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MANIPAL MEDICAL JOURNAL

SHARING KNOWLEDGE EMPOWERING CARE

A QUARTERLY PUBLICATION OF
MANIPAL HOSPITALS, NORTH WEST CLUSTER

EDITORIAL TEAM

From the Editor-in-Chief's Desk

As we enter into the third year of publishing Manipal Medical Journal (MMJ), I am delighted to have on board the consultants of Manipal Hospitals Pune, Patiala, Ghaziabad, Gurugram and Jaipur along with our core team at Manipal Hospital Dwarka.

We continue with our commitment of "Sharing Knowledge Empowering Care" as we showcase articles, case reports and interesting clinical developments. The volume has a new look and a new Editorial Board. It has been a wonderful journey bonding with clinicians across the Manipal Hospitals of North West Cluster as we share our common love for Academics.

With the new Editorial board we hope to improve academic content in coming years.

Wishing you all a very happy and safe new year.

Dr (Lt. Col) Leena N Sreedhar
Editor-in-Chief

Message From The Chairman

In general corporate hospitals are recognised as Centres of Excellence in delivering healthcare with some of the best talent in the field being there with exceptionally high-end technology and infrastructure available to help them practice their excellence in the field.

However, at Manipal Hospitals, we do believe in addition to having all of these, we also need to have a strong focus on academics and research. With Manipal Hospitals adding more hospitals to the group, we reiterate this commitment and I am glad that Vol.4 of Manipal Medical Journal will be released in January 2022.

I encourage all our consultants to actively participate in this program by sharing articles, case reports and interesting clinical developments and research articles in their field to this journal.

I wish Dr. Leena Sreedhar, HOD, Department of Academics & Research and the entire team of MMJ the very best in their endeavour.

Dr Sudarshan Ballal
Chairman – Manipal Hospitals
Manipal Health Enterprises Pvt Ltd

MESSAGE FROM OUR MD & CEO

Knowledge is the base on which all innovations are built. Dire situations of the last 18 months have compelled us to find new answers in each passing day. However, finding the answers also required a willingness to learn and adapt. I am glad that we as an organisation have consistently demonstrated these traits and I am very grateful to our clinical team for leading this effort from the front.

Clinical excellence has always been the core value for us at Manipal Hospitals. Through this journal, we wish to continue giving our doctors, researchers and associates a platform to share their expertise and knowledge to steer us to a future that is built on innovation, efficiency and resilience which is backed by a strong knowledge base.

Recently, we have seen our biggest expansion to date. Keeping in line with that vision, this journal stands true on our belief that we are #TogetherStronger. I am happy to note that the Editorial Board has been reconstituted to become more broad-based with clinical representations from all the hospitals. The Journal showcases some examples of outstanding clinical efforts that our team have made in the recent past.

Let us embrace the learnings and leverage the strength of the integrated teams to provide our patients with world class care backed by cutting edge intelligence. So, with “Sharing Knowledge and Empowering Care” as the theme, let us make this Journal a glimpse of what we can achieve when we stand together.

Yours Sincerely,
Dilip Jose,
MD & CEO, Manipal Health Enterprises Pvt. Ltd.

Table of Contents

SECTION	ARTICLES	PAGE NO.
COMMENTARIES	Turning Point of My Life - Randeep Wadhawan, Leena N Sreedhar, Lona Mohapatra	01
SPECIAL ARTICLES	Balancing Cardiac Morbidity with Thoracic Radiotherapy - Anusheel Munshi, Khushboo Rastogi	06
REVIEW ARTICLES	F-18 FDOPA and F-18 FDG PET CT Scan in Movement Disorders: Case Series with Literature Survey from a Tertiary Care Centre in India - Ankur Pruthi, Abhishek Behera, Harvinder Singh, Navjot Kaur, Parmeshwar Joshi, Yogender Rawath	10
	Current Practices in Pediatric Cardiology: Management of Holes in Heart. - Smita Mishra	19
	Vasoplegia in Cardiac Surgery – Not so Benign - Naresh Kumar Aggarwal, Arun Subramanian, Rakesh Kumr Solanki	25
CASE REPORTS	Cervical Ectopic Pregnancy Management – A Multimodality Approach - Yogita Parashar, Leena N Sreedhar, Harleen Saimbi	30
	Amlodipine Atenolol Poisoning in Emergency Room A Case Report - Malaya Kumar Mishra	35
	Type 5 Cardiorenal Syndrome in a Patient with Systemic Lupus Erythematosus - Ashish Nandwani, Saurabh Pokhriyal, Shailender Kumar Singh, Ajay Kumar	39
	Cervical Metastasis in a Case of Glioblastoma Multiformae - Jaskaran Singh, Jasleen Kaur	45
	Infant with Hypotonia with Rare Disorder: A Case Report - Sachin Jain	47

Table of Contents

SECTION	ARTICLES	PAGE NO.
CASE REPORTS	Role of Carbon Dioxide Angiography in Critical Limb Ischemia- A Case Report - Deepa Kizhakke Veetil, Nitish Anchal	50
	Early Intervention with ECMO in Severe Celphos Poisoning: A Case Report - Vipin Jain, Ram Sharan Chaturvedi, Amit K Singh	54
	Polyembolokoilamania: Urethral Self-inserted Electric Wire in a 20-year-old Boy - Yogesh Garg	58
	Osteochondral Autograft Transfer System (O.A.T.S.) for an Osteochondral Lesion of Talus-A Case Report - Gurdeep Singh Ratra, Pranshul Bishnoi	61
	Kanavel's 5th Sign - High frequency Ultrasound in Pyogenic Flexor Tenosynovitis in Diagnosis and Management of Tenosynovitis in a post-Covid 19 patient. - Gaurav Malhotra, Gaurav Rastogi, Simran Singh	66
	Anesthetic Management of Patient of Achalasia Cardia with Coronary Artery Disease for CABG - Rakesh Kumar Solanki, Naresh K Aggarwal, Yugal K Mishra	69
	A Rare Case of Wandering Fibroid: Case Report - Arti Mahla, Neha Godara	71
	Rare Refractory Multisystem Inflammatory Syndrome in Children (MIS-C): Case Report - Pranajli Deshpande, Ganesh Badge, Abhishek Zanwar, Prabhat Kumar	75
JOURNAL SCAN		80
5 STEPS IN CREATING YOUR DIGITAL MARKETING ECOSYSTEM		92
INFORMATION CORNER		95
INSTRUCTIONS TO AUTHORS		100

Turning Point of My Life

Dr. Randeep Wadhawan
Consultant & HOD, General & Minimally Invasive Surgery, Manipal Hospitals, Delhi

Friends, as I look back, several events in my life laid the foundation of my destiny.

I recall, very early in my childhood at the age of 7 years, on my visit to Haridwar with my parents, we happened to meet a Bhrigu Maharaj. I must confess my family does not follow or believe in gurus. However, this gentleman was highly recommended by friends and family members, hence I met him. It is natural for any parent to ask for the future of their child. He, after due calculations, mentioned that I would become a Surgeon one day. Now, this was very pleasing for the young parents, and on that day, my profession and future were sealed.

After that, I never had a chance to decide on any other profession, though I must admit that I enjoy being in this profession every day.

Another incident that comes to mind laid the foundation for my career in Laparoscopic GI Surgery. After completing post-graduation in the early '90s, I considered Urology a subspecialty to further pursue my career. At that time, I got the opportunity to work at Sir Ganga Ram Hospital (SGRH) in Minimally Invasive Surgery. Laparoscopy was still in a very nascent stage in India though SGRH had the unique distinction of having some of the pioneers in Laparoscopic surgery working with them. I got an excellent opportunity to learn & practice Laparoscopy with the leaders very early in my career, which interested and enthused me in pursuing this branch further.

Laparoscopy has evolved over years, and what began as a modality to treat benign disorders of the abdomen can now safely be used for most advanced GI surgical procedures, including Bariatric procedures and GI malignancies. In 2005, Bariatric surgery came to India and I had the opportunity to attend the first obesity surgery conclave held in Delhi. The burden of obesity and associated metabolic syndrome is enormous in the world, and India is no different. Obesity, weight loss and the surgical treatment of obesity interested me in pursuing this science further. At the time, I was already looking at newer challenges, having been performing a high volume of laparoscopic procedures for a decade. I traveled extensively to Europe and the US for several fellowships to learn all about this subject & associated procedures. In the next few years, I started a new Bariatric & Metabolic Surgery Department at a corporate hospital in Delhi. It was amongst the first few dedicated departments in the country and in a short period of time made it a Centre of Excellence accredited with the Obesity Surgery Society of India.

By 2015, my Department was well established in Laparoscopic GI & Bariatric surgery in the city and I was a National faculty and office bearer for major surgical societies in the country. At the time,

Intuitive- Da Vinci launched a new XI Robotic system. Again I had the urge to acquire knowledge and adapt to the new technology. I traveled to Sunnyvale (the head office of Intuitive) and Florida (Training center) in the US to get the certification and learn Robotic GI and Bariatric procedures from the pioneers themselves. The usage of Robotics in GI and Bariatric procedures is still evolving, but I do not doubt that it will play a significant role in the future.

In 2016, Abdominal Wall Reconstruction (AWR) was coming up in a big way for complex ventral hernias. This again motivated me to travel to University Hospitals, Cleveland, and again to Good Samaritan Medical Center, West Palm Beach town, USA, to learn and get fellowship in this new field. In the last 5 years, we have been one of the few Departments that perform these very complex and challenging ventral hernia surgeries.

My wife, a Director Professor and a unit head in Anaesthesia and Critical Care at Maulana Azad Medical College (MAMC) and associated hospitals have been a pillar of strength to me and our two boys. She ensured that I follow my passion for surgery and the zest to learn new and innovative techniques while she managed the home front and her career with aplomb. Both our boys have followed their dreams in choosing career options. Our elder son is pursuing M.S in Orthopaedics at MAMC, Delhi while the younger son a Computer Engineer is working in the Research and Development wing of Samsung along with being attached in research at IIT, Delhi.

Two and a half decades later, several fellowships abroad, a personal experience of more than 30,000 Laparoscopic, Robotic GI & Bariatric procedures, along with presently the Hon. Secretary of Obesity Surgery Society of India, Treasurer of Hernia Society of India, FALS Board convener and Executive council member of IAGES (Indian Association of Gastrointestinal Endosurgeons), Visiting Professor at IRCAD, Taiwan, Associate Editor of Journal of Bariatric Surgery and Editorial Board member of JMAS. I recall these events to have shaped my professional career.

Turning Point of My Life

Dr. (Lt. Col) Leena N Sreedhar
HOD, Department Of Academics & Research, Manipal Hospitals, Delhi

It was in the year 1976. I was 11 years old. My father, an army officer, was posted in Srinagar [J&K]. We were living in a civil area in a huge house owned by a Kashmiri businessman. There was no militancy then and the valley was peaceful. Nusrat was the beautiful daughter of our landlord whose wedding we attended. I remember our long conversations and discussing my ambition of becoming a veterinarian. Soon Nusrat was in the family way with twins. We were excited about this. All of a sudden in the

eighth month of pregnancy she died due to high blood pressure and its complications. As a school-going kid I was shocked. How could anyone die in labour? I gradually understood that the health infrastructure was quite bad in the valley. I shelved the idea of veterinary science [although I still care for animals] and decided to be a doctor. This was a turning point in my life.

There was no one in my family who was a doctor. Practically everyone was in the regular Army, Navy or Air force.

My father supported my decision and encouraged me. Thankfully I was a good student and got admission in a reputed medical college and it was in the year 1987 when I passed my MBBS from Maulana Azad Medical College, New Delhi. Ours was the first batch allowed to appear for MD/MS entrance exam right after internship. I expressed my desire to be an Obstetrician-Gynaecologist. A lot of relatives and friends told my father "It is too demanding a speciality! Why are you letting her opt for Obs & Gynae? She has a good rank. Let her take something else. How will she manage her home when she gets married?"

I still remember my father clearly saying "She will do whatever she wants". Indeed a turning point in my life.

In those days we never disagreed with parents. So it was great getting his approval and strengthened my resolve to do well in my chosen career.

Safdarjang Hospital, the largest maternity hospital in Asia proved to be a great training ground and despite the hard work and sleepless nights I enjoyed it ! When you love your work it ceases to be work!

I married an army doctor in my second year of post-graduation and after completing senior residency decided to do a short service in the Army Medical Corps. So from Safdarjang Hospital I went to various army hospitals and in many places I was the only gynaecologist. It made me more determined to be a competent gynaecologist as I realised the problems women of our jawans and officers face in far flung areas. I was fortunate to have an understanding and supportive husband who helped me bring up 2 children and we spent quality family time as we moved from army hospitals in Pune, Jammu, Kolkata, Udhampur and Chandigarh.

