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Editorial

A few weeks ago, a colleague requested me to prescribe an antidepressant to a friend of his whom I had just diagnosed with major depression. The patient was traveling next day to Europe and the United States. In the course of the trip, he would be travelling through four time zones in a week. I expressed my reluctance to prescribe being uncertain of his response to the drug given the disruption in his chronobiologic rhythms. I cited the work of Jeffery Hall and Michael Roubash to justify my decision. This was not the first time that I had refused to medicate someone just prior to travel to another time zone.

My colleague pleaded with me that his friend was not covered by medical insurance in Europe nor in the United States. Hence he wanted to carry medication from India. I conceded reluctantly though emphasizing that he should not commence medication till he had crossed all the time zones and was under the supervision of a colleague in Washington. To my surprise and utter delight, next day the Nobel Prize Committee announced that the Prize in Medicine had been awarded to Jeffery Hall, Michael Roubash and Michael Young for their path breaking work on the genetics of chronobiology.

Quite simply, chronobiology is a field of biology that examines periodic physiological activities in organisms as a result of solar and lunar rhythms. The term is derived from the ancient Greek *chrónos,* meaning time and biology. Chronobiology research covers diverse disciplines such as comparative anatomy, physiology, genetics, molecular biology and behaviour within biological rhythms. Elsewhere in this issue, our colleague Nihar Mehta has compiled an excellent description of the pioneering work that was recognised with the Nobel Prize. Let us review some of its implications.

Chronobiology research has resulted in the recognition that functions of cell-based clocks play an integral and causative role in a variety of diseases. Recent research suggests a role for circadian rhythms in the mechanisms of some liver diseases, gastrointestinal disorders, and certain mental illnesses, particularly depression. Sleep disorders correlate with increased risk of weight gain, obesity and diabetes mellitus. The efficacy and side effects of chemotherapies vary based on the time of administration.

Almost certainly the commonest instance of chronobiology in our experience is jet lag. It results from the disruption caused in our physiological processes due to sudden changes in time zones and our exposure to light. This disruption can have pharmacodynamic effects. Hence my reluctance to prescribe an antidepressant to someone traversing multiple time zones. The last thing one would want is a depressed, exhausted, jet lagged banker with multiple side effects moving dizzyingly through important financial presentations.

Rajesh M. Parikh, M.D., D.P.M., D.N.B.
Director, Medical Research

Research News

Dr. Ambika Sharma won the First Prize for her oral presentation "Clinical profile and outcome of patients admitted with swine-origin influenza A (H1N1) virus infection at a tertiary care hospital in western India" at the 19th National Conference on Pulmonary Diseases (NAPCON2017) held at Kolkata in November 2017. (Abstract on Pg. 5).

Dr. Hemant Rathore won the RSNA Trainee Research Prize for his oral presentation "177 Lutetium PSMA Radioligand Therapy in patients with metastatic castration resistant prostatic cancers - Assessment of response, clinical evaluation, toxicity: First study in India" at the 103rd Scientific Assembly and Annual Meeting of the Radiological Society of North America (RSNA2017) held at Chicago, USA, in November 2017.

Dr. Poornima Shah presented an oral paper entitled 'Analysis of outcome of intraoperative neuromonitoring (IONM) at a metro hospital in India' at the 6th Asian-Oceanian Congress of Clinical Neurophysiology (AOCCN2017) held at NIMHANS, Bangalore in November 2017. This paper from India was highly appreciated as it was one of only two on IONM.

Abstracts

Temporary efficacy of pyrimethamine in juvenile-onset Tay-Sachs disease caused by 2 unreported HEXA mutations in the Indian population

Udwadia-Hegde A, Hajirnis O

Child Neurology Open 2017 Jan 17;4: doi:10.1177/2329048X 16687887.

BACKGROUND: Juvenile Tay-Sachs disease is rarer than other forms of Tay-Sachs disease and is usually seen in children between the age of 2 and 10 years. Pyrimethamine as a pharmacological chaperone was used to increase β-hexosaminidase A activity in this patient.

PATIENT: We describe a patient with Tay-Sachs disease from the Indian population, a juvenile case who presented with developmental regression starting at the age of three, initially with motor followed by language regression. She is currently incapacitated with severe behavioral issues.

CONCLUSION: This brief communication gives an insight into the efficacy of pharmacological chaperones. It also describes two unreported mutations in hexosaminidase A gene from the Indian population. After commencing Pyrimethamine, though initial benefits with increase in levels corresponded with briefly halting the motor regression, the observed increase was only transient and not associated with discernible beneficial neurological or psychiatric effects.

Course, outcome and complications in children with systemic onset juvenile idiopathic arthritis

Dewoolkar M, Cimaz R, Chickermane PR, Khubchandani RP

Indian Journal of Pediatrics. 2017,84:294-8.

OBJECTIVES: To assess the course, outcome and complications in a mono-centric cohort of 53 patients with systemic onset juvenile idiopathic arthritis (s-JIA).

METHODS: In an observational study, 53 consecutive patients diagnosed with s-JIA on or before October 2009 were enrolled and followed up between October 2009 and September 2012. At each 6-12 weekly visit, clinical examination, laboratory investigations and details of on-going treatment were recorded. Disease course was classified as monocyclic, intermittent and persistent. At last visit, outcome was studied with respect to remission (Wallace criteria) and Steinbrocker functional classification. Juvenile Arthritis Damage Index (JADI) was measured on a subset.

RESULTS: In 53 patients analysed, the mean follow-up period was 5.5 ± 1.85 y, with a cumulative follow-up period of 291.5 patient-years. The mean age at diagnosis was 6.3 ± 3.4 y. Thirty-three patients suffered from disease and/or drug related complications. Infections were observed in 16 (30%) and macrophage activation syndrome in 5 (9.4%). Nine (17%) had a monocyclic course, 31 (58.5%) had an intermittent course and 13 (24.5%), a persistent course. At last visit, 9/9 patients of the monocyclic group, 17/31 in the intermittent group and 3/13 in the persistent group were in remission. At the end of the study, 96.2% of the index patients were Steinbrocker functional class I and II with the monocyclic group having the best functional outcome. JADI was performed on 20/53 patients. Nine had significant articular damage. The range of Juvenile arthritis damage index-articular (JADI-A) was 0-25/72 (median-6) and of Juvenile arthritis damage index-extra articular (JADI-EA) was 0-4/17 (median-1).

CONCLUSIONS: The outcome of patients with s-JIA in a resource limited setting where early diagnosis, multidisciplinary care and availability of biologics are hurdles, is further altered by complications related to longstanding disease and over use of steroids.

Multicentric intradural extramedullary ependymoma: Report of a rare case

Vats A, Ramdasi R, Zaveri G, Pandya S

Journal of Craniovertebral Junction and Spine 2015,6:134-6.

Spinal ependymoma commonly presents as an intramedullary tumor. We present a rare case of multicentric intradural extramedullary spinal ependymoma. A 59 years old female presented to us with spastic quadriparesis for 10 months. Magnetic resonance imaging of the spinal cord showed discretely located enhancing tumor masses from at C1-C2, C6-C7, and D4 to L3 level. Subtotal resection of the symptomatic tumor at C6-C7 and D7-D9 was done. The patient underwent radiotherapy with 50.4 Gy. At follow-up of 11 months, patient is doing well. The relevant literature is reviewed.

Perianal Paget's disease-a case report and a review of current diagnosis and management.

Godbole C, Mehta J, Methil B, Palep R, Bhuta P

Indian Journal of Surgical Oncology. 2017;8:619-21.

Paget's disease is an intraepithelial adenocarcinoma arising from the apocrine gland component of the skin. Paget's disease is most common in the breast but extra mammary disease is also seen. Perianal Paget's disease is a rare form of extramammary disease with few cases reported in literature. It can be primary-arising from the skin or secondary-cutaneous metastases of anorectal or genitourinary malignancy. We hereby wish to report a case of perianal Paget's disease that presented as an eczematous lesion and was diagnosed incidentally on biopsy. After appropriate staging, the patient underwent wide local excision till negative margins were obtained. The resultant tissue defect was successfully covered by split-thickness skin grafting.

A phase II, single-arm, open-label, multicenter study to evaluate the efficacy and safety of P276-00, a cyclin-dependent kinase inhibitor, in patients with relapsed or refractory mantle cell lymphoma

Cassaday RD, Goy A, Advani S, Chawla P, Nachankar R, Gandhi M, Gopal AK

Clinical Lymphoma, Myeloma & Leukemia **2015,15:392-7.**

INTRODUCTION: Overexpression of cyclin D1 is a hallmark feature of mantle cell lymphoma (MCL). Many of the oncogenic effects of cyclin D1 are mediated through cyclin-dependent kinases (CDKs). P276-00 is a potent small molecule inhibitor of CDK4-D1, CDK1-B, and CDK9-T, with promising activity in preclinical models. In phase I studies of P276-00 in patients with refractory solid neoplasms, it was well-tolerated with a mild trend toward single-agent efficacy.

PATIENTS AND METHODS: A phase II study of P276-00 was conducted in patients with relapsed or refractory MCL at the recommended dose of 185 mg/m(2)/day from days 1 to 5 of a 21-day cycle. Thirteen patients were enrolled in the present study.

RESULTS: Of the 13 patients, 11 experienced disease progression, 1 patient was withdrawn because of an adverse event (AE), and 1 patient died. Also, 11 patients (84.6%) experienced a treatment-emergent AE deemed related to P276-00. Of the 13 patients, 9 (69.2%) received $\geq$ 2 cycles of treatment, which was the predefined threshold to be evaluable for efficacy. Treatment was discontinued early in 2 patients because of AEs (1 of which was attributed to P276-00 administration) and in 2 patients because of disease progression. Finally, 2 patients experienced stable disease for an estimated median duration of 60.5 days (range, 58-63 days). The estimated median time to progression for the predefined efficacy population was 43 days (range, 38-58 days).

CONCLUSION: Given the results observed in the present study, if evaluation of CDK inhibition in MCL continues, it should be considered earlier in the disease course or as a part of combination strategies for relapsed or refractory disease.

Diffuse large B-cell lymphoma in the era of precision oncology: How imaging is helpful
Shah HJ, Keraliya AR, Jagannathan JP, Tirumani SH, Lele VR, DiPiro PJ
Korean Journal of Radiology 2017,18:54-70.

Diffuse large B cell lymphoma (DLBCL) is the most common histological subtype of Non-Hodgkin's lymphoma. As treatments continues to evolve, so do imaging strategies, and positron emission tomography (PET) has emerged as the most important imaging tool to guide oncologists in the diagnosis, staging, response assessment, relapse/recurrence detection,and therapeutic decision making of DLBCL. Other imaging modalities including magnetic resonance imaging (MRI), computed tomography (CT), ultrasound, and conventional radiography are also used in the evaluation of lymphoma. MRI is useful for nervous system and musculoskeletal system involvement and is emerging as a radiation free alternative to PET/CT. This article provides a comprehensive review of both the functional and morphological imaging modalities, available in the management of DLBCL.

Clinical profile and outcome of patients admitted with swine-origin influenza A (H1N1) virus infection at a tertiary care hospital in western India
Ambika Sharma, R S Mathur (1st Prize at NAPCON2017)

BACKGROUND: Most of the studies on swine flu H1N1 have been done during the pandemic phase. The present study will help to assess the current status and pattern of H1N1 infection.

OBJECTIVES: Primary: To study the clinical profile of patients admitted with Swine-origin influenza A (H1N1) virus infection. Secondary: To study the clinical outcome in terms of morbidity and mortality.

METHODS: This is a retrospective observational study done at a tertiary care centre from March 2015 to April 2016. All admit confirmed cases of H1N1 swine flu infection were studied for demographic details, co-existing medical conditions, presenting symptoms and physical examination at admission. They were also observed for course and progression of disease, complications, treatments and outcomes.

RESULTS: Common presenting symptoms were cough and fever (95%) and signs were fever (62.5%), tachycardia, tachypnea and crepitation on auscultation (58.5%).Common comorbidities were Diabetes (19.5%), Chronic kidney disease (17%), immunosuppression (9.8%). Commonest radiological abnormality was consolidation seen in nearly half of the patients. Common complications noted in our patients were pneumonia (45%), respiratory failure (31%) and ARDS (14.6%). 17% patients required non-invasive and invasive mechanical ventilation. 24% required ICU admission and 2 patients died during the hospital stay.

CONCLUSION: The study emphasizes and restates the morbidities caused by swine flu as nearly half of the patients in our study experienced severe illness and complications from H1N1 swine influenza infection. Patients at high risk for severe disease and complications include patients with diabetes, chronic kidney disease and immunosuppressive states.

Nobel Prize in Physiology or Medicine 2017

Jeffrey C. Hall, Michael Rosbash and Michael W. Young were awarded the Nobel Prize in Physiology or Medicine 2017 for their discoveries of molecular mechanisms that control **circadian rhythms**.

Hall and Rosbash, collaborating at Brandeis University, and Young, at Rockefeller University, isolated and molecularly characterized *The Period Gene*, using mutants of the fruit fly Drosophilia that displayed alterations in their normal 24h cycle. A series of additional breakthroughs, from Hall, Rosbash and Young, including the identification of other genes that partner with Period gene, eventually led to the notion of a *Transcription-Translation Feedback Loop (TTFL).*

Further studies revealed a series of self-sustaining TTFLs that regulated protein phosphorylation, degradation, protein complex assembly, nuclear translocation and other post-translational modifications, generating oscillations with a period of ~24 hours. These circadian oscillators within individual cells respond to various physiological functions such as sleep patterns, body temperature, hormone release, blood pressure, and metabolism.

Ablation of circadian clock genes in animal models results in arrhythmic production of hormones, such as corticosterone and insulin. It can influence metabolism through the control of gluconeogenesis, insulin sensitivity and oscillation of blood glucose. Circadian dysfunction has been linked to sleep disorders, as well as depression, bipolar disorder, cognitive function, memory formation and some neurological diseases.

Disorders of our endogenous circadian clock may be associated with various diseases including cancer, neurodegenerative diseases, metabolic disorders and inflammation. Efforts are underway to develop approaches to modify the phase or amplitude of circadian clocks to improve human health.

The seminal discoveries by Hall, Rosbash and Young have revealed a crucial physiological mechanism explaining circadian adaptation, with important implications for human health and disease. Due to the seminal discoveries by the three laureates, elucidating a fundamental physiological process, circadian biology has developed into a vast and highly dynamic research field, with significant implications for our health and wellbeing.