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Editorial

Aequanimitas and William Osler

I consider myself fortunate to have been introduced to William Osler's seminal work of essays, 'Aequanimitas' during my first year of medical school. Today, more than 40 years later, I often re-experience the thrill of that first essay and some of the others that followed it. In a reverse Proustian manner, the aroma of the leather bound text wafts across the decades with the beautiful brown edition standing like a sentinel by my bedside.

William Osler revolutionised medical education by introducing the bedside clinic at the John's Hopkins University School of Medicine in the 1890s. The benefits of the bedside clinic caught on throughout the world and today, it continues to be the mainstay of medical education. Few individuals have had such an overarching impact on the teaching and practice of medicine. Rare, indeed, is the physician, who excels uniformly in the research, practice and teaching of medicine. Osler is rightly called the Father of Modern Medicine.

Aequanimitas epitomises Osler's philosophy. It was, in its inception, a speech that he delivered as a valedictory address to the graduating medical students of the University of Pennsylvania on May 1st, 1889. He begins by pointing out that, "in the physician or surgeon no quality takes rank with impurtability" and proceeds to describe its mental equivalent as 'Aequanimitas'. Osler recalls the Roman emperor Antonius Pius who as he lay dying in 131 AD summed up his life's philosophy in one word: Aequanimitas.

Osler cautions the graduating medical students that they will soon experience the distressing feature of their professional lives, "uncertainty which pertains not only to our science and art, but to the very hopes and fears which make us men" (the 19th century was not one of political correctness in gender specifics). The medical researcher in the quest for certainty often encounters more uncertainty. Unless, we consciously cultivate the quality of equanimity, a low frustration tolerance is likely to result in one giving up entirely on research. Equanimity promotes and ensures persistence. Aequanimitas has become for me a 'Let it Be' of my professional life.

Osler sounds like a Spartan or a Rajput warrior when he states, "Even with disaster ahead and ruin imminent, it is better to face them with a smile, and with the head erect, than to crouch at their approach". Far too often, the fear of failure precludes medical research.

In the mid-80's, I was fortunate enough to be accepted into the prestigious Neuropsychiatry fellowship at Johns Hopkins under the legendary Dr. Robert G. Robinson who epitomised Oslerian equanimity. It was one thing to experience the thrill of reading Aequanimitas, it was something else altogether to witness it over four years in a mentor. As for oneself, it is always an ongoing work in progress. The original speech is at www.medicalarchives.jhmi.edu/osler/aequessay.htm

Rajesh M. Parikh, M.D., D.P.M., D.N.B.

Director, Medical Research

Research News

Dr. Azad Irani won the 1st Prize for the oral presentation "An unusual case of recurrent symptomatic and asymptomatic strokes" at the Bombay Neuroscience Association meeting held in January 2017 in Mumbai. The co-authors were Drs. Sudheer Ambekar, Preeti Nagnoor, Shaila Khubchandani, Shaji Marar and Fali Poncha.

Abstracts

Comparison of ^{68}Ga-DOTANOC PET/CT and contrast-enhanced CT in localisation of tumours in ectopic ACTH syndrome

Majunath R Goroshi, Swati S Jadhav, Anurag R Lila, Rajeev Kasaliwal, Shruti Khare, Chaitanya G Yerawar, Priya Hira, Uday Phadke, Hina Shah, Vikram R Lele, Gaurav Malhotra, Tushar Bandgar, and Nalini S Shah

Endocrine Connections 2016;5:83-91.

Background

Localising ectopic adrenocorticotrophic hormone (ACTH) syndrome (EAS) tumour source is challenging. Somatostatin receptor-based PET imaging has shown promising results, but the data is limited to case reports and small case series. We reviewed here the performance of ^{68}Ga-DOTANOC positron emission tomography (PET)/computed tomography (CT) and contrast-enhanced CT (CECT) in our cohort of 12 consecutive EAS patients.

Materials and methods

Retrospective data analysis of 12 consecutive patients of EAS presenting to a single tertiary care centre in a period between January 2013 and December 2014 was done. CECT and ^{68}Ga-DOTANOC PET/CT were reported (blinded) by an experienced radiologist and a nuclear medicine physician, respectively. The performance of CECT and ^{68}Ga-DOTANOC PET/CT was compared.

Results

Tumours could be localised in 11 out of 12 patients at initial presentation (overt cases), whereas in one patient, tumour remained occult. Thirteen lesions were identified in 11 patients as EAS source (true positives). CECT localised 12 out of these 13 lesions (sensitivity 92.3%) and identified five false-positive lesions (positive predictive value (PPV) 70.5%). Compared with false-positive lesions, true-positive lesions had greater mean contrast enhancement at 60s (33.2 vs 5.6 Hounsfield units (HU)). ^{68}Ga-DOTANOC PET/CT was able to identify 9 out of 13 lesions (sensitivity 69.2%) and reported no false-positive lesions (PPV 100%).

Conclusion

CECT remains the first-line investigation in localisation of EAS. The contrast enhancement pattern on CECT can further aid in characterisation of the lesions. ^{68}Ga-DOTANOC PET/CT can be added to CECT, to enhance positive prediction of the suggestive lesions.

First successful pregnancy after pre-implantation genetic diagnosis by FISH for an inversion together with a cryptic translocation in India

Rupesh R. Sanap, Arundhati S. Athalye, Prochi F. Madon, Nandkishor J. Naik, Dattatray J. Naik, Trupti V. Mehta, Firuza R. Parikh

Journal of Fetal Medicine 2016;3:25-30.

The technique of pre-implantation genetic diagnosis (PGD) by fluorescence in situ hybridization (FISH) in cases of repeated miscarriages due to parental balanced inversions and translocations is relatively new in India. In a couple with a history of recurrent miscarriages and implantation failures, karyotyping done in three laboratories showed that the husband had an insertion or inversion of chromosome 12. Hence, they were referred to us for PGD. The anomaly turned out to be more complex. A pre-PGD workup using a series of FISH probes on metaphases accompanied by reflex FISH was required to characterize the anomaly. For subsequent PGD, single blastomeres were biopsied from seven embryos obtained by intracytoplasmic sperm injection. FISH analysis had to be carried out using ten probes in four rounds. On pre-PGD workup for inversion 12 by FISH, an additional anomaly of a cryptic translocation between 9qter and 12qter was detected in the husband. His complex karyotype according to the detailed ISCN nomenclature was therefore 46,XY,t(9;12)(9pter→9q34.1::12q24.2 → 12qter), der(12)inv(12)(12pter→12p11.2::12q24.2→12p11.2::9q34.1→9qter). After PGD, the normal and balanced embryos transferred resulted in the birth of healthy twins conceived in the first cycle itself. Therefore, a pre-PGD workup is important and needs reflex FISH in the event of an unexpected cytogenetic anomaly. PGD will need the analysis of additional chromosomes on the same cell by FISH in such cases. An experienced in vitro fertilization and Genetics team is essential for success. This is the first report of PGD by FISH for an inversion coupled with a cryptic translocation from India.

When flexibility is not necessarily a virtue: a review of hypermobility syndromes and chronic or recurrent musculoskeletal pain in children

Cattalini M, Khubchandani R, Cimaz R.

Pediatr Rheumatol Online Journal 2015;13:40 (9 pgs.)

Chronic or recurrent musculoskeletal pain is a common complaint in children. Among the most common causes for this problem are different conditions associated with hypermobility. Pediatricians and allied professionals should be well aware of the characteristics of the different syndromes associated with hypermobility and facilitate early recognition and appropriate management. In this review we provide information on Benign Joint Hypermobility Syndrome, Ehlers-Danlos Syndrome, Marfan Syndrome, Loeys-Dietz syndrome and Stickler syndrome, and discuss their characteristics and clinical management.

Consensus on guidelines for stereotactic neurosurgery for psychiatric disorders

Nuttin B, Wu H, Mayberg H, Hariz M, Gabriëls L, Galert T, Merkel R, Kubu C, Vilela-Filho O, Matthews K, Taira T, Lozano AM, Schechtmann G, Doshi Paresh, et al.

J Neurol Neurosurg Psychiatry 2014 Sep;85(9):1003-8. doi: 10.1136/jnnp-2013-306580.

Background

For patients with psychiatric illnesses remaining refractory to 'standard' therapies, neurosurgical procedures may be considered. Guidelines for safe and ethical conduct of such procedures have previously and independently been proposed by various local and regional expert groups.

Methods

To expand on these earlier documents, representative members of continental and international psychiatric and neurosurgical societies, joined efforts to further elaborate and adopt a pragmatic worldwide set of guidelines. These are intended to address a broad range of neuropsychiatric disorders, brain targets and neurosurgical techniques, taking into account cultural and social heterogeneities of healthcare environments.

Findings

The proposed consensus document highlights that, while stereotactic ablative procedures such as cingulotomy and capsulotomy for depression and obsessive-compulsive disorder are considered 'established' in some countries, they still lack level I evidence. Further, it is noted that deep brain stimulation in any brain target hitherto tried, and for any psychiatric or behavioural disorder, still remains at an investigational stage. Researchers are encouraged to design randomised controlled trials, based on scientific and data-driven rationales for disease and brain target selection. Experienced multidisciplinary teams are a mandatory requirement for the safe and ethical conduct of any psychiatric neurosurgery, ensuring documented refractoriness of patients, proper consent procedures that respect patient's capacity and autonomy, multifaceted preoperative as well as postoperative long-term follow-up evaluation, and reporting of effects and side effects for all patients.

Interpretation

This consensus document on ethical and scientific conduct of psychiatric surgery worldwide is designed to enhance patient safety.

Cortical Cystic Necrosis in Wilson Disease

Aakash Shetty, Ritu Kashikar, Aabha Nagral, Pettarusp Wadia

JAMA Neurology 2016;73:350-1.

Wilson disease is an autosomal recessive neurodegenerative disease secondary to abnormal copper metabolism. It is caused by mutations in ATB7B and up to 500 mutations are known to date. Magnetic resonance imaging changes are very common in Wilson disease predominantly affecting the subcortical structures and basal ganglia. Cortical involvement is known to occur pathologically; however, it is rarely demonstrated on magnetic resonance imaging. This case shows unusual extensive cortical cystic lesions with partial poor response to decupuration and seizures.

Molecular and phenotypic characterization of CD133 and SSEA4 enriched very small embryonic-like stem cells in human cord blood
Shaikh A, Nagvenkar P, Pethe P, Hinduja I, Bhartiya D
Leukemia 2015;29:1909-17.

Very small embryonic-like stem cells (VSELs) are immature primitive cells residing in adult and fetal tissues. This study describes enrichment strategy and molecular and phenotypic characterization of human cord blood VSELs. Flow cytometry analysis revealed that a majority of VSELs (LIN(-)/CD45(-)/CD34(+)) were present in the red blood cell (RBC) pellet after Ficoll-Hypaque centrifugation in contrast to the hematopoietic stem cells (LIN(-)/CD45(+)/CD34(+)) in the interphase layer. Thus, after lyses of RBCs, VSELs were enriched using CD133 and SSEA4 antibodies. These enriched cells were small in size (4-6 μm), spherical, exhibited telomerase activity and expressed pluripotent stem cell (OCT4A, OCT4, SSEA4, NANOG, SOX2, REX1), primordial germ cell (STELLA, FRAGILIS) as well as primitive hematopoietic (CD133, CD34) markers at protein and transcript levels. Heterogeneity was noted among VSELs based on subtle differences in expression of various markers studied. DNA analysis and cell cycle studies revealed that a majority of enriched VSELs were diploid, non-apoptotic and in G0/G1 phase, reflecting their quiescent state. VSELs also survived 5-fluorouracil treatment in vitro and treated cells entered into cell cycle. This study provides further support for the existence of pluripotent, diploid and relatively quiescent VSELs in cord blood and suggests further exploration of the subpopulations among them.

Management of REM sleep behavior disorder: An evidence based review
Devnani P, Fernandes R.
Annals of the Indian Academy of Neurology 2015;18:1-5.

Rapid eye movement (REM) sleep behavior disorder (RBD) is characterized by dream enactment behavior resulting from a loss of REM skeletal muscle atonia. The neurobiology of REM sleep and the characteristic features of REM atonia have an important basis for understanding the aggravating etiologies the proposed pharmacological interventions in its management. This review outlines the evidence for behavioral and therapeutic measures along with evidence-based guidelines for their implementation, impact on falls, and effect on polysomnography (PSG) while highlighting the non-motor, autonomic, and cognitive impact of this entity. PubMed databases were reviewed upto May 2013 in peer-reviewed scientific literature regarding the pathophysiology and management of RBD in adults. The literature was graded according to the Oxford centre of evidence-based Medicine Levels. An early intervention that helps prevent consequences such as falls and provides a base for intervention with neuroprotective mechanisms and allocates a unique platform that RBD portrays with its high risk of disease conversion with a sufficiently long latency. RBD provides a unique platform with its high risk of disease conversion with a sufficiently long latency, providing an opportunity for early intervention both to prevent consequences such as falls and provide a base for intervention with neuroprotective mechanisms.

Looking at "thunderclap headache" differently? Circa 2016
Ravishankar K
Annals of the Indian Academy of Neurology 2016;19:295-301.

The term "thunderclap headache" (TCH) was first coined in 1986 by Day and Raskin to describe headache that was the presenting feature of an underlying unruptured cerebral aneurysm. The term is now well established to describe the abrupt onset headache seen with many other conditions and is also now included in The International Classification of Headache Disorders 3(rd) edition beta version rubric 4.4. An essential to label an acute headache as "TCH" and differentiate it from other "sudden onset, severe headaches" is the arbitrary time frame of 1 min from onset to peak intensity for "TCH." What happens in practice, however, is that even those "sudden onset, severe headaches" that do not strictly fulfill the definition criteria are also labeled as "TCH" and investigated with the same speed and in the same sequence and managed based on the underlying cause. This article begins by questioning the validity and usefulness of this "one minute" arbitrary time frame to define "TCH," particularly since this time frame is very difficult to assess in practice and is usually done on a presumptive subjective basis. The article concludes with suggestions for modification of the current investigation protocol for this emergency headache scenario. This proposal for "a change in practice methodology" is essentially based on (1) the fact that in the last two decades, we now have evidence for many more entities other than just subarachnoid hemorrhage that can present as "TCH" or "sudden onset, severe headache" and (2) the evidence from literature which shows that advances in imaging technology using higher magnet strength, better contrast, and newer acquisition sequences will result in a better diagnostic yield. It is therefore time now, in our opinion, to discard current theoretical time frames, use self-explanatory terminologies with practical implications, and move from "lumbar puncture (LP) first" to "LP last!"

Making medical care and research rational and affordable
Pandya SK
Indian Journal of Medical Ethics 2015;12:97-103.

Expenditure on insurance, consultations, the multitude of tests ordered by the doctor, and very expensive drugs make the treatment of illness a great burden. Should the patient need admission to a hospital and, worse, an intensive care unit, the load becomes almost unbearable. Medical research has moved from the domain of the single keen observer to that of highly qualified experts working in laboratories containing costly equipment. The budget for these projects now runs into lakhs or crores of rupees.