After 10 years in the Army Medical Corps I left that wonderful organisation so as to be in one place and help my children pursue their higher studies. That was again a turning point as I was hurled into the competitive world of private practice. I enjoyed every bit building my practice as I settled down in Delhi. My son did his Engineering and is now a Physicist in the United States while my daughter did Medicine and is now working towards her MS in Obstetrics and Gynaecology.

Life brings choices and turning points and it is really upto us to work it to our advantage and enjoy it!

Turning Point of My Life

Dr. Lona Mohapatra
Consultant & Laboratory Director, Manipal Hospitals, Delhi

Can you imagine if you didn't have any turning points in life? There would be no Ah-Ha's. Nothing would awaken you and cause you to look deeply at your life. You wouldn't have a chance to make a choice to change for the better. There would be no one moment or event or circumstance you can point to and say that's the day I knew I had a choice to make.

A turning point might come in the form of an epiphany—a vision. Or, a gentle tap on the shoulder. On the other hand, it might not be so tender at all—perhaps it's an unmistakable shove in a new direction.

Regardless of how you experience it, you can look back on it and say, if it were not for that circumstance or that person, I would not be where I am today! And I'm happier, more confident, and stronger than ever!

Turning points have that kind of power to transform.

For me, it is difficult to define an exact moment in my life that was a turning point. In my opinion, for every situation we have to draw conclusions and make useful lessons. I have met a lot of people in this long journey and they are all different, as well as their way of life and their outlook on life. Some of them learn from their mistakes and constantly use their own life experience, while others fall under the influence from the external side. These could be our parents, friends or mass opinion, which we all are constantly pressed by TV screens, magazines, newspapers, and internet.

I think that most people try to live in accordance to a well-defined pattern that is already fixed. For instance, we have to be good at school, then we should enroll in a prestigious university, get a well-paid job. But despite these seemingly positive directions, there are a number of negatives. All of them can be seen in films. We can notice as young people smoke, drink alcohol, and spend most of their free time partying, concerned about their appearance etc.

I personally believe that in every human's life there are turning points that change their outlook, change attitudes, interests, attitudes towards life and other people.

Being an army officer's kid, my childhood was spent in various cantonments with the vast experience of attending six different schools. Since the age of seven or eight, my grandfather started calling me Dr Lona. I am what I am only for my Baba. So the first major turning point in my young life was getting into medical school. Graduation and post-graduation happened subsequently. Was wed to an upright and competent civil servant. First posting was in Ahmednagar. In addition to my regular job in the sarkari hospital, I took care of the soldiers and their families in Mechanized Infantry and Armoured Corps Centre. This was indeed a very pleasant turning point where I could fulfill my dreams of working in the “Fauj” even though it was just temporary.

In the civil too, we lived a nomadic life shifting from one district to another, quite happily meeting new people, making new friends, learning new things.

The next significant phase in life was that of motherhood - my bundle of joy, my lifeline and later, motherhood renewed with my second born. Those were the most wonderful feelings. The best turning point I would say!

The journey has been long and arduous with special and sweet memories.

I feel blessed, life's treated me well.

It is strange, but true, that the most important turning-points of life often came at the most unexpected times and in the most unexpected ways

They say when you reach a crossroad or a turning point in life, it really doesn't matter how we got there, but it's what we do next after we got there. Usually you arrive there by adversity, and then it is then and only then that we find out who we truly are and what we're truly made of. It's a process, a gift and a journey, and if we can travel it alone, although the road may be rough at the beginning, you find an ability to walk it. A way to start fresh again. It's neither a downfall nor a failure, but a new beginning!

Some turning points are staggering experiences; others are teaching moments, and if we're lucky, some lead us to fulfill our purpose in life. Under which category do your turning points fall?

Manipal Hospitals Logo Launch - North West Cluster

Balancing Cardiac Morbidity with Thoracic Radiotherapy

Anusheel Munshi[A], Khushboo Rastogi[B]

[A] Head, Department Of Radiation Oncology, Manipal Hospitals, Delhi

[B] Clinical Specialist, Department Of Radiation Oncology, Manipal Hospitals, Delhi

Introduction

Cardiac toxicity is a concerning side effect of anti-cancer therapy. The gain achieved by anti-cancer treatment in terms of life expectancy can be compromised by increased morbidity and mortality associated with cardiac complications. Currently, heart is one of the most critical dose-limiting organs in radiotherapy especially in thoracic and breast malignancies.

A high dose of radiation to thorax is mainly seen in the context of adjuvant radiotherapy after conservative or radical breast surgery, adjuvant or definitive radiotherapy for lung and esophageal cancer and as a complement to systemic therapy in lymphoma. Thoracic radiotherapy increases the risk of incidental irradiation of heart, thereby increasing the risk of radiation induced heart disease (RIHD). The manifestations of RIHD most often become clinically apparent several years after radiation therapy. RIHD can have a wide range of negative effects on the heart like coronary artery disease (CAD), pericarditis, myocardial infarction (MI), valvular heart disease, arrhythmias, non-ischemic MI and conduction system abnormalities. Presence of risk factors such as obesity, physical inactivity, substance abuse (tobacco and alcohol) can further accelerate and worsen the implications of RIHD.

Many clinical trials have identified adverse clinical consequences of radiation-induced heart disease (RIHD) on the outcome of long-term cancer survivors. [1,2]

Current knowledge about radiation effects on heart have mainly been studied on animals. [3] Furthermore, the transition from acute cardiac injury to progressive cardiac disease and the relation between short term cardiac effects and long term risks are still not well understood. [2]

Risk factors for RIHD [4,5]

- Anterior or left chest wall irradiation
- High overall dose of radiation (>30 Gy)
- Young patients (<50 years)
- High dose per fraction of radiation (>2 Gy/fraction/day)
- Presence or extent of tumour in or next to heart
- Lack of cardiac shielding
- Chemotherapy (anthracyclines, traztuzumab)
- Cardiovascular risk factors (i.e.

smoking, diabetes mellitus, overweight, ≥ moderate hypertension hypercholesterolemia)

- Pre-existing cardiovascular disease

Mechanism of RIHD

Radiation induced injury to the heart occurs via three mechanisms namely, endothelial injury and dysfunction, macrovascular injury and microvascular injury. Post radiotherapy, the early events in the cascade are loss of endothelial cells with subsequent inflammatory responses. [6-8] Microvascular damage is a critical insult that is associated with eventual fibrosis and diastolic dysfunction and heart failure. Primary radiation fibrosis is also a well-known pathological feature of late sequelae of radiation [9,10] Micro and macro vascular damage also includes accelerated atherosclerosis and leads to endothelial dysfunction and coronary artery stenosis. [2,11,12]

Limiting the heart dose

The heart is now identified as an organ at risk (OAR) and contoured routinely in radiotherapy practice. Current guidelines recommend reducing dose to the whole heart or pericardium. Existing cardiac dose constraints used in daily clinical practice are based on Qualitative Analysis of Normal Tissue Effects in Clinic (QUANTEC) [13] and these are derived majorly from studies in patients with esophageal cancers and lymphoma. As per QUANTEC, volume of heart receiving greater than or equal to 30Gy should be below 46% (V30 ≤ 46%) and mean heart dose (MHD) should be kept below 15Gy. However, QUANTEC had drawbacks as it did not take into consideration studies for patients with lung cancer. Furthermore, challenges in delineation of cardiac substructures as well as dose to the same, patient and treatment risk factors and dose-volume dependence for cardiac toxicity were not taken into account. In contrast, Darby et al [14] reported that the risk of MACE (defined as MI or death from IHD) in survivors of breast cancer survivors increase linearly with respect to cardiac radiation dose, even at low dose levels. The rate of MACE increases by 7.4% (relative) per one gray increase in MHD.

Cardiac substructures – role in RIHD

To date, there are controversies on whether to reduce the dose to whole heart or the substructures. Several cardiac contouring atlases have also been developed with the aim of consistent dose reporting in clinical practice and trials. Several studies have shown that dose to left ventricle and coronary arteries are more relevant in terms of assessing cardiac toxicity. Recently, emerging data has shown that dose to cardiac substructures are more important than dose to the entire heart. Heart is comprised of substructures with different physiological functions. These substructures have been found to be associated with cardiac events or mortality [15-17] Cardiac substructures found to be significantly associated with cardiac events or overall survival include aortic valve, left atrium, left anterior descending coronary artery, left ventricle, pulmonary artery, right atrium, right coronary artery, right ventricle and superior vena cava.

Preventing RIHD

History of cardiovascular disease is a predictor for cardiac events after thoracic radiotherapy and thus, risk factor modification is crucial in these patients before and after thoracic radiotherapy. This includes cessation of smoking, control of blood sugar, and lowering of blood pressure and lipid profile. Radiation dose received by the heart is another modifiable risk factor. There is emerging evidence that clinical benefit could be found with defined heart avoidance regions and tolerance doses combined with improved image-guided radiotherapy. A daily on-treatment imaging strategy has been found to improve patient survival. [18] Several advanced radiotherapy technologies can be considered to further reduce the radiation dose to the heart. For example, deep inspiratory breath hold (DIBH) can increase lung capacity and reduce tumor motion. MR-guided radiation therapy has the potential to allow reduced planning target volume (PTV) margins and reduced heart dose. In the context of lung cancer, proton beam therapy (PBT) has been proposed as a modality to reduce MHD and spare more cardiac volume at all dose levels compared with intensity modulated radiotherapy, particularly at low-dose levels. [19] However, convincing clinical data regarding the incremental benefit of proton therapy in this scenario is awaited.

Conclusion

To conclude, thoracic radiotherapy is known to cause a variety of cardiac damage through inflammatory pathways as described above. To have a better understanding of RIHD, several issues should be addressed. A major limitation of existing literature on cardiac toxicity is that the published work consists of small, retrospective or single institute studies. Lastly, a better understanding about various cardiac substructures in terms of identification and delineation of the same, incorporation of echocardiography, electrophysiological and cardiac perfusion studies as well as collaboration of radiation oncologists and cardiologists are needed.

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F-18 FDOPA & F-18 FDG PET CT Scan in Movement Disorders: Case Series with Literature Survey from a Tertiary Care Centre in India

Ankur Pruthi[A], Abhishek Behera[B], Harvinder Singh[C], Navjot Kaur[D], Parmeshwar Joshi[D], Yogender Rawath[D]

[A] Consultant & HOD, Department Of Nuclear Medicine & PET CT, Manipal Hospitals, Delhi

[B] Associate Consultant, Department Of Nuclear Medicine & PET CT, Manipal Hospitals, Delhi

[C] RSD, Department Of Nuclear Medicine & PET CT, Manipal Hospitals, Delhi

[D] Technologist, Department Of Nuclear Medicine & PET CT, Manipal Hospitals, Delhi

Abstract

Positron emission tomography or PET provides a comprehensive range of imaging agents supporting the clinical diagnosis of movement disorders. PET imaging has focused on the assessment of neurotransmitter systems, predominantly the dopaminergic system. Additionally, PET imaging with F-18 Fluorodeoxyglucose (F-18 FDG) has been used extensively to assess local synaptic activity and changes in glucose metabolism in movement disorders. PET imaging has provided us with diagnostic agents for evaluation of novel treatment options. It has also served as an effective means for understanding pathophysiological changes at various stages of movement disorders.

Introduction

Movement disorders constitute a spectrum of neuro-degenerative disorders affecting balance, posture, movement, intellect, memory etc. Predominantly, these disorders are divided into two main categories, Idiopathic Parkinson's Disease (IPD) and Atypical Parkinsonian Syndromes.

Idiopathic Parkinson's disease is caused by nigro-striatal degeneration and is characterised by bradykinesia, resting tremors, postural instability and rigidity. Patients usually demonstrate good response to dopaminergic treatments. Atypical parkinsonian syndromes comprise of multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and diffuse lewy body dementia (DLB). Patients usually demonstrate poor treatment response with dopaminergic agents such as levodopa. Early and accurate diagnosis is fundamental for both as prognosis and treatment options differ substantially between IPD and atypical parkinsonian syndromes. [1]

PET is a useful imaging modality to visualize pathophysiological changes in various movement disorders. Over the last few years, PET imaging has provided multiple diagnostic agents for treatment response evaluation, and has served as a potent means for evaluating different stages of movement disorders. The combined PET and CT imaging in modern PET CT scanners provide improved image quality and localisation of site of abnormal radiotracer uptakes.

F-18 FDG is used for the assessment of regional cerebral glucose metabolism. It is a useful marker of neuronal function as well as post-synaptic activity. F-18 FDG PET has become an integral part in the diagnostic work-up of patients with neurodegenerative disorders, most notably dementia. The role of F-18 FDG PET for differential diagnosis of parkinsonism has been well recognised in last few years.

F-18 FDOPA or Fluorodopa is another useful radiopharmaceutical to evaluate the first step in dopaminergic transmission, namely dopamine synthesis, which takes place in the "presynaptic" dopaminergic neurons. There is significant reduction of FDOPA striatal uptake in PD patients compared to control subjects.

Analysing the radiotracer uptake patterns in both F-18 FDOPA PET (pre-synaptic) and F-18 FDG (post-synaptic) scans helps us in reaching the early and accurate diagnosis of various movement disorders. (Figure 1) An illustrative F-18 FDOPA PET CT scan image of an asymptomatic control elderly male is shown for reference. (Figure 2)

This case series intends to highlight the advantage of these imaging modalities in diagnosing, prognosticating and choosing effective treatment options for patients suffering from various movement disorders.

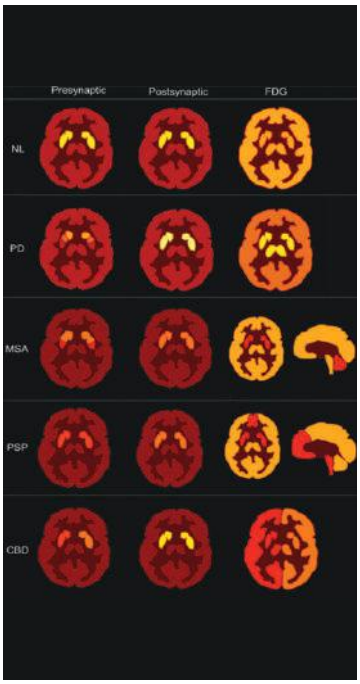


Figure 1 : Illustration of main findings in movement disorders with presynaptic (left) & postsynaptic dopaminergic (middle), & FDG PET imaging. Bright areas (Bright yellow) depict areas of hyper metabolism, whereas dull areas (pink/ red) depict hypo metabolic areas

(Source: Berti et al, Author manuscript; Ann N Y Acad Sci. 2011 June; 1228: 93–108). [2]

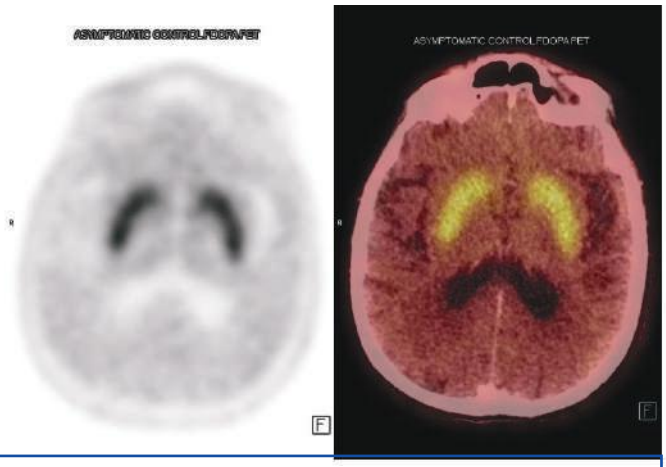


Figure 2 : F-18 Fluorodopa PET CT scan of the brain in an asymptomatic elderly male showing symmetrical radiotracer uptake in bilateral basal ganglia.

Material and methods

F-18 FDG and F-18 Fluorodopa (FDOPA) PET CT scans of the brain are performed on separate days in our department. FDG PET brain was available since the inception of the department in 2018, however, FDOPA PET scans were introduced lately in August 2019, after the commercial availability of this radiopharmaceutical. We have performed 40 F-18 FDOPA PET scans in our

department from August 2019 – April 2021 for various clinical indications of which 35 scans were done to evaluate movement disorders. We hereby present few interesting cases, where the application of these PET scans led to changes in clinical diagnosis and management.

Results
Idiopathic Parkinson's disease (IPD)

Clinically, IPD is characterized by resting tremor, bradykinesia, rigidity, and postural instability. Other clinical criteria supporting IPD are the response to dopaminergic treatments, asymmetric onset of symptoms, and the absence of atypical signs suggesting other forms of Parkinsonism. [3]

In IPD patients, FDOPA PET CT scan demonstrates asymmetrically reduced radiotracer uptake in bilateral basal ganglia with a rostro-caudal gradient (putamen affected more compared to caudate nucleus). F-18 FDOPA uptake correlates with clinical disease severity and disease progression, showing 8–9% annual decline in uptake in the putamen and 4–6% decline in caudate nucleus of clinical PD patients. [4, 5]

FDG PET CT scan shows a pattern of relative cortical hypo metabolism, particularly involving temporo-parietal regions with increased metabolism in the basal ganglia, thalamus and primary sensory-motor cortices. [6, 7] (Figure 1)

Case A:

61 year old / male, presented to the neurologist with complaints of right upper and lower limbs tremors, rigidity, stiffness in back and lower limbs with bradykinesia since last 1-2 years. He was underwent F-18 FDG and F-18 FDOPA PET CT scan for evaluation. The images of FDOPA PET and FDG PET scans are shown in Figure 3. Patient was started on Syndopa plus medication and he showed improvement.

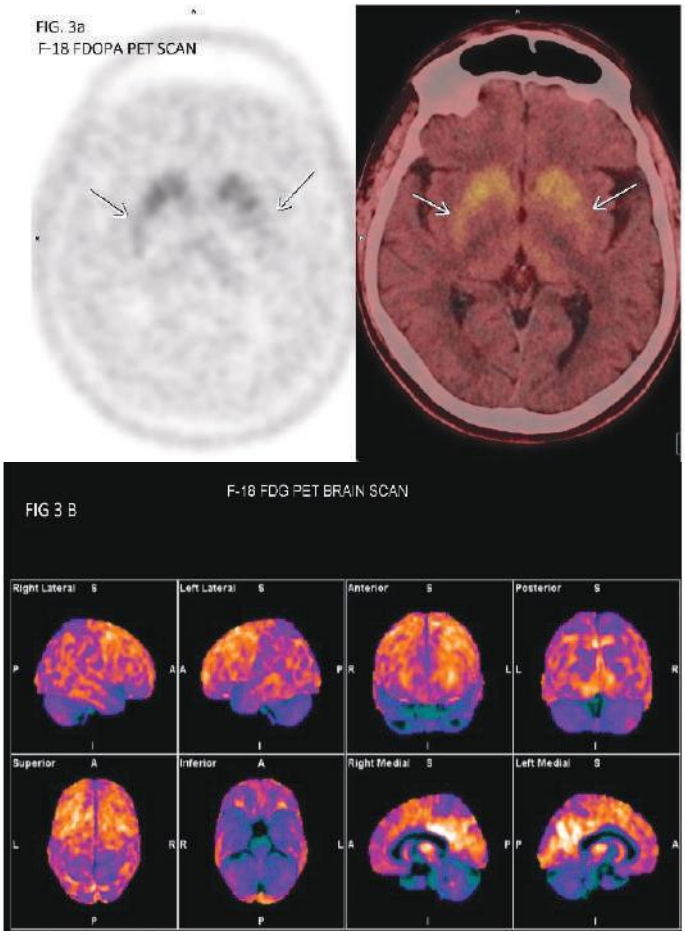


Figure 3 : F-18 FDOPA PET CT scan (fig. 3a) showing asymmetrically reduced radiotracer uptake in bilateral basal ganglia (left more than right) with putamen affected more than caudate nucleus. FDG PET scan (fig. 3b) showing mild diffuse hypometabolism in bilateral temporo-parietal regions of the brain with preserved uptake in the bilateral basal ganglia, suggestive of Idiopathic Parkinson's disease (IPD).

Case B:

53-year-old man presented to the neurology department with complaints of

slowness of activities of daily living with insidious onset since last 1 year. On examination, reduced arm swing was noted on the left side with mild postural instability. There was no resting tremor or history of falls. The images of the FDOPA PET and FDG PET scan scans are shown in Figure 4. He was diagnosed as a case of IPD, was started on Syndopa plus medication and he showed improvement.

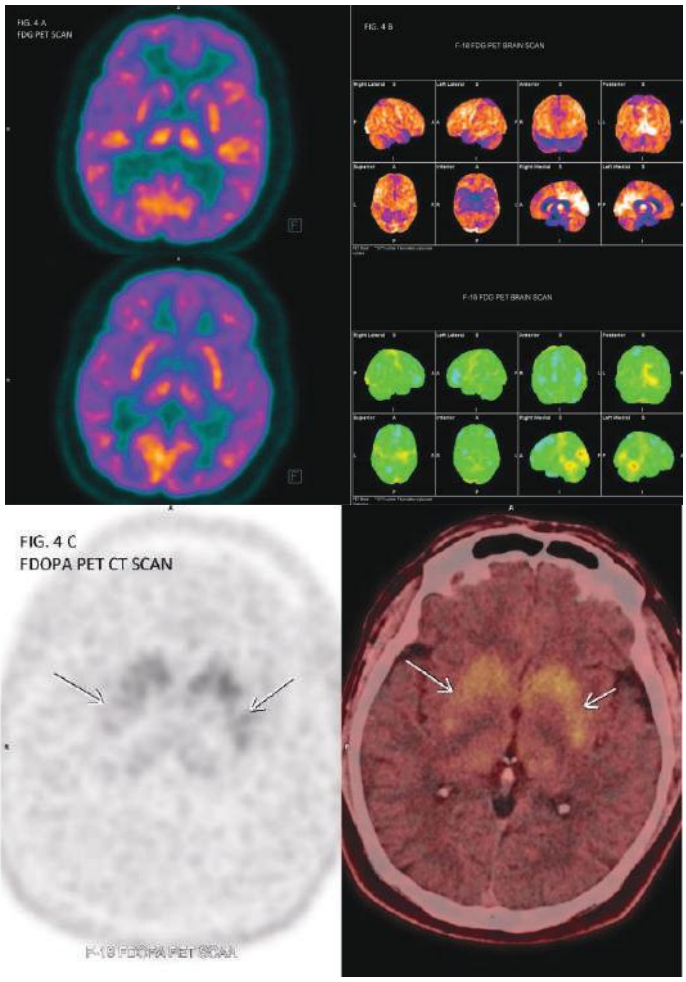


Figure 4 : FFDG PET scan (Fig. 4a & b) demonstrates mild hypo metabolism in bilateral parietal and temporal cortices with preserved tracer uptake in bilateral basal ganglia. FDOPA PET scan (Fig. 4c) shows asymmetrically reduced FDOPA uptake in bilateral basal ganglia (right more than left) with putamen more severely affected than the caudate nucleus.

Progressive supranuclear palsy (PSP)

Progressive supranuclear palsy (PSP) is an akinetic-rigid syndrome clinically characterized by early postural instability with history of falls, supranuclear vertical gaze palsy, Parkinsonism not responsive to levodopa treatment, and dementia. [8]

Striatal FDOPA uptake is reduced in PSP patients, with similar uptake reductions in the putamen and caudate. [9] F-18 FDG PET studies in PSP patients show diffuse reductions in uptake, mostly involving the frontal cortex, particularly in midline frontal areas, basal ganglia, brainstem [10] and anterior cingulate, motor and premotor cortex, striatum, and thalamus. [7,11]

Case C:

64-year-old male presented to neurology department with complaints of postural instability with history of recurrent falls, bradykinesia, axial rigidity, cognitive decline and behavioural changes. His FDOPA PET and FDG PET brain scan images are shown in Figure 5.

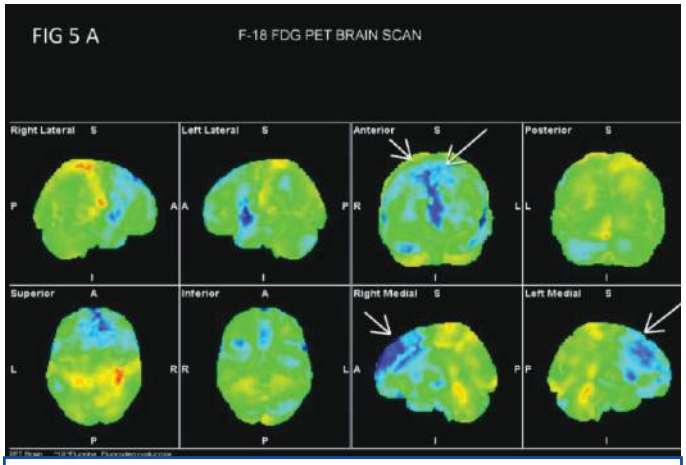
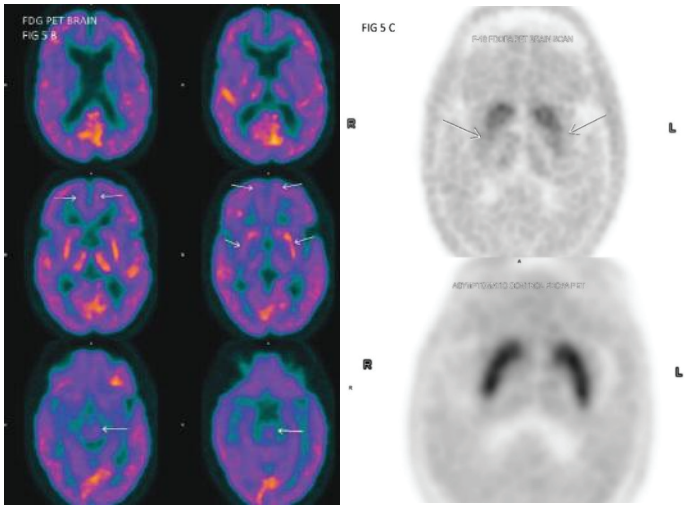


Figure 5 : FDG PET scan (fig. 5a & 5b) findings are suggestive of mild hypo metabolism in bilateral frontal cortices in the midline including anterior cingulate, bilateral temporal lobes, bilateral basal ganglia, thalami and

midbrain (white arrows). FDOPA scan findings (fig. 5c) demonstrate symmetrically reduced dopamine synthesis in bilateral basal ganglia. He was diagnosed as a case of progressive supra-nuclear palsy (PSP). Patient developed complaints of dysphagia and neck pain & rigidity on follow-up.



Case D:

60 year old male presented with complaints of recurrent vertigo, akinetic-rigid syndrome, slurred speech with bradykinesia. He was dependent in all activities of daily living. His FDOPA PET and FDG PET brain scan images are shown in Figure 6.

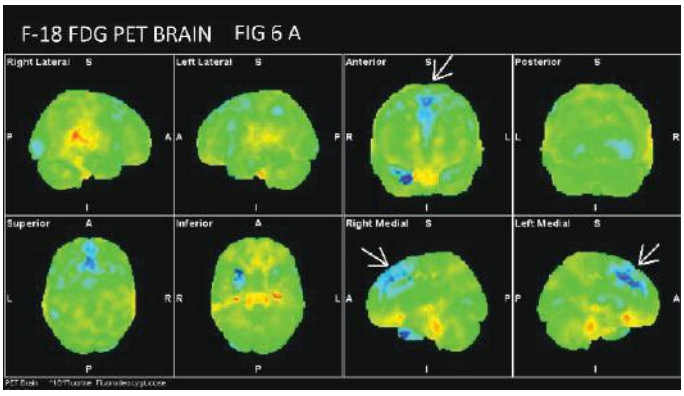
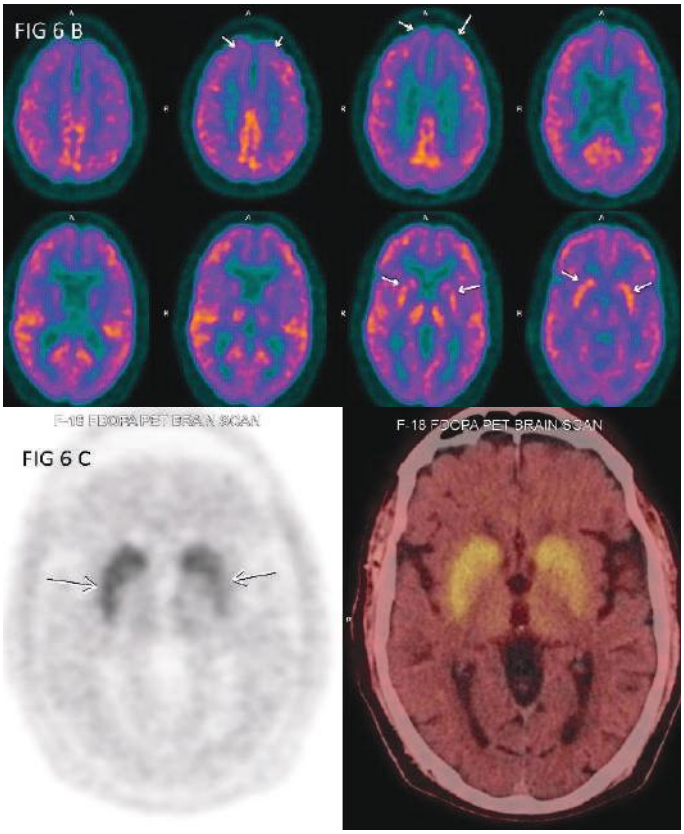


Figure 6 : F-18 FDG PET scan (fig. 6a and 6b) findings are suggestive of mild hypo metabolism in bilateral basal ganglia, bilateral frontal cortices in the midline including anterior cingulate and bilateral parieto-temporal lobes. F-18 FDOPA scan (fig. 6c) findings are suggestive of symmetrically reduced dopamine synthesis in bilateral basal ganglia. He was diagnosed as a case of progressive supra-nuclear palsy (PSP).



Multisystem atrophy (MSA)

Multiple system atrophy (MSA) is the most common among atypical parkinsonian disorders, and is most frequently misdiagnosed. Clinical features include Parkinsonism, autonomic dysfunction, cerebellar ataxia, and pyramidal symptoms. [12] Parkinsonism prevails in 80% of patients (MSA-P subtype) and cerebellar ataxia (ataxia, dysarthria, oculomotor cerebellar symptoms) in 20% of patients (MSA-C subtype).

F-18 FDOPA studies report severe reductions of striatal uptake in MSA (30% in putamen and 10% in caudate nucleus) compared to healthy subjects. [9, 13-15] F-18 FDG PET studies in MSA showed significant metabolic reduction in the striatum, particularly in the putamen, as well as in the brainstem and cerebellum,

when compared to both normal subjects and patients with IPD. [6,7, 16-18]

Case E:

70-year-old female patient presented to the neurologist with complaints of weakness right half of body, resting tremors, dysarthria, postural instability with history of multiple falls, urinary incontinence and visual/auditory hallucinations. She was bed-bound since onset of illness and was dependent in all activities of daily living. She underwent F-18 FDG and F-18 Fluorodopa PET CT scans. (Figure 7)

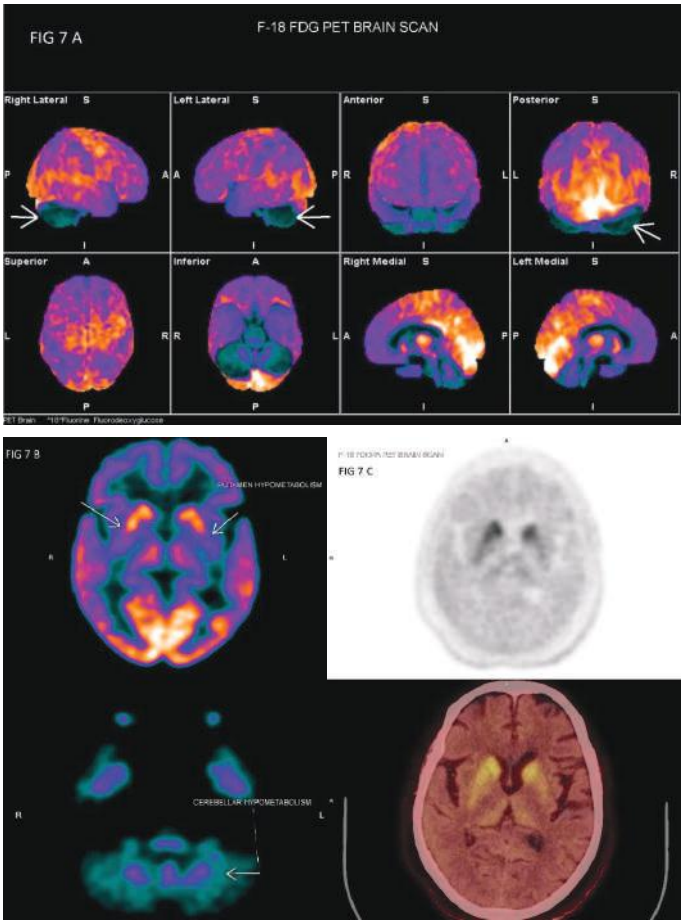


Figure 7 : FDG PET scan (fig. 7a & 7b) findings showed severe hypo metabolism involving bilateral basal ganglia (putamen much more than caudate) and bilateral cerebellar hemispheres (white arrows). FDOPA scan (fig. 7C) findings demonstrated reduced dopamine concentration in bilateral basal ganglia with putamen more severely affected than the caudate. She was diagnosed with Multisystem atrophy or MSA. She was started on Syndopa plus. Her course was stable at the time of collection of data for this review.

Cortico-basal syndrome

Cortico-basal degeneration (CBD) is an adult-onset progressive neurodegenerative disorder characterized by cortical and basal ganglionic degeneration. The cardinal manifestations of CBD include motor symptoms that are typically asymmetric at early stages and similar to those seen in PD (i.e., rigidity, bradykinesia, and tremor). Patients with advanced disease show a progressive decline of cognitive function. [19]

F-18 FDOPA PET studies performed in early CBD patients show more severe reductions of tracer uptake in the putamen, while uptake in the caudate nucleus is relatively preserved [20]. On F-18 FDG PET, CBD patients present with asymmetrical cortical and subcortical hypometabolism, affecting the hemisphere contralateral to the first affected limb [21, 22].

Case F:

62-year-old male patient presented with significant cognitive decline, postural instability, gait imbalance with recurrent falls, since last one and a half years. He demonstrated significant rigidity on the left side of the body. Patient also had a history of emotional lability, lack of interest and incontinence. FDG PET scan of the brain was done for further evaluation. (Figure 8)

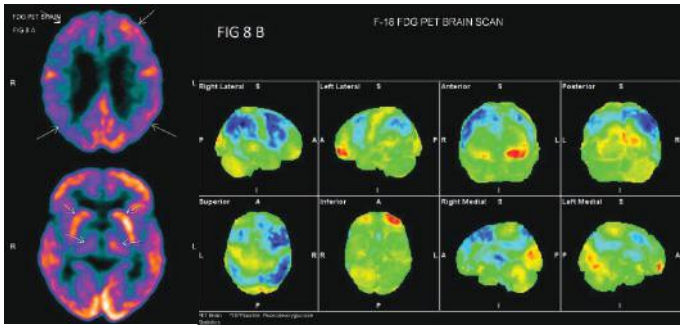


Figure 8 : FDG PET brain scan (figure 8a and 8b) demonstrate asymmetric hypo metabolism in bilateral cortical and subcortical structures

including the basal ganglia and thalami (right more than left). This patient was diagnosed as a case of cortical basal syndrome.

Cases where Fluorodopa and FDG PET CT scans ruled out Parkinsonism and provided an alternative diagnosis

Case G:

65-year-old female patient presented with difficulty in walking with a history of falls, bradykinesia, rigidity and urinary incontinence. FDOPA PET scan is shown in Figure 9.

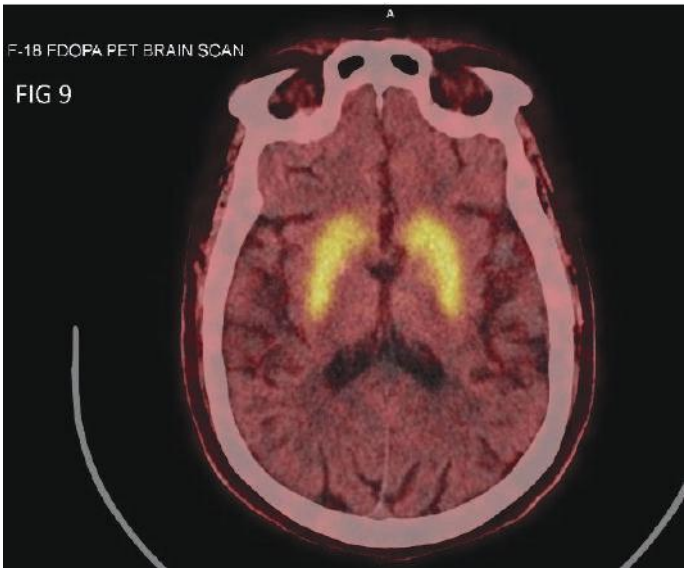


Figure 9 : FDOPA PET scan shows "preserved dopamine concentration" in bilateral basal ganglia thereby ruling out parkinsonian pathology. Cerebellar pathology was given as differential diagnosis for this patient.

Case H:

72-year-old male patient presented with complaints of bradykinesia with postural tremors of bilateral upper limbs. FDOPA PET scan is shown in Figure 10.

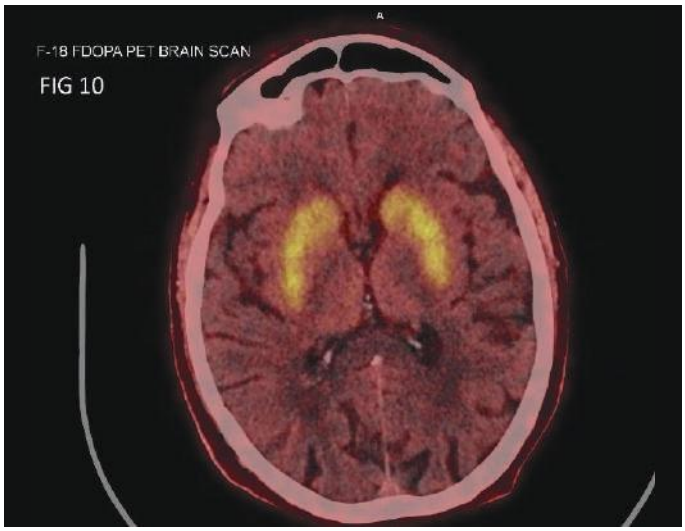


Figure 10 : FDOPA PET scan shows "preserved dopamine concentration" in bilateral basal ganglia thereby ruling out parkinsonian pathology. A diagnosis of Essential tremors was made.

Discussion

F-18 FDG PET has been used extensively to study various neuro-degenerative disorders including dementia, parkinsonism etc. in the past. The various scan patterns obtained on FDG PET imaging in parkinsonian disorders have been published extensively in the past. F-18 Fluorodopa PET is a relatively newer modality, which is now commercially available in our country since last 2 years. Currently, the data suggesting exact clinical role of FDOPA PET in movement disorders appear limited. However, with wider yet judicious use of FDOPA PET scan in this group of patients, guidelines for its appropriate use in various clinical situations will emerge.

The combination of F-18 FDOPA and F-18 FDG not only helps us in reaching an accurate diagnosis but also helps in understanding the pathophysiology and prognosis of these disorders. Another important role of FDOPA PET scan is to rule out parkinsonian pathology in cases of

Drug-induced Parkinsonism, Essential tremors etc. At present, the therapeutic options for various Parkinsonian syndromes appear limited. However, multiple clinical trials and drug-development studies are underway. Hence, accurate selection of patients for various clinical trials is another potent application of these imaging modalities.

This case series intends to generate wider awareness and acceptability among neurologists, geriatric care specialists and general physicians regarding the use of FDOPA PET scan for evaluation of movement disorders. The authors also felt an unmet need of a non-invasive gold standard for accurately diagnosing various movement disorders. The commercial availability of newer radiotracers such as tau and amyloid imaging agents in the near future may help us in more effectively evaluating various neuro-degenerative disorders.

Conclusion

FDG and FDOPA are useful imaging modalities for diagnosing, prognosticating and deciding treatment strategies for patients suffering from various movement disorders. These methods can also help detect the onset of brain pathology, identify people likely to develop Parkinson's disease, provide a measure of disease progression, help in patient selection for various clinical trials and thereby helping in drug-development.

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Current Practices in Pediatric Cardiology: Management of Holes in Heart

Smita Mishra

HOD Ped Cardiology, Manipal Hospitals, Delhi

Keywords: Hole, shunt, ASD, VSD, PDA, AP window, PA pressures, pulmonary hypertension

Introduction

"Hole in heart" or isolated shunt lesions are commonest of congenital heart diseases (CHDs). They can be treated with low morbidity and mortality if detected on time and before a comorbidity like pneumonia sets-in. A group of patients may grow in total oblivion of their problems due to two reasons:

Disease was milder to begin with and effective hemodynamic changes came into play later;

Lack of clinical suspicion and complimentary diagnostic facilities.

According to the limited statistics available in our country, 7-10 babies per 1000 live birth, are born with cardiac problems. If we see the western data, the early neonatal deaths are heavily contributed by congenital cardiac defects. About 3% neonatal death or 10% of mortality in otherwise healthy term newborns can be attributed to heart defects.

Hemodynamics of Hole in Heart

As mentioned above, 'hole in heart' is a generalized term for the group of CHDs known as shunt lesions. In presence of a larger shunt lesion, pulmonary blood flow is almost double of systemic flow (high Qp:Qs Ratio). Pulmonary artery pressure is 1/5th of aortic/systemic pressure. In presence of a post tricuspid shunt (VSD, AP window or PDA), systolic lung pressure equals to aortic pressure but diastolic and mean pressures remain low for a while. This condition is called as the hyperkinetic pulmonary hypertension. If the lesion is not corrected, slowly pulmonary vasculature stops accommodating blood volume due to the medial and intimal changes of arterioles. This condition is known as obstructive PAH. If that happens, desaturated systemic venous blood start entering into the aorta bypassing the lungs, leading to the systemic desaturation. This condition is known as Eisenmenger syndrome.

Anatomical basis of the Shunt lesions (Holes in Heart)

Heart is a four chambered structure with shared wall at atrial, ventricular and proximal arterial levels. The aorta, main pulmonary artery (MPA) and proximal right pulmonary artery.

In fetal life descending aorta communicates with PA through the ductus arteriosus. Postnatally pulmonary vasculature provides the site for oxygenation. It receives systemic venous blood which has SpO2 of 60-65%.

Pulmonary pressures are low (25/0-5 / mean < 15 mm Hg) in comparison to aorta (100-120/60-80 / mean of 70-95 mm Hg).

Fetal placenta plays the role of lungs in fetus. Consequently, umbilical vein, ductus venosus and right side of heart received oxygenated blood which through the patent foramen ovale (PFO) and ductus arteriosus (DA) get diverted towards the left side of heart. These channels would close eventually in postnatal life in most of the babies.

Type of Shunt Lesions

Common holes in pediatric practice are as follows:

- Atrial septal defect (ASD):
- Ventricular septal defect (VSD)
- Patent ductus arteriosus (PDA)
- Aorto-pulmonary window (AP window)

Pre-tricuspid Shunt

Atrial septal defect, also known as pre-tricuspid shunt, remains asymptomatic in first 1-2 years of life. Because both right and left atria are low pressure chambers, even a big ASD cannot raise PA pressure unless prolonged high blood flow brings out the desired intimal changes. Only 10-12 % patients with ASD present with obstructive PAH.

Post-tricuspid Shunt

The post-tricuspid shunt lesions like ventricular septal defect, aorto-pulmonary window and patent ductus arteriosus lead to equalization of PA and aortic pressure since beginning.

Common findings of shunt lesions: Large shunt lesions cause following changes in hemodynamics:

A. Increased lung blood flow : Increased work of breathing, vulnerability for lung infection;

B. Decreased systemic flow: Poor weight gain, poor circulation, fluid retention.

C. Altered pulmonary pressure: Hyperkinetic or obstructive PAH

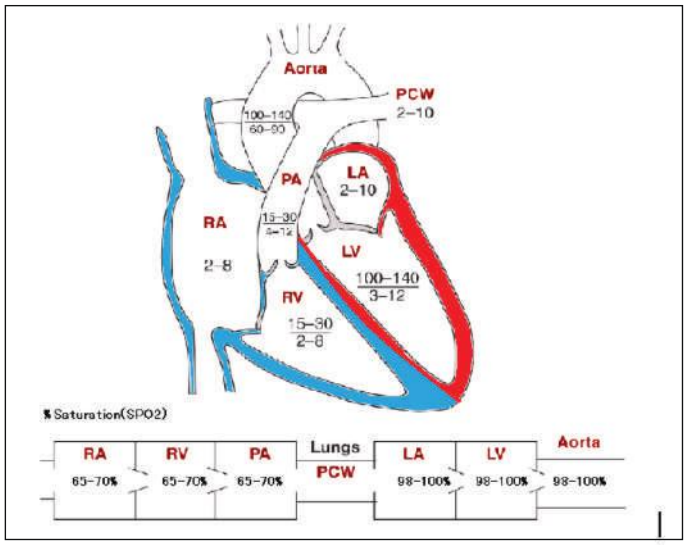

Figure 1

Classification of Various Shunt Lesions

1. Atrial Septal Defect

Type: ASD type is decided by location of ASD.

I: Fossa Ovalis ASD, II: Ostium Primum ASD, III: Sinus venosus ASD, IV: Coronary sinus ASD

2. Ventricular Septal Defect

I: Peri-membranous VSD, II: Doubly committed VSD, III: AV canal or Inlet VSD, IV: Muscular VSD.

3.Aorto-Pulmonary window

Proximal defect (type 1), Distal defects (type 2), Total defects (type 3) .

4. Patent Ductus Arteriosus

Conical (Type A), Window type (Type B), Tubular (Type C), Complex (Type D), Elongated (Type E)

Clinical Features of Hemodynamically Significant Shunt Lesions

Pre-tricuspid Shunt: Babies with ASD are usually asymptomatic, initially but afterwards, may present with dyspnea of exertion, palpitation. Rarely, they present classical heart failure.

Post-Tricuspid Shunt: Infants with large post-tricuspid shunt present with following features:

1. Feeding difficulty
2. Excessive sweating
3. high heart and respiratory rate
4. Hepatomegaly
5. Recurrent chest infections
6. Failure to gain weight also known as failure to thrive.

Murmur of a Shunt Lesion

ASDs only create a flow murmur and a large lesion presents with S3 and mid-diastolic rumble.

Small VSD, PDA are more noisy but rarely cause any clinical effect.

Individual Shunt Lesions Atrial Septal Defect

Clinically they are recognized by wide and fixed S2 split, ejection systolic murmur, RVS3 and mid diastolic rumble. X-Ray chest shows right ventricular enlargement, increased pulmonary blood flow. Electrocardiogram shows right axis deviation, right ventricular hypertrophy, rsr' pattern in V1. Echocardiography provide information about site and size of defect. ASDs are closed after the age of 2 years.

Ventricular Septal Defect

Clinically they are recognized by wide and variable S2 split, loud P2, Pan-systolic / Ejection murmur LVS3 and mid diastolic rumble at apex. X-Ray chest shows left ventricular enlargement, increased pulmonary blood flow. Electrocardiogram shows left axis deviation, biventricular ventricular hypertrophy, Deep Q and prominent T in left chest leads. Echocardiography provide information about site, number and size of defects.

Patent Ductus Arteriosus

Clinically they are recognized by narrow S2 split, loud P2, continuous murmur (infra clavicular region), or only systolic or diastolic component, LVS3 and mid diastolic rumble at apex. X-Ray chest shows left ventricular enlargement, increased pulmonary blood flow. Electrocardiogram shows left axis deviation, left ventricular hypertrophy, Deep Q and prominent T in left chest leads. Echocardiography provide information about site, number and size of defects.

Aorto-Pulmonary Window

Clinically they present with a systolic or continuous murmur, mid diastolic rumble, narrow split S2, loud P2. ECG and X-Ray chest show changes like a classical VSD or PDA. Echocardiography, rarely may miss the diagnosis and CT angiography may be needed.

Complete Atrio-Ventricular Septal Defect

AVSD or AV canal defect is a complex acyanotic lesion often seen in association with Down's syndrome.

Eisenmenger Syndrome

Eisenmengerization of a shunt lesion is characterized by decreased intensity of systolic murmur and loudness of P2. X-Ray chest starts showing tapering of pulmonary arteriole and decreased cardiac size, in case of VSD, PDA, AP window.

Management of Moderate to Large Shunt Lesions Issue of Spontaneous Closure of "Hole in Heart"

Depending on size, type and site of a shunt lesions, there is a possibility of spontaneous closure. But to prognosticate a spontaneous healing, pediatric cardiologist must be consulted and frequent echo evaluation is mandated.

Medical Management

Medical management has no effect on healing process and usually are recommended to ensure the growth and weight gain. Normally ASDs require no treatment in early childhood. Babies with large VSDs, AP window or PDA become symptomatic after 4-6weeks of life and need decongestive therapy, Iron/nutritional supplement and high caloric diet.

Diuretic (Furosemide) and digoxin are recommended till the definitive treatment is done. Angiotensin enzyme inhibitors may be prescribed beyond 8-12 weeks of age.

Definitive Treatment Non-surgical or Device Closure of Holes in Heart

A sizable number of babies can be treated with Cath interventions particularly the ASDs and PDAs. However many of other shunt lesions can also be closed by these procedures.

Hemodynamically significant (HS) PDA in preterm newborn can be closed by drugs like Indomethacin/ paracetamol and Ibuprofen. If medical closure fails then surgical or coil closure is attempted.

Advantage of Cath Intervention (Device Closures)

1. Majority of ASD secundum defects (central ASD) and PDAs can be amenable to it.

2. Less time consuming and short hospital stay

3. Safe/ user friendly procedures

4. Less psychological trauma to child & family

5. High success rate with good case selection

Disadvantage of Device Closure

1. The VSDs are commonest disorders and need to be treated in infancy. Most of the VSDs and AP windows cannot be treated by this modality.

2. Only ASD secundum of appropriate site and size can be treated with devices.

3. PDAs device closure in preterms may be associated with long term complications like -aortic or LPA co-arctation.

4. Only few cases of AP window can be closed by devices.

General consideration of the Procedure of the Device Closure

The Amplatzer and its imitation devices (life-tech), coccoon device etc., are most widely used in India. These devices are user friendly and are deployed by long venous sheath under fluoroscopy and trans-esophageal echo guidance. Intracardiac devices are deployed under general anesthesia. PDA device closure is done under local and ketamine infusion. The ASD device closure can be taken as prototype of description of procedure.

The Amplatzer septal occluder and its imitation devices are self-expanding, self-centering, repositionable device which consists of two round discs made of 0.004 to 0.005 inch Nitinol wire mesh that are linked together by a short connecting waist. The device is available in various sizes and in customized shapes according to the defects. The polyester fabric is securely sewn to each disc by a polyester thread.

Summary of Device Placement

A Successful Device Placement needs:

1. A suitable shunt lesion as evaluated by echocardiography for proper patient selection

2. Cath lab, fluoroscopy, Trans-esophageal Echo

3. GA for intracardiac device and ketamine for PDA device

4. Femoral arterial and venous access. Heparin bolus to prevent instantaneous clotting

5. Placement of long sheath and extra stiff wire from venous side across the defect

6. A check for device position and device release under fluoroscopy with or without TEE.

Device is introduced across the defect through a long venous sheath. It is deployed in a manner that it saddles over the defect. A membrane of epithelial cell covers it in approximately 72 hours but it takes around 3 to 12 weeks to get proper strength of the membrane.

Post procedure patient is kept under monitoring for 4-6 hours. Patient can be allowed to walk same day and can be discharged the next day. Antiplatelet drugs are recommended after the ASD device for 6 months. Infective endocarditis prophylaxis is also recommended for 6 months to allow the complete epithelization of the device. Avoidance of strenuous exercise or direct trauma on chest wall is recommended for 3 months.

Conclusion

Holes in heart or isolated shunt lesions have classical clinical findings until obstructive PAH develops. They must be identified early and must be subjected to the appropriate procedure at the appropriate time if they are hemodynamically significant. The decision of intervention depends on clinical features and echocardiographic findings. IE prophylaxis is recommended for small defects. Maintaining a good Oro-Dental hygiene, prompt treatment of infection and if required supervised antibiotic therapy is recommended to prevent IE.

Suggested reading

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Allen HD, Driscoll DJ, Shaddyy RE, Feltes TF. Moss & Adams Heart Disease in Infants, Children, and Adolescents, including fetus & young adults. 8th edition, 2012, William and Wilkins.

Vasoplegia in Cardiac Surgery – Not so Benign

Naresh Kumar Aggarwal[A], Arun Subramanian[B], Rakesh Kumar Solanki[C]

[A] HOD, Department of Cardiac Anaesthesia, Manipal Hospitals, Delhi

[B] Consultant, Department of Cardiac Anaesthesia, Manipal Hospitals, Delhi

[C] Consultant, Department of Cardiac Anaesthesia, Manipal Hospitals, Delhi

Introduction

Vasoplegic syndrome (VS), a form of vasodilatory shock may affect up to half of all patients undergoing major cardiovascular surgery. [1] It is an increasingly recognized challenge considering the increasing amount of heart failure surgery, in which alone, the incidence may be 20%-30%. [2] It also occurs in a multitude of scenarios like liver transplantation, sepsis and anaphylaxis. Vasoplegia in adults has multiple numerical definitions but is frequently defined as a normal or high output state (cardiac index > 2.2 L/min/m2) with difficulty maintaining a mean arterial pressure (MAP) of 60 mm Hg due to a low systemic vascular resistance (<800 dynes.sec/cm5) despite high-dose vasopressor therapy (0.5 mcg/kg/min of noradrenaline equivalents). [3] Even though currently there is no "standard of care" treatment algorithm for vasoplegia, recent developments in pharmacotherapy allow treatment options for virtually all patients. Several trials have investigated the role of non-vasopressor adjuncts in cases where traditional agents have failed. In this review, we shall be discussing the risk factors, mechanisms, and various management strategies for VS following cardiovascular surgery.

Risk Factors and Outcomes

VS occurs in 5-25% in groups without risk factors but in those with known predisposing factors, this rate can be anywhere between 30-50%. It is associated with high rates of renal failure, prolonged hospital stay, and death. [4] Many risk factors during cardiac surgery have been associated with a higher incidence of postoperative vasoplegia, namely pre-operative use of angiotensin- converting enzyme inhibitors and beta-blockers. [5] Patients with significant co-morbid conditions and low preoperative systolic ejection fraction have shown a high affinity for the development of vasoplegia. [6] Patients undergoing cardiovascular surgery particularly those performed on cardiopulmonary bypass (CPB) have a higher propensity for the development of VS. CPB leads to a profound inflammatory reaction coupled with a relative deficiency of vasopressin. This is more true for those surgeries that require a prolonged CPB duration.

Pathophysiology

VS is complex but is fundamentally a deficit in vascular smooth muscle contraction. In general, vascular smooth muscle contracts when intracellular calcium levels rise. This process is balanced by vasodilatory molecules like nitric oxide (NO) and atrial natriuretic peptide which triggers smooth muscle relaxation and vasodilation by increasing the levels of intracellular cyclic guanosine monophosphate (cGMP). NO, as an activator of ATP-sensitive potassium channel opening, is a particularly im-important intercellular mediator of vasodilatory shock. NO is synthesized by NO synthase (NOS) family of enzymes which are usually dependent on calcium for activation. Inducible, calcium-independent NOS isoforms (iNOS) synthesize NO on-demand after being exposed to physiologic stress. This iNOS is often implicated as the mediator of distributive shock and may precipitate mitochondrial dysfunction, apoptosis, and multi-organ failure. [7] In addition to NO, vasopressin deficiency is also an important contributor of vasodilation. Prolonged shock, as well as CPB, lead to relative vasopressin deficiency, which may be inadequate for the severity of physiologic stress. This deficiency is believed to be caused by depletion of neuro-hypophyseal stores after prolonged baroreflex stimulation. The end result of both the above described mechanism is an increase in cGMP levels and calcium-sensitive potassium efflux channels, which lead to smooth muscle relaxation and vasodilation. [8]

Management Strategies

Early management of postoperative VS focuses on the recognition of the problem. The clinician should confirm the presence of hypotension, low SVR with a normal/supra-normal cardiac output. The physician should simultaneously consider the other causes of vasodilation like infections, etc.

Prevention

Many of the risk factors previously listed for vasoplegia either may not be modifiable in the immediate pre-operative period or are inherent components of the surgical procedure to be performed. Thus, the clinician must be aware of the treatment options described in the next section.

Fluid and Blood Product Resuscitation

Identifying fluid responsiveness is an important component of early treatment of postoperative vasoplegia. Judicious transfusion of blood products should be used to correct anemia that may accompany hypovolemia and vasoplegic shock. However, overzealous fluid administration (>20-30 mL/kg) can lead to an unnecessary increase in cardiac filling pressures and accumulation of extravascular lung water.

Pharmacological Options

Pharmacological management strategies for post CPB — VS can be broadly classified into vasopressor and non-vasopressor therapy. (Table 1) Vasopressors are typically the first-line treatment for vasoplegia after a fluid challenge is unsuccessful.

Catecholamines

Sympathomimetic agents like noradrenaline, adrenaline, and phenylephrine are commonly used though no established first-line vasopressor is recommended at this point in time for post-CPB vasoplegia. Noradrenaline may be the most tolerated catecholamine as it is less arrhythmogenic when compared to dopamine or adrenaline. All these agents can cause arrhythmias, increase myocardial oxygen demand, hyperglycemia, and lactic acidosis at high doses.

Vasopressin

Vasopressin has an established track record for the management of catecholamine-resistant shock. It binds to AVPR 1a receptor, thereby inhibiting NO production and potassium channel opening. It has been shown to decrease the dose of catecholamines when used concurrently, though no differences in mortality has been reported when compared to catecholamines. [9] There is no significant difference in the incidence of renal failure in patients receiving vasopressin as compared to noradrenaline. Patients with post-CPB vasoplegia may benefit more from vasopressin than those due to septic shock.

Terlipressin

It is an established vasopressin analog used primarily outside North America. It has a longer half-life than vasopressin and can be used intermittently. It has a preferential selection for AVPR 1 receptors and thus may allow for more selective vasoconstriction. When compared head-head with vasopressin, it performed similarly but was associated with a reduction in platelet counts. [10] Ultimately, larger controlled trials need to be performed before terlipressin can be advocated as an appropriate anti-vasoplegia agent.

Angiotensin-II (Ag-II)

Ag-II is an endogenous hormone that makes up the component of the renin-angiotensin-aldosterone axis and is a direct, potent vasoconstrictor with a serum half-life of approximately 30 seconds. It increases sodium and water retention while ensuring appropriate vascular tone and therefore has been scrutinized as a non-catecholamine rescue vaso- pressor. Undesirable side effects include reduction in glomerular filtration, increased pulmonary vascular pressures, and asthma exacerbations.

Corticosteroids

Steroids are used to treat vasodilatory shock with the assumption that they may supplement a depleted adrenal axis in critical illness. Their role in post-CPB vasoplegia has not been evaluated but their adverse effects like hyperglycemia, delayed wound healing and increased risk of gastrointestinal bleeding should be considered. Cumulatively, studies do not show an increased mortality benefit in patients who have vasodilatory shock. [11]

Ascorbic acid (Vitamin C)

The rationale for the use of ascorbic acid stems from its anti-inflammatory properties and its role as an electron donor in the synthesis of noradrenaline from dopamine by dopamine beta-hydroxylase. Studies combining vitamin C with steroids and thiamine have shown a decrease in vasopressor requirements but warrant further research.

Methylene Blue (MB)

MB competes with guanylyl cyclase, thereby interrupting the production of cGMP as well as inhibiting iNOS production. Hence, NO-mediated dephosphorylation of myosin and associated vasodilation are antagonized. Adverse effects include coronary vasoconstriction, decreased splanchnic blood flow, and an increase in pulmonary vascular resistance. It should be used cautiously in patients with glucose-6-phosphate dehydrogenase deficiency and in patients receiving monoamine oxidase inhibitors, selective serotonin reuptake inhibitors, and phenylpiperidine narcotics as it can precipitate hemolytic anemia and serotonin syndrome re- respectively. MB can interfere with pulse oximeter readings and cause bluish-green discoloration of urine. Early reports identified successful use of MB to rapidly and dramatically improve MAP of post-CPB VS. [12] However, not all studies have been supportive of the use of MB. [13] Therefore, until more rigorous trials are performed, its use is limited to additive and/or rescue roles in the management of vasoplegia.

Hydroxocobalamin

There have been isolated case reports of hydroxocobalamines successful use in the setting of VS. [14] The possible mechanism of benefit may arise from its ability to bind hydrogen sulfide, which may have a role in the pathogenesis of vasoplegia. Unlike MB, it does not cause serotonin syndrome, although it is more expensive and can cause chromaturia.

Conclusion

VS is common after cardiac surgery, especially after CPB. Alternative diagnoses with similar presentations, such as sepsis must be considered. In patients with a low systolic ejection fraction, any technology that helps in determining the cardiac index and SVR may guide the clinician in an appropriate management of VS. After appropriate fluid resuscitation has been performed, vasopressors must be considered as the primary form of treatment. Catecholamines, especially noradrenaline are suggested as the first-line treatment agents. Recent investigations have supported the use of vasopressin and methylene blue as additive and/or rescue agents. Other agents which are capable of increasing SVR may have expanded roles in the near future while treating vasoplegia.

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Table 1: Vasoactive drugs for the management of vasoplegia

CLASS	DRUG	DOSE
VASOPRESSOR	Noradrenaline Adrenaline	0.01-0.1 mcg/kg/min 0.01-0.5 mcg/kg/min
	Vasopressin	1.2-6 U/h
	Terlipressin	1.3 mcg/kg/h
	Angiotensin - II	20 ng/kg/min upto 80 ng/kg/min
NON-VASOPRESSOR	Corticosteroids	Hydrocortisone 50 mg/6 hours
	Ascorbic Acid	1.5 g/6 hours
	Methylene Blue	1.5-2.5 mg/kg over 10 minutes followed by 0.25-0.5 mg/kg/h.
	Hydroxocobalamin	5-10 gm over 10 minutes

Cervical Ectopic Pregnancy Management – A Multimodality Approach

Yogita Parashar[A], Leena N Sreedhar[B], Harleen Saimbi[C]

[A] Senior Consultant, Department of Obstetrics & Gynecology, Manipal Hospitals, Delhi

[B] HOD, Department of Academics & Research, Manipal Hospitals, Delhi

[C] Senior Registrar, Department of Obstetrics & Gynecology, Manipal Hospitals, Delhi

Abstract

Cervical pregnancy, a rare type of ectopic pregnancy is one in which the embryo implants and grows inside the endocervical canal. Early diagnosis is essential so as to allow conservative (medical and surgical) treatments timely. Though many treatment approaches are available, the most effective treatment is still unclear. We report a case of 31 year Nulliparous lady with anemia and thickened endometrium admitted at a tertiary care hospital. After blood and radiological investigations, cervical ectopic pregnancy was noted. Patient was managed conservatively with Inj. Methotrexate followed by ultrasound guided dilatation and curettage and balloon tamponade. On postoperative day 2 patient was discharged in stable condition and diagnosis was confirmed on histopathology.

Introduction

Cervical pregnancy is a rare form of ectopic pregnancy which is often associated with significant morbidity and mortality. It is assumed < 1% of pregnancies are ectopic and even in this < 1% are cervical pregnancies.

Cervical ectopic pregnancy is an uncommon form of ectopic pregnancy in which the pregnancy implants into the cervical mucosa, below the level of internal os. The first report of cervical ectopic pregnancy diagnosed using ultrasound was in 1978. [1] The incidence of cervical pregnancy varies between 1 in 1000 to 1 in 16,000. [2] The highest incidence is reported from Japan which incidentally also has highest figures of antenatal curettage.

Diagnosis of cervical pregnancy is challenging and often diagnosis is made retrospectively when torrential bleeding may occur often warranting hysterectomy in approximately 50% of cases. As there have been an improvement in the radiological techniques and easy availability of 3D scans nowadays, early diagnosis at lower gestational age is feasible.

The last ten years have seen more conservative management of cervical pregnancy with the lab diagnosis of βHCG and 3D scans. The various conservative methods include ultra-amniotic or systemic Methotrexate, cervical cerclage, hypogastric iliac artery ligation and arterial

embolization as reviewed by Ushakor et al in 1996.

In this case report we present one of the conservative methods used to preserve the future fertility by giving systemic Methotrexate and after 24 hours, conducting D&C followed by tamponade, below the level of internal os and above the implantation site with help of 22 F Foley's catheter. Thus, we see conservative management can be offered to women with low βHCG levels and early gestational age as they are more stable.

Case Report

A 31 year old woman communicated through teleconsultation (due to Covid Pandemic). Her LMP was 8th May 2021, having previous regular cycles with average flow. Past and family history was insignificant. She had 25-27 day cycles. Her periods were overdue by 5-7 days. She had mild lower abdominal pain and no other complaints. She was advised a urine pregnancy test (UPT) and pelvic scan. She started with painless vaginal bleeding the next day. Patient considered it as normal periods and did not get any tests done.

As the flow increased over the next two days, patient presented to Emergency Room with dizziness and weakness. Her βHCG and other investigations were sent and a Trans-abdominal Sonogram (TAS) was performed & was suggestive of thickened endometrium ~7-8mm with blood clots in vagina.

Patient was clinically pale though her vitals were stable. She was admitted and her βHCG report was 6151 IU/ml and Hb was 8.6 gm/dl. Thus, two units of blood were transfused. Her bleeding decreased on conservative management but did not stop completely.

A repeat Transvaginal Scan (TVS) + 3D scan was done and diagnosis of cervical pregnancy was confirmed. A gestational sac ~4m 4d was seen just below the level of internal os with increased vascularity on doppler. A typical hour glass appearance of uterus with ballooned out cervix was seen.

Patient was administered Inj. Methotrexate in dose of 1gm per kg body weight. After 24 hours, an ultrasound guided D&C was performed followed by tamponade just below the level of internal os with help of Foley's catheter (22F) and bulb was inflated with 30 ml normal saline. To prevent expulsion of Foley's catheter, a tight vaginal packing was done. Bleeding was minimal in intraoperative and postoperative period. Beta βHCG was 1937 IU/ml after 24 hours and Hb increased to ~9gm/dl. Foley's tamponade was removed after 24 hours and minimal bleeding was observed in postoperative period. Patient was discharged on postoperative day 2 in a stable condition.

Her βHCG on 7th postoperative day was 74 IU/ml and histopathology report confirmed the diagnosis of cervical pregnancy. In follow up patient was advised serial βHCG weekly.

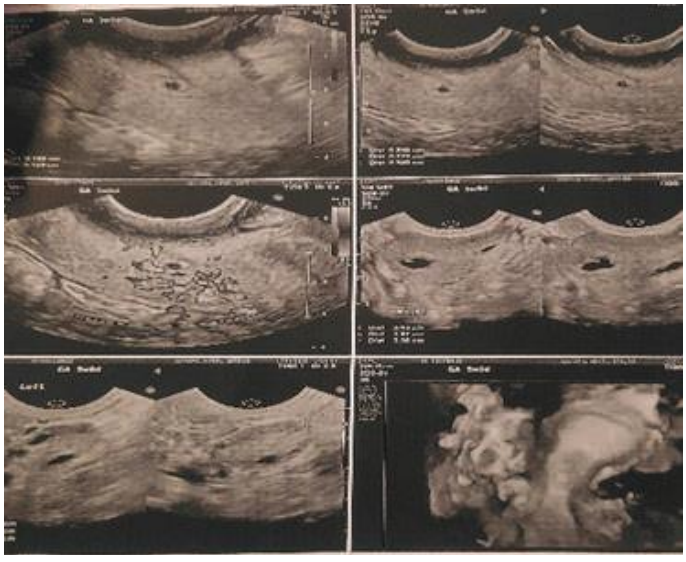

Figure 1: USG Lower Abdomen

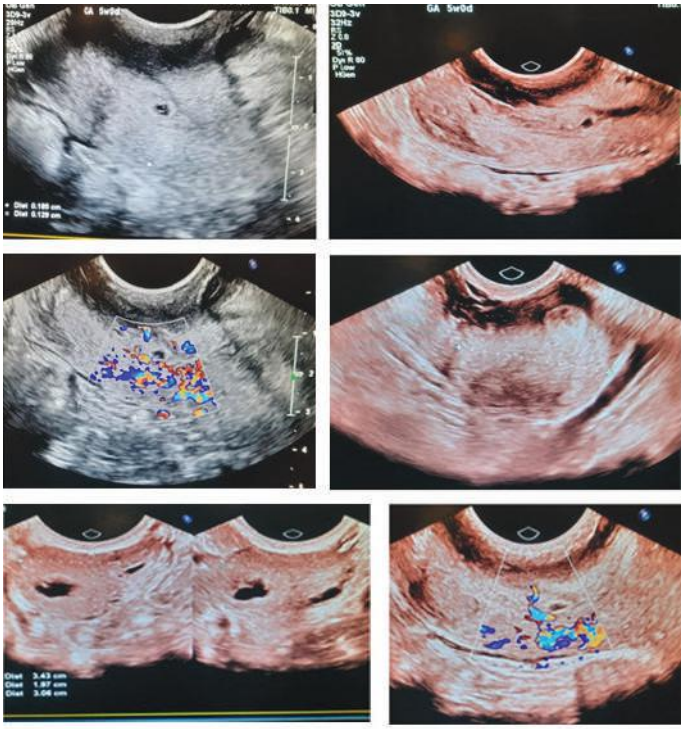

Figure 2: Serial USG TVS Images

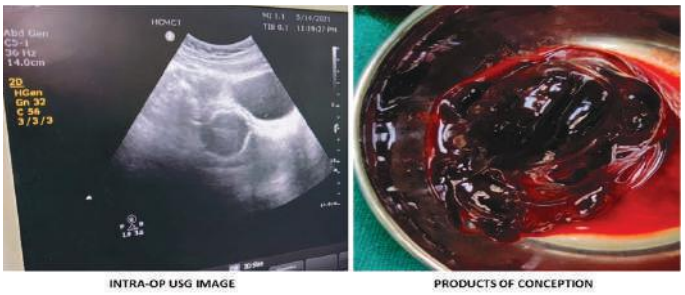

Figure 3

Discussion

Cervical pregnancy is a rare form of ectopic pregnancy which can be life threatening with reported incidence of 1:1000 to 1:16000 pregnancies. Early diagnosis helps in successful treatment and preservation of future fertility. Though common etiologies for cervical pregnancy are previous curettage, Asherman's syndrome, [3,4] previous cesarean section, previous cervical or uterine surgery [5] & in vitro fertilization, [6,7] surprisingly, patient had none of the above mentioned risk factors. Rubin has described the histopathological diagnosis criteria but it is of limited value as hysterectomy is taken as last resort for life saving procedure. [8]

Clinical criteria as proposed by Palman and McElin [9] are:

1. Uterine bleeding without cramping pain following a period of amenorrhea.

2. A soft, enlarged cervix equal to or larger than the fundus (hour glass appearance of uterus).

3. Products of conception entirely located within endocervical canal within and firmly attached to endocervical canal.

4. A closed internal os.

5. A partially opened external os.

Cervical pregnancies may be diagnosed earlier, with advanced radiological techniques and lab values for serial βHCG assessment. Also women are reporting in OPD's at earlier gestational age. In a study conducted by Kirl et al [10] which was a retrospective study done to evaluate conservative management in cases of cervical pregnancy, it was found to be very effective and safe approach.

Conservative surgical techniques such as D&C and uterine artery ligation have been found to be successful in certain cases. [11] Antimetabolite cytotoxic drug, Methotrexate now a days plays a pivotal role in conservative management of ectopic pregnancy. Success rate of primary systemic methotrexate treatment was 03%. [12,13]

Tamponade with Foley's catheter has been used [14] after other techniques (like curettage) by placing it gently past the external os, followed by inflation of the bulb with 30ml saline for reduction of blood

supply during cervical curettage, vaginal ligation of descending cervical arteries, ligation of uterine arteries/internal iliac artery or angiographic embolization of cervical, uterine or internal iliac arteries. They are usually done prior to surgical therapy. Surgical excision of trophoblast are the classic methods. Curettage is an age old process used for fertility preservation.

It has been observed that chemotherapy with methotrexate works well in stable patients with gestational age < 9 weeks. When gestational age is > 9 weeks and there is presence of cardiac activity on ultrasound, additional procedures like intra-amniotic potassium chloride infusion may be required. But if diagnosis is made as late as second or third trimester, a hysterectomy is generally required. In patients with active bleeding, either a tamponade with Foley's catheter or large vessel ligation are treatment options. But in cases of intractable bleeding, hysterectomy is the last resort. Generally, in termination of cervical pregnancy, more than one methods are used.

In our case, as the patient was actively bleeding but gestational age was between 4-5 weeks, with no cardiac activity, we choose to first decrease the vascularity around the sac with administration of systemic Methotrexate 50 mg IM.

After 24 hours, ultrasound guided D&C was performed and Foley's catheter tamponade was placed intra-cervically. It was found to be effective with significant reduction in bleeding. The resolution of 3D ultrasound is much better than 2D scans and have aided in diagnosis of cervical pregnancies at much earlier gestations, thus aiding in preservation of fertility.

Conclusion

A case of cervical pregnancy when diagnosed early with multimodal investigations, results in a better management with non-invasive techniques, which may be used alone or in conjunction with each other.

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Manipal Hospitals Logo Launch - Dwarka

Amlodipine-Atenolol Poisoning in Emergency Room - A Case Report

Malaya Kumar Mishra

Registrar, Department of Emergency Medicine, Manipal Hospitals, Jaipur

Abstract

We report successful management of a case of young female who had ingested large dose (60 tab) of amlodipine/ atenolol combination. This case highlights how the early and aggressive management in emergency department and intensive care management can result in a favourable clinical outcome.

Introduction

Beta blockers and Calcium Channel Blockers (CCBs) represent the most important classes of cardiovascular drugs. Intentional ingestion of these agents are associated with high mortality rate. Co-ingestion of Beta blocker and CCB are lethal owing to the similar changes they produce in cardiovascular physiology. We present a patient who intentionally consumed 60 tablets of Beta blocker and CCB combination (A total of 300mg of Amlodipine and 3000mg of Atenolol).

Case Report

A 33 year old female patient working as an ECG technician in a govt hospital was brought to the Emergency Department (ED) with complain of recurrent vomiting, pain abdomen and decrease urination following ingestion of 60 tabs of amlodipine and atenolol combination. Each tablet contained amlodipine 5 mg and atenolol 50 mg.

She was brought to our ED 24 hrs after ingestion. Initially she was taken to the govt hospital where gastric lavage was done approximately 5-6 hrs after ingestion and IV Fluids had been given. At the time of presentation she was conscious but confused, her GCS was E4V4M6. Her vitals showed HR-74/min, RR-24/min, BP-70/40 mm Hg, RBS-115mg/dl, axillary body Temp-98.4* F, SPO2-100% @ 6lit/min with face mask. B /L pupils were 3mm, reactive to light.

On Primary Survey airway was patent, lungs were clear to auscultation, there were no heart murmurs or gallop rhythm. Abdominal examination revealed mild epigastric tenderness and exposure of the patient didn't reveal any signs of physical injury or mark in the body. Secondary survey and detailed examination from head to toe was unremarkable. Her initial ABG showed PH-7.37, PCO2-29.6 mm Hg, PO2-60 mm Hg, HCO3-17.4 mmol/l, Lactate-2.5 mmol/l, Ionized Calcium-0.92 mmol/l, Na-128 mmol/l, K-3.4mmol/l. [Fig.1] ECG showed sinus rhythm with no ST-T changes. [Fig.2] 2D Echo screening done showed no regional wall motion abnormality with EF-62% Initially she was given 1 litre normal saline iv bolus then after checking the volume status of patient by ultrasound of IVC, another 1 litre of normal saline was given. Anticipating the need for

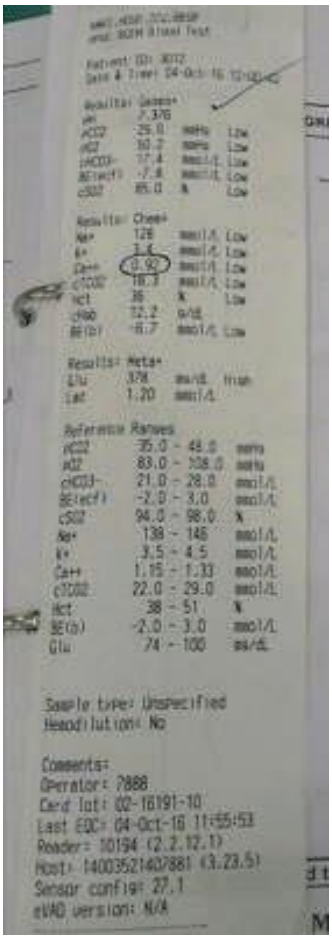

Figure 1

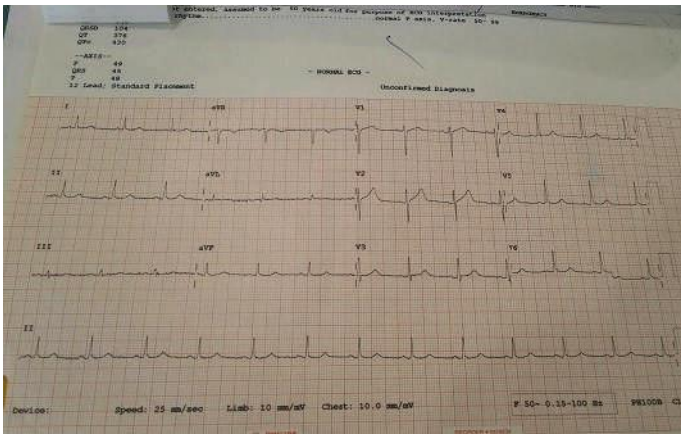

Figure 2 : Normal Sinus Rhythm

vasopressors, Right internal jugular vein (IJV) was cannulated in the ED and patient was started on dopamine & nor adrenaline infusions. Patient was also given 20 ml of 10% calcium gluconate slow iv under cardiac monitoring followed by 20 ml/hr infusion to maintain normal ionized calcium levels.

Patient was shifted to MICU with insulin infusion (@ 0.5 unit/kg/hr) along with potassium and dextrose infusion. In the first 5 hrs of admission patient had decreased urine output (15ml/hr) but later improved. Patient started showing improvement by day 4 and she was completely recovered and discharged in a good health by day 10 after psychiatry consultation.

Discussion

Overdoses with cardiovascular drugs are associated with significant morbidity and mortality. [6] Beta adrenergic blockers and calcium channels blockers represent two of the most important classes of cardiovascular drugs.

Beta blockers selectively antagonize B-adrenergic receptors that are linked to G proteins. In an overdose situation, receptor selectivity is lost and effects, not normally seen at therapeutic doses, can occur. Highly lipophilic agents such as propranolol, carvedilol cross the blood brain barrier and can result in CNS effects. Atenolol has a low lipid solubility. [5] Beta-blocker toxicity can produce clinical manifestations including bradycardia, hypotension, arrhythmias, hypothermia, hypoglycemia, and seizures. The presentation may range from asymptomatic to shock. [3][6]

All existing CCBs function by binding to the L-subtype, voltage-sensitive, slow calcium channels in cell membranes. Amlodipine is a dihydropyridine group of CCBs having a half-life of 30-50 hours, a large volume of distribution (21 L/Kg), and act predominantly on peripheral vasculature. [1] This peripheral action reduces afterload and systemic blood pressure. Because dihydropyridine-type CCBs only act peripherally, the vasodilation

they cause may induce a compensatory increase in the heart rate. Within the pancreas, calcium channel antagonism results in decreased insulin secretion. Effects on pancreatic tissue and insulin secretion are less well studied but all three subclasses of CCBs appear to have this effect. [4][7]

In overdose, β-blockers and CCBs often have similar presentation and there is much overlap in treatment. Cardiotoxicity characterized by hypotension and bradycardia is the common clinical feature, but other effects may help differentiate the exposure. It is important to understand the different features of such poisonings by class and specific agents.

The patient had hypotension that were initially treated with IV Fluids and inotropic agents (dopamine and noradrenaline). In view of persistent hypotension, intravenous insulin along with dextrose and potassium was also administered. Insulin increases plasma levels of ionized calcium, improves hyperglycemic acidotic state and myocardial utilization of carbohydrates and also exerts on inotropic action. Hyperinsulinemic euglycemia therapy should be considered for patients with calcium channel blocker overdose who are refractory to supportive therapy. [2][7]

Currently all available information on Hyperinsulinemic euglycemia therapy is limited to case reports and series. Probably it should be considered for patients with CCB overdose who do not respond to initial supportive therapy. Intravenous calcium supplementation in the forms of calcium gluconate and calcium chloride have also proved to be beneficial in augmenting extracellular calcium and overcomes competitive antagonism.[7]

Intravenous glucagon as an inotropic agent has been the treatment of choice for massive beta-blocker overdose. [1] However there are no human studies evaluating the efficacy of glucagon in beta blocker or CCB overdose. Multiple case reports are there in literature reporting clinical improvement following glucagon administration.[8]

High-dose glucagon is recommended for cardiotoxicity produced by β-blocker poisoning. An initial bolus dose of 50–150 μ g/kg should be administered i.v. over 1-2 minutes. [2] This initial dose will have a transient effect that should occur within approximately five minutes. If a benefit is seen, the initial dose should be followed by a continuous i.v. infusion at a rate of 2–5 mg/hr (maximum: 10 mg/hr) diluted in 5% dextrose injection. The infusion rate can then be tapered down as the patient improves. We gave 5 mg of glucagon to our patient but there was no increase of heart rate, so we did not start the infusion of glucagon in view of the possible side effects of glucagon.

There is no definitive evidence that gastrointestinal decontamination either in the form of activated charcoal or the whole bowel irrigation alters the clinical outcome in the CCB & β-blocker overdose. However, GI decontamination is still advocated because of the potential lethal nature of this overdose and lack of specific antidote. However in case it is done, the patient's airway should be protected and should be done within 1 hour of ingestion of toxic substance/drugs. [4][5]

In our case gastric lavage was done in another hospital 5-6 hrs after ingestion which is questionable. Many other treatment modalities have been described in the literature. Tranvenous pacing may be required in patients with severe symptomatic bradycardia not responding to atropine,

dopamine, and epinephrine infusion. [6] Surprisingly in our case patient didn't develop any bradycardia or arrhythmia during the course of stay in hospital.

Hemodialysis is also useful in severe cases of atenolol overdoses because atenolol is less than 5% protein bound and 40-50% excreted unchanged in urine. Nadolol, sotalol, and atenolol, which have low lipid solubility and low protein binding, reportedly are removed by hemodialysis. Although CCBs are highly protein bound, some physicians believe that hemodialysis may be used as a last resort in severely toxic patients who have no other hope. In our case patient had oliguria on day 1 which was improved gradually by day 2 with adequate fluid resuscitation and inotropic support.

Extracorporeal membrane oxygenation (ECMO) has also been attempted in patients who have hypotension refractory to all pharmacologic therapies. One case reported from Dehradun described a massive diltiazem ingestion (12 g Cardura CD) that resulted in prolonged cardiac standstill. However, after 48 hours of ECMO and 15 days in the critical care unit, the patient made a very good recovery and was discharged home "fit and well," showing "no evidence of neurologic dysfunction. [7][8]

Conclusion

Overdose of Beta blockers or CCBs or combination of both may present with vague symptoms but usually present with hypotension and bradyarrhythmia, which may be refractory to standard resuscitation measures and prompt treatment should be initiated without delay. High-dose insulin euglycemia is commonly recommended as a first-line treatment in these poisonings, to improve myocardial contractility, and should be instituted early when myocardial dysfunction is suspected. Optimizing serum calcium concentration can confer some benefit to improving myocardial function and vascular tone after CCB poisoning.

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Type 5 Cardiorenal Syndrome in a Patient with Systemic Lupus Erythematosus

Ashish Nandwani[A], Saurabh Pokhriyal[B], Shailender Kumar Singh[C], Ajay Kumar[D]

[A] Consultant, Department of Nephrology, Manipal Hospitals, Delhi

[B] Senior Consultant & HOD, Department of Nephrology, Manipal Hospitals, Delhi

[C] Consultant, Department of Nephrology, Manipal Hospitals, Delhi

[D] Associate Consultant, Department of Nephrology, Manipal Hospitals, Delhi

Introduction

Type 5 Cardiorenal Syndrome (CRS) is characterized by concomitant presence of cardiac and renal dysfunction due to acute or chronic systemic disorders. There is limited insight into how the combined cardiac and renal failure will affect the outcome of the disease. In the acute setting severe sepsis represents the most common condition which leads to the acute kidney injury and myocardial dysfunction. Several chronic conditions e.g. systemic lupus erythematosus, amyloidosis, sarcoidosis and diabetes mellitus can lead to type 5 cardiorenal syndrome. [1] In this article, we will discuss a case of Systemic Lupus Erythematosus (SLE) leading to Type 5 Cardiorenal Syndrome.

Case

A 40 year old female with no previous comorbidities presented with complaints of chest discomfort and palpitations of 1 week duration. Chest pain was retrosternal, non-radiating and was increasing with forward bending. There was no history of fever, cough or dyspnea. Her clinical examination was unremarkable, and ECG was normal except for few isolated ventricular ectopics. Echocardiogram revealed normal ejection fraction and evidence of mild septal hypokinesia. Her cardiac Troponin levels were normal. Patient improved with symptomatic treatment with analgesics. She was planned for outpatient follow up in clinic after 4 weeks for repeat echocardiogram.

She was admitted 3 weeks later with increased intensity of chest pain, palpitations and increasing shortness of breath. She had also developed swelling of the feet in last few days. There was no history of orthopnea, periorbital puffiness, weight loss, fever, abdominal pain, joint pains, or hematuria. There was no history of oral ulcers, hair loss or photosensitivity in the past.

On clinical examination, she was afebrile. Her blood pressure was 