the pipeline - Monteplase, pamiteplase, lanoteplase, alfimeprase.

"BLIND SPOTS" IN CLINICAL NEUROLOGY: CHALLENGES AND REMEDIES

Dr Arun B Taly, Bengaluru

- Diagnostic errors are common despite advancement in technology. Most clinicians experience at least one error during their practice, though only a very few admit.
- Errors have not received comparable attention and remain a blind-spot. Missed or misdiagnosis leads to unnecessary or delayed treatment, considerable disability or even death.
- Less often recognized and acknowledged is the impact of medical errors on the "second victim" i.e., the clinician who has to deal with negative emotions such as frustration, guilt, anger, anxiety, loss of confidence, reduced job satisfaction, poor performance, fear of lawsuit, etc.
- Errors are hardly ever intentional. A number of factors contribute to medical errors and can be broadly categorized as "No Fault" errors, "System" errors, "Cognitive" errors and "Medication" errors.
- "Cognitive" errors on the part of clinicians are attributed to knowledge gap, limited experience, adopting short-cuts, diagnostic anchoring, premature closure, faulty hypothesis/cognitive reasoning and over reliance/faulty interpretation of test results, to name but a few.

- Amidst uncertainty and varied probability in clinical neurology, following a "checklist", active knowledge seeking and cognitive flexibility may prevent potential diagnostic errors, ensure patient safety, reduce cost of treatment and improve overall quality of healthcare.

THERAPY OF CONGENITAL MYASTHENIC SYNDROMES

Dr A Nalini, Bengaluru

- Congenital myasthenic syndromes (CMS) are potentially treatable and reversible disorders. They usually begin at birth or early childhood with ocular, bulbar and limb muscles with prominent fatigue. Majority are labeled as congenital myopathies or mitochondrial disorders. Several types can have late adolescent or adult onset.
- The limb-girdle type do not have cranial muscle involvement or have minimal ocular and bulbar symptoms and are frequently mislabeled as limb-girdle muscular dystrophy.
- The fluctuations classically may be diurnal, but may occur over weeks or months, around menstrual cycles and also be seasonal. Tendon reflexes are well preserved and may be exaggerated, except may be hypoactive in the group with CMS and dystroglycanopathies. Creatine kinase level is elevated in CMS-dystroglycanopathy group.
- It is important to do repetitive nerve stimulation (RNS) in all cases of muscle diseases with easy fatigability. Perform sub-tetanic stimulation if routine RNS is negative.
- CHRNE, GMPPB, DPAGT1, GFPT1 respond well to pyridostigmine/neostigmine along with salbutamol. DOK7, MUSK, COLQ respond well to salbutamol; may significantly worsen with acetylcholinesterase inhibitors. Slow channel syndromes respond to fluoxetine and salbutamol. Many of the CMS cases are mislabeled or have a delayed diagnosis and hence should be detected early and treated.

PULSE STEROIDS: NEW DEVELOPMENT IN NEUROMUSCULAR DISORDERS

Dr Birinder Singh Paul, Ludhiana

- Treatment with glucocorticosteroids is an art. A balance must be maintained between the severity of patient's disease and clinical condition.
- Pulse dose of glucocorticosteroids (>250 mg MPS) exhibits, apart from genomic action, an additional nongenomic action. This results in faster, stronger response and fewer side effects compared to classic therapy. Keep in mind concurrent medical issues. Clinical experience is the key factor in using pulse steroids.

MEDIA MANAGEMENT FOR NEUROLOGISTS

Dr Sudhir Shah, Ahmedabad

- Many social media tools are available for Neurologists and healthcare professionals.
- These tools can be used to improve or enhance professional networking and education, organizational promotion, patient care and education, public health programs and research purpose.
- Social media is disruptive, addictive and pervasive.
- There are risks regarding the distribution of poor-quality information, damage to professional image, breaches of patient privacy, violation of personal-professional boundaries and licensing or legal issues.
- There are few ethical and common guidelines available.
- Remember, if it's on social media, it's not private.
- It can affect physical and mental health and can lead to depression, guilt, anxiety, disorientation, insomnia, weight and mood fluctuations.
- So, to prevent career burnout and addiction, one needs to "digital detox".
- Use of social media needs carefully balancing between professional ethics and maintaining personal-professional boundaries.

PATTERN RECOGNITION ON MUSCLE IMAGING IN VARIOUS MYOPATHIES

Dr Rajesh Benny, Mumbai

- MRI is a useful, noninvasive modality to study muscle disease.
- Changes on MRI are due to inflammation, fatty infiltration or SOL in the muscle.
- Some myopathies may have specific imaging characteristics, e.g., collagen VI myopathies.
- Imaging can help choose an involved muscle for biopsy (as the muscle involvement may be focal) or track disease progression (dystrophies)/response to treatment (inflammatory myopathies).

CERVICAL DYSTONIA

Dr Hrishikesh Kumar, Kolkata

- Botulinum toxin injection is the treatment of choice for patients with cervical dystonia.

- Contrary to prevalent belief, it is a simple procedure and only requires some basic knowledge of anatomy and biomechanics of neck muscles.
- There are more than 50 muscles resulting in neck movement and that makes the task of recognizing the dystonic muscles seemingly daunting. But again, there is a silver lining- if we know the anatomy, orientation and function of 6 muscles (sternomastoid, splenius capitis, levator scapulae, trapezius, scalene complex, semispinalis capitis), that suffices for injecting botulinum toxin in majority of patients with cervical dystonia.
- Cervical dystonia can be classified as per the direction of predominant posturing of neck (torticollis, lateral-collis, retrocollis and anterocollis). All of them can be grossly addressed by injecting varying combination of these muscles.
- One may be fooled by compensatory movement of neck and wrong muscles can be selected for the injection. Careful observation and spending some time with the patients will help us determine primary dystonic movement and the muscles involved.
- Concern about safety and side effects can be offset by following some basic principles of injection.

ELECTROPHYSIOLOGY IN CENTRAL AND PERIPHERAL DEMYELINATING DISORDERS

Dr Meena A Kanikannan, Hyderabad

- Myelin plays a key role in transmission and conduction of nerve impulses by insulating the axons.
- Demyelination of the pathological substrate in many inherited and acquired primary central nervous system (CNS) and peripheral nervous system (PNS) disorders leads to slowing the conduction, and if severe, failure of the transmission of nerve impulses leading to motor, sensory and cognitive disturbances.
- Visual evoked potentials (VEP), somatosensory evoked potentials (SSEP) (especially lower limb SSEP) and motor evoked potentials (MEP) are the common evoked responses used in clinical practice and they are useful in detecting silent asymptomatic lesions, especially optic nerve involvement in MS.
- Although MRI is a very sensitive test for showing dissemination in space, it is less sensitive in determining the disability. MMEP is particularly useful in MS in predicting the disability development as well as assessing the severity of the disability. It is very useful for determining the activity of the disease. It is readily available and inexpensive. Hence, evoked potentials do have a role in identifying silent lesions, and when there is a diagnostic dilemma, both clinically as well as on the basis of MRI.
- Nerve conduction studies are an essential neurophysiological test in demyelinating neuropathies.
- It helps distinguish demyelinating from axonal neuropathy and allows accurate diagnosis of treatable and inherited demyelinating neuropathies. Conduction slowing and conduction block (CB) are the hallmark of these neuropathies.
- Several criteria are laid for conduction slowing and CB parameters. Criteria sets for the diagnosis of specific neuropathies require that several variables of demyelination are present in several nerves.
- Inherited demyelinating neuropathies are characterized by uniform slowing in all nerves with absence of CB and TD, whereas acquired neuropathies are marked by asymmetrical multifocal slowing, CB and TD.

HOT TOPICS - EPILEPSY

Dr Manjari Tripathi, New Delhi

- The International League Against Epilepsy (ILAE) announced a new classification of seizures in May 2017. Seizures are now focal (focal- aware, impaired awareness, motor, nonmotor, epileptic spasm, focal to bilateral tonic-clonic convulsive), generalized seizures and unknown onset. Videos of each seizure type are available for viewing on the ILAE website.
- Precision therapies have entered the epilepsy realm based on genetics.
- Evidence concerning the potential anti-seizure efficacy of cannabinoids reached a turning point in the last year, with the completion of three high-quality placebo-controlled adjunctive-therapy trials of a purified CBD product in patients with Dravet syndrome and Lennox-Gastaut syndrome. In these studies, CBD was found to be superior to placebo in reducing the frequency of convulsive (tonic-clonic, tonic, clonic and atonic) seizures in patients with Dravet syndrome, and the frequency of drop seizures in patients with Lennox-Gastaut syndrome. For the first time, there is now Class I

evidence that adjunctive use of CBD improves seizure control in patients with specific epilepsy syndromes.

- The highlight is of course our very own trial in *NEJM* at the end of 2017. Children with medication-resistant epilepsy who were randomly assigned to undergo surgery were far likelier to be seizure-free afterward compared to those assigned to continued medical management, according to the first randomized trial of surgery in this pediatric population. About 77% of the patients assigned to surgery were seizure-free, compared to 7% of those assigned to medical management. Significant between-group differences were seen in the change from baseline to 12 months in favor of surgery on the Hague Seizure Severity scale, on the Child Behavior Checklist, on the Pediatric Quality of Life Inventory and on the Vineland Social Maturity Scale (Dwivedi R, et al. Surgery for drug-resistant epilepsy in children. *N Engl J Med*. 2017;377:1639-47).
- Special populations of women with epilepsy (WWE) - Results on major congenital malformations were published showing higher rates across registries in a dose-dependent manner for valproate and least for levetiracetam. This was confirmed by a network meta-analysis too. The effect on infant and childhood IQs also took a hit with valproate which must preferably be avoided in WWE of child-bearing age.

CROSSROADS IN THE PRACTICE OF NEUROLOGY

Dr Sanjeev V Thomas, Thiruvananthapuram

- There have been exciting innovations in neurosciences. However, there are bioethical dilemmas associated with the progress. Dr Thomas quoted HH 14th Dalai Lama, who had stated that humanity is at a critical crossroad. The radical advances that took place in neuroscience and particularly in genetics have led to a new era in human history. The session was based on a talk given by the Dalai Lama at the annual meeting of the Society for Neuroscience in 2005 in Washington, DC. Dr Thomas mentioned an editorial published in *Ann Indian Acad Neurol* in 2008 that highlighted the topic of 'Advocacy'. He had stated the important objectives of advocacy for neurologists in the editorial.
- It was stressed that we should learn the term - "Gene Drive". It could one day transform the world. Emphasis was laid on the National Academies of Science, Engineering and Medicines Principles of Governance of Genome Editing - Promote well-being; due care; responsible science; respect for persons; distributive justice; Trans-National cooperation.
- He mentioned about the United Against Rabies Collaboration: A global catalytic platform to achieve zero human rabies deaths by 2030 (WHO), which focuses on dog immunization; post-exposure prophylaxis; awareness programs; reduce dog bite risk. There are limited number of advanced medical research centers; shortage of research grants; poor coordination between public health and clinical scientists; no institutions like NINDS/NIH Brain Initiative.
- Stroke interventions and stroke prevention were discussed - Statins, antiplatelet drugs, thrombolysis and stroke units, control of high BP, control of diabetes, better lifestyle, awareness.
- What can we do and advise - If you smoke, quit; strive to maintain a healthy weight; stay physically active (at least 30 min of moderate intensity exercise); make vegetables and fruits half of every meal; for the other half, healthy proteins and whole grain carbohydrates; cut back on the amount of salt and sodium you take in; drink water instead of sugary beverages; if you drink alcohol, keep it moderate.
- The Millenium Development Goals (MDG) 2000-2015 were discussed. These include: Extreme poverty eradication; universal primary education; gender equality; reduction in child mortality; improvement in maternal health; combat HIV/malaria; ensure environmental sustainability and global partnership for development.
- There was special mention of victory over Nipah in Kerala in 2018. It was stated that a 28-year-old patient was admitted on May 17 at 2 am and by 9 am, Dr Jayakrishnan had suspected Nipah encephalitis. On May 18, Nipah encephalitis was confirmed. A special mention was also made about Helen Keller who had once said "Alone we can do so little; together we can do so much." It was stressed that helping mankind should be our purpose.

CAN A THERAPEUTIC PLATFORM TO TREAT DMD BE EXTENDED TO OTHER DISEASES?

Dr Steve Wilton, Australia

- Duchenne muscular dystrophy (DMD) is the most common and serious childhood muscle wasting.

- The Eureka moment - Ryszard Kole described suppressing abnormal splicing - AOs targeted to mutant splice site. It was shown in 1999 that molecular intervention at dystrophin pre-mRNA splicing can reduce the severity of a Duchenne mutation to the milder Becker phenotype. Abnormal splicing induced: Exon 23 skipping.
- The US FDA approved the first exon skipping compound in 2016. Eteplirsen is the first drug approved to treat patients with DMD. It is specifically indicated for patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping.
- Therapeutic alternative splicing - Designing compounds to modify pre-mRNA splicing: Dystrophin and exon skipping; correct abnormal splicing; induce specific isoforms.
- Hypothesis driven translational research - Monitor changes in RNA and protein; if no change in RNA/protein: drug lacks potency or efficient delivery. The DMD future - Gene therapy; next generation PPMOs and delivery; multi-exon skipping; addressing rare DMD mutations.
- Future challenges for precision medicine: Limitations of genomic/exome mutation detection - Comprehensive RNA-based screening; Oligomer production - scale, cost, potency, sustainability; Patient registries, databases and biobanks; Clinical trial challenges - limited patient numbers stratified on mutation, age, disease progression; Quality-of-life issues can be broken down; Stratifying orphan diseases based on mutation type.
- DMD can be the exemplar for so many other diseases.

TÊTE-À-TÊTE WITH PROF (DR) PA MOHAMMED KUNJU

Prof (Dr) PA Mohammed Kunju, Thiruvananthapuram

Can lacosamide monotherapy be used in clinical practice?

The FDA has approved lacosamide as monotherapy in treating partial-onset seizures (POS) in epilepsy patients aged 17 years or older in 2014 and as an oral option for pediatric patients 4 years and older in 2017.

A retrospective, noninterventional study assessed a total of 439 patients (98 first-line and 341 conversion to monotherapy) with focal seizures. Kaplan-Meier estimates of 12-month retention rates were 81.2% and 91.4% for first-line and conversion to monotherapy, respectively. About 66.3% of first-line and 63.0% of conversion to monotherapy patients were seizure free. Lacosamide was effective and well-tolerated as first-line or conversion to monotherapy in a clinical setting in adult and elderly patients with focal seizures.

What is the role of lacosamide in patients with uncontrolled partial-onset seizures?

Patients with uncontrolled seizures experience significant morbidity and mortality and face social stigma and discrimination as well. About 60% of people living with epilepsy have POS and one-third remain uncontrolled, despite trying treatment with a range of antiepileptic drugs (AEDs). Adjunctive therapy with lacosamide significantly reduces seizure frequency in patients with uncontrolled POS.

What is the long-term efficacy of lacosamide in partial-onset seizures?

Lacosamide has demonstrated long-term (5.5 years) efficacy as adjunctive treatment in patients with POS. The median percentage reduction in seizure frequency per 28 days from baseline was 45.9% and the 50% responder rate was 46.6%.

What is known about seizure free days and reduction in seizure frequency with lacosamide?

Lacosamide is able to increase seizure free days in patients. In a clinical trial, it was found that lacosamide 400 mg was able to provide 12% increase in seizure free days while lacosamide 200 mg provided 8% seizure free days compared to 6% with placebo in treatment-resistant seizures.

Can lacosamide be used in patients with renal impairment?

No dose adjustment is necessary in patients with mild-to-moderate renal impairment. A maximum dose of 300 mg/day lacosamide is recommended for patients with severe renal impairment.

At what dose can lacosamide be used in patients with hepatic impairment?

Exercise caution! A maximum dose of 300 mg/day is recommended for patients with mild or moderate hepatic impairment. It is not recommended in severe hepatic impairment.

Can we use lacosamide in pregnancy and pediatric patients?

Safety of lacosamide has not been established in pregnant women.

Lacosamide is approved in the European Union (EU) and the USA for use as monotherapy and adjunctive

therapy for the treatment of focal-onset seizures in adolescents and children aged ≥4 years.

Can we use lacosamide in geriatric patients?

Yes. However, caution should be exercised for dose titration in elderly patients. Blood level may be higher in elderly as, the dose and body weight normalized pharmacokinetic parameters AUC and C_{max} were approximately 20% higher compared to young subjects.

Source: Villanueva V, et al. *Acta Neurol Scand.* 2018; 138(3):186-94.

IDIOPATHIC LATE ONSET CEREBELLAR ATAXIA: A DIAGNOSIS REVISITED

Dr Achal Kumar Srivastava, Meena Lanjiwar; New Delhi

In 1981, the term idiopathic late onset cerebellar ataxia (ILOCA) was first coined by Harding. It is categorized as a group of sporadically occurring degenerative diseases involving cerebellum, its connections and brainstem, of unknown origin, in order to distinguish it from symptomatic ataxias due to identified exogenous and endogenous causes. Estimates of prevalence for ILOCA are limited, but a minimum prevalence of 10.8/1,00,000 has been suggested for UK. ILOCA is a diagnosis of exclusion. One hypothesis is that these disorders may represent monogenic diseases, either as late onset autosomal recessive ataxias or new dominant mutations. Since recessively inherited disorders are more likely to occur sporadically rather than clustered in families, sporadic late onset ataxias might represent late onset variants of Friedreich's ataxia (FRDA) or other recessive ataxias. Also, the occurrence of new dominant mutations in spinocerebellar ataxia (SCA) genes is possible, but appears to be rare. However, the parent who transmitted the disease may have died before clinical symptoms became apparent, making the family history less informative. Additionally autosomal dominant disorders may be apparently sporadic due to false fatherhood. Keogh et al, found that 33% of 'idiopathic' cases harbor compound heterozygous mutations in known ataxia genes, namely SPG7, SYNE1 and ANO10 using whole exome sequencing (WES).

A pilot study done by Nemeth et al, in 50 patients with ataxia who were refractory to diagnosis using next-generation sequencing (NGS) found 58 known human ataxia genes. The overall detection rate was 18% and varied from 8.3% in those with an adult onset progressive disorder to 40% in those with a childhood or adolescent onset progressive disorder. They have found 13 different mutations in eight different genes which are PRKCG, TTBK2, SETX, SPTBN2, SACS, MRE11, KCNC3 and DARS2, of which nine were novel including one causing a newly described recessive ataxia syndrome. Thus, genetic testing using targeted capture followed by NGS was efficient and enabled a molecular diagnosis in many refractory cases. ILOCA includes either pure cerebellar syndrome or additional extracerebellar symptoms such as parkinsonism, bulbar symptoms, vertical gaze paresis, dementia, urinary incontinence, spasticity and other pyramidal tract signs. Noncerebellar symptoms appear in parallel with the worsening of the cerebellar syndrome, thus patients with cerebellar plus syndrome have more pronounced cerebellar symptoms and signs. A retrospective study among 28 patients of ILOCA found that all 13 patients with cerebellar plus syndrome had features of parkinsonism while rest of other symptoms were encountered less frequently. Within 5 years of onset of symptoms, 29-33% ILOCA plus syndrome patients will meet diagnostic criteria for possible or probable multiple system atrophy (MSA) and have a poor prognosis, accumulate greater disability, remain ambulant for a median of 6 years, and survive only 7-9 years. Barbosa et al, in their study of 38 ILOCA patients, also found that 32% patients had a diagnosis of possible or probable MSA. Clinical studies by Schulz et al and Wenning et al showed that many of ILOCA plus patients suffered from MSA. In one large study of over 100 ILOCA patients, less than 30% met the criteria for MSA even after 4 years of onset of symptoms, less than 15% were found to have an identifiable genetic cause and nearly 60% were diagnosed as idiopathic.

Brain imaging, especially MRI is essential in the diagnostic work-up of patients presenting with ILOCA. Besides the most important benefit that is exclusion of an acquired cause, it also provides clues to other causes of sporadic and familial ataxia. In a study of Klockgether et al, brain imaging of patients with pure cerebellar syndrome showed cerebellar atrophy without apparent involvement of brainstem structures while there was atrophy of brainstem along with cerebellum suggestive of olivopontocerebellar atrophy in majority of patients with cerebellar plus syndrome.

Median survival duration from onset of symptoms in pure cerebellar syndrome patients was 20.7 years as compared to 7.7 years in cerebellar plus patients, suggesting faster progression of disease in cerebellar plus syndrome. Patients with pure cerebellar syndrome had a significantly better prognosis as compared to that of patients with additional noncerebellar involvement (annual progression rate: 0.40 vs. 0.80). Prognosis was

even worse in patients who had additional noncerebellar symptoms from the very beginning of disease course as compared to those who developed such symptoms in later course of disease. Early and accurate diagnosis is immensely important not only in guiding treatment but also for patient counseling and support. Availability of WES has further purified the diagnosis of ILOCA.

Suggested Reading: [1]Harding AE. J Neurol Sci. 1981;51:259-71. [2]Muzaimi MB, et al. J Neurol Neurosurg Psychiatry. 2004; 75(8):1129-34. [3]Keogh MJ. J Neurol. 2015;262(8):1822-7. [4]Nemeth AH, et al. Brain J Neurol. 2013;136:3106-18. [5]Abele M, et al. Brain. 2002;125(Pt 5):961-8. [6]Gilman S, et al. Neurology. 2000;55(4): 527-32. [7]Klockgether T, et al. Brain. 1998;121(Pt 4):589-600. [8]Watanabe H, et al. Brain. 2002;125(Pt 5):1070-83. [9]Barbosa R, et al. J Neurol Sci. 2016;365:156-7. [10]Schulz JB, et al. J Neurol Neurosurg Psychiatry. 1994;57:1047-56. [11]Wenning GK, et al. Brain. 1994;117:835-45. [12]Klockgether T, et al. J Neurol Neurosurg Psychiatry. 1990;53:297-30.

IN CONVERSATION WITH DR JS KATHPAL

Dr JS Kathpal, Indore

How should we manage atrial fibrillation patients presenting with acute ischemic stroke while on NOACs?

According to current guidelines and official labeling, thrombolytic therapy with rtPA is approved within 4.5 hours of onset of stroke symptoms but should not be administered in patients on full anticoagulation. Thrombolytic therapy cannot be given within 24 hours after the last intake of a novel oral anticoagulant (NOAC) due to their plasma half-lives, which may even be prolonged in renal insufficiency, the elderly and other situations. The case is different for dabigatran due to the availability of the rapid acting specific reversal agent, idarucizumab.

What are the considerations for NOACs in patients with acute intracranial bleeding?

About two-thirds of all NOAC-related intracranial bleedings (ICBs) are intracerebral and about one-third of all ICBs are subdural bleedings. A recent and large retrospective analysis of the Get With the Guidelines-Stroke program found a more favorable outcome with NOACs compared with vitamin K antagonist (VKA). A neurologist/stroke physician should examine all patients presenting with ICB on an NOAC, and neurosurgical consult should be solicited.

What are the considerations for NOACs in frail (≥75 years) patients?

The incidence of atrial fibrillation (AF) rises steadily with each decade. Stroke prevention in older AF patients is important as stroke risk rises dramatically with age. However, oral anticoagulant (OAC) remains underutilized in older age groups. Older people with AF do better on OAC than not and on NOACs rather than VKA.

Does anticoagulation work in dementia patients?

Dementia is common in older age groups. A stroke is a very significant event for patients with dementia with a greater risk of cognitive and functional decline, loss of independence and institutionalization, compared to nondementia patients. Indeed, AF is itself a risk factor for dementia and there is encouraging evidence that use of OAC may reduce the risk of dementia in AF patients.

What to do if there is (suspected) overdose without bleeding, or a clotting test is indicating a potential risk of bleeding?

In case of a suspected overdose, coagulation tests can help to determine its degree and possible bleeding risk. A normal aPTT excludes high levels of dabigatran; similarly, a normal PT excludes very high levels of rivaroxaban and edoxaban. Given the relatively short plasma half-life of the NOACs, a 'wait-and-see' strategy can be used in most cases without active bleeding. The elimination half-life can be estimated taking into account age and renal function.

What are the considerations for oral anticoagulation in epilepsy patients?

A risk of seizures has been reported in >5% of overall post-stroke patients. Following an unprovoked seizure after stroke, the risk of subsequent unprovoked seizures is about 65% within 10 years. OAC poses a special risk for patients with epilepsy due to the risk of injury during a seizure (with or without falling). Anticoagulation is affected by antiepileptic drugs via various potential interactions. The choice of drug and dose should be as per the clinical judgment of the treating physician.

Source: Steffel J, et al. *Eur Heart J.* 2018;39(16):1330-93.

PREVENTIVE EFFECT OF ROSUVASTATIN IN STROKE

Dr Tapas Kumar Banerjee, Kolkata

Statins are the guideline therapy for primary and secondary stroke prevention. Several large randomized, double-blind trials have shown that statin use in ischemic stroke reduces the risk of incident and recurrent stroke. Statins are known to have lipid-lowering effects. They inhibit HMG-CoA reductase, resulting in a reduction of cholesterol and several other intermediate metabolites. Besides reducing cholesterol, statins also have non-lipid dependent, pleiotropic effects on ischemic stroke. These include improvement in endothelial function

and vasomotor reactivity, antithrombotic effects, anti-inflammatory effects, reduction of oxidative stress and promotion of angiogenesis.

The CARE study revealed significant reduction in incidence of stroke by 31% in patients with myocardial infarction (MI) with pravastatin therapy. Rosuvastatin has also been shown to reduce stroke risk. In the JUPITER trial, rosuvastatin significantly reduced major cardiovascular events and also stroke risk (RRR: 48%; p = 0.002) in apparently healthy individuals but with elevated hsCRP levels. Other statins have also been shown to reduce stroke risk. Several meta-analyses have also shown that pre-stroke statin use is associated with stroke risk reduction. A large meta-analysis of 38 trials revealed that pre-stroke statins use was associated with a stroke RRR of 26%. Yet another meta-analysis including 1,21,000 patients revealed that statins yielded an obvious protection against all-cause mortality and nonhemorrhagic stroke.

Statins thus clearly have a potential preventive effect in stroke. It is noteworthy that statins reduce the risk of stroke in patients with vascular disease or at high risk of vascular disease and their benefit seems to be independent of baseline cholesterol level. Additionally, individuals with normal cholesterol have been found to experience a similar degree of risk reduction as those with high levels of cholesterol.

Suggested Reading: [1]Zhao J, et al. Curr Neuropharmacol. 2014;12(6):564-74. [2]Sacks FM, et al. N Engl J Med. 1996;335(14): 1001-9. [3]Ridker PM, et al. N Engl J Med. 2008;359(21):2195-207. [4]Corvol JC, et al. Arch Intern Med. 2003;163(6):669-76. [5]O'Regan C, et al. Am J Med. 2008;121(1):24-33. [6]Becker K, et al. Stroke. 2004;35(Suppl I):2706-7.

BOTULINUM A TOXIN IN POST-STROKE UPPER LIMB SPASTICITY

Dr Nirmal Surya, Mumbai

Botulinum toxin A (BTXA) is a useful tool to reduce the focal spasticity in upper limb following stroke. Advantages of BTXA are that it can be used with other treatments like splinting, casting and active physiotherapy. The effect is local without any systemic side effects and can be repeated after 3 months, if needed. The selection of muscle depends on the spasticity at shoulder, elbow, wrist or fingers. The Modified Ashworth scale is a useful scale to asses the severity of spasticity and to calculate the dose; higher the MAS scale, larger is the dose. The injection can be given under the electromyographic (EMG) guidance or ultrasound use. The treatment aim could be to improve the function, like mobility, transfer or gait improvement or symptomatic, like reduction of pain and spasm, self-care and hygiene, prevention of contracture, etc. The goal of the therapy should be discussed with the patient and caregiver before planning the treatment and should be well documented. Multidisciplinary team care should be ideal for post-stroke care and better outcomes are reported. Post injection treatment could be stretching, electric stimulation or splint and casting, as required by the individual. Finally, outcome will depend on patient selection, appropriate muscle and dosage, post injection treatment and supervised therapy from MDT.

RABIES ENCEPHALITIS - LUCKNOW EXPERIENCE

Dr Neeraj Kumar, Lucknow

Rabies is a preventable neurotropic infection. Rabies infection can occur from many wild and pet animals. Most cases occur in Asia and Africa, especially in children. Timely diagnosis and treatment may be life-saving. Rabies encephalitis is almost 100% fatal. Immunization of animals and pre-exposure prophylaxis in high risk humans is important. Shelter home, immunization, sterilization and monitoring of dogs will be an effective way to eliminate rabies.

DECIPHERING EPILEPTOGENIC AND FUNCTIONAL ZONES USING STEREO EEG

Dr Dinesh Nayak, Chennai

Cortical electrical stimulation is the most reliable form of localizing cerebral functions including language, motor, sensory and visual. Bipolar electrical stimulation is more accurate than monopolar stimulation. Bipolar stimulation is precise focal depolarization block between 2 electrodes. Stereo EEG can simultaneously record activity from superficial and deep cortical structures, in anteroposterior and supro-inferior directions 3-dimensionally. Stereo EEG is a good technique for studying insula, operculum, cingulate, orbital-frontal cortex, depths of the sulcus. Stereo EEG can also be used when bilateral hemispheric coverage is needed.

CURRENT MANAGEMENT STRATEGIES IN MSA

Dr Hrishikesh Kumar, Kolkata

Like other atypical Parkinsonism, multiple system atrophy (MSA) has remained generally unresponsive to treatment. But devising a careful management strategy and modulating it as per the situation often helps in improving the quality-of-life of affected patients. Current treatment strategies target motor impairment, autonomic dysfunction (orthostatic

hypotension, erectile dysfunction, urinary symptoms, etc.), sleep disturbance, sialorrhea, depression and other symptoms. Levodopa remains the mainstay of therapy for motor manifestation despite its modest and non-sustained effect. For orthostatic hypotension, various pharmacological and nonpharmacological measures are being used. Among medications, midodrine has the best evidence as compared to a host of others. Botulinum toxin has limited role in alleviating some of the symptoms like sialorrhea, stridor, overactive bladder, but evidence is not very promising till date. With better understanding of pathogenesis of MSA, novel targets of neuroprotection are being explored and disease-modifying agents are being tried. But as with other neurodegenerative conditions, disease modification still has remained elusive and it seems that there is a long way to go.

THE ROLE OF VITAMIN D IN MULTIPLE SCLEROSIS

Dr Bassem I Yamout, Beirut

There is a strong association between serum vitamin D levels and the risk of MS, supported as a possible causative factor by genome-wide association studies. There is a strong association in patients with MS between serum vitamin D levels and development of relapses or new lesions on MRI. Clinical studies including large randomized controlled trials have shown a consistent effect of vitamin D supplementation on radiological parameters but inconsistent effects on relapse rates and disability progression. Given the strength of indirect evidence, and the low risk of adverse events, it is reasonable to recommend vitamin D replacement at 10,000-50,000 IU weekly, aiming at a serum 25(OH)D level of 75-100 nmol/L to: Persons at high risk of developing MS such as first-degree relatives of MS patients, especially with multiple affected family members; Patients with MS in whom such replacement might prevent disease activity.

PREVENTION OF STROKE

Prof Subhash Kaul, Secunderabad

Risk factors for stroke - *Nonmodifiable*: Age, race, sex, low birth weight, genetic factors; *Modifiable*: High BP, abnormal lipid profile, diabetes, smoking, atrial fibrillation, alcohol, oral contraceptives, diet and physical inactivity. Twin studies data suggest an inheritance of stroke risk. Babies weighing <1.5 kg have a double risk of developing stroke, heart disease or MI before age 50. Men have high age-specific stroke incidence rates. Oral contraceptives/pregnancy put women at risk. Risk doubles for each decade after age 55 years. The good news is that age alone is not a risk factor for stroke. Stroke is a result of interaction of risk factors. Controlling more risk factors reduces the risk. We must know our risk factors. Risk factor assessment in adults should begin at age 20 years. Smoking status, diet, alcohol intake, physical activity and family history should be assessed periodically. High BP increases the risk. Higher the BP, higher the risk. Diabetes doubles the risk of ischemic stroke. All lipid fractions increase the risk and should be treated. High risk patients, even with normal LDL levels, should be treated with statin. Initiate weight management program through caloric restriction and increased caloric expenditure. Body weight in obese should be reduced by 10% in the first year. Should aspirin be used in primary prevention? - As per AHA, you should, if you have >2 risk factors; If you have high-grade asymptomatic vascular disease. Air pollution is now a leading stroke risk factor. Stroke is therefore a result of gene-environment interaction. Strict risk factor control can minimize the risk. Risk factor control is an umbrella for protection.

INVASIVE BIOPSY IN NEUROLOGY: NEUROSURGICAL EXPERTISE

Dr Sumit Thakar, Bengaluru

Invasive biopsy in Neurology must be carefully planned with multidisciplinary input. It is crucial to select an optimal biopsy site to maximize the chance of obtaining representative sample with minimal complications. Patients with focal neurological signs/encephalopathy/focal findings on imaging/cerebrospinal fluid pleocytosis/an abnormal inflammatory screen are more likely to have positive brain biopsies. Brain biopsy can be either open (for superficial or potentially vascular lesions) or more commonly, stereotactic (frame-based or frameless; for well-defined, deep seated or infiltrative lesions or lesions in eloquent cortex). Even though both brain and spine biopsies are not technically demanding, they can be associated with complications, some of which can be irreversible. Given the low overall diagnostic yield, surgical risks and also the added costs, the pros and cons of the procedure should be carefully weighed.

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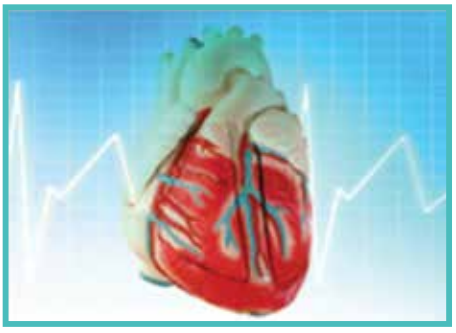

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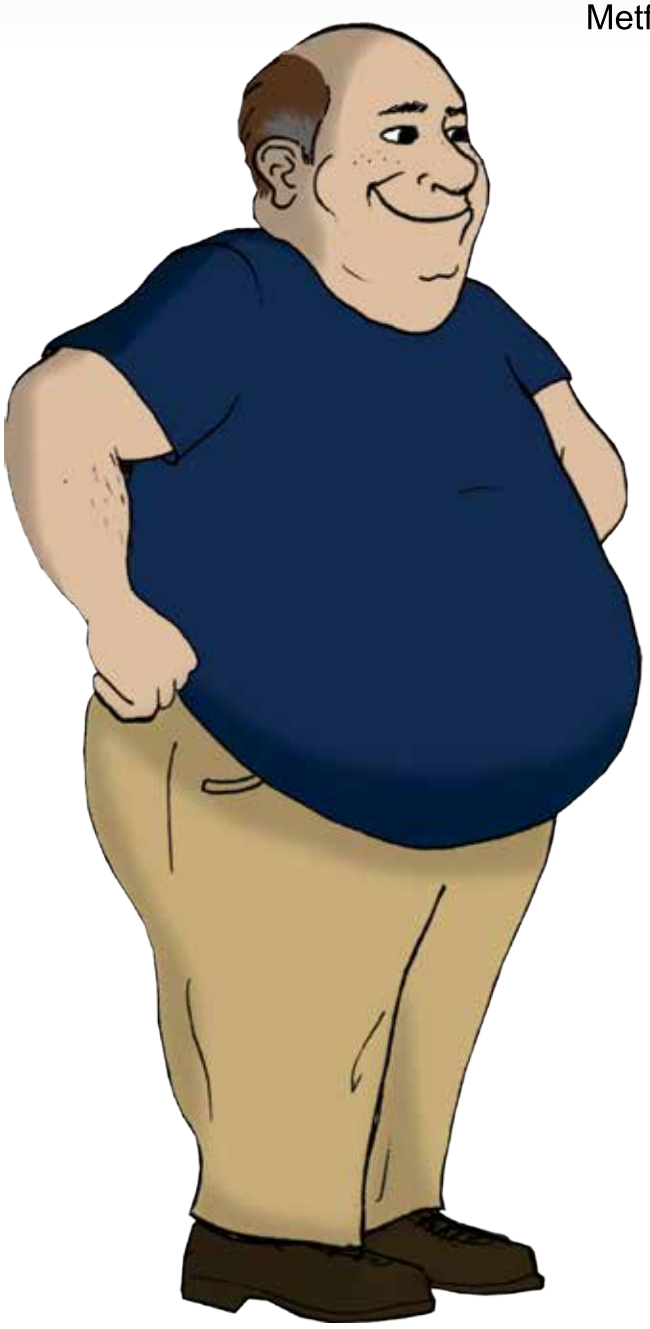

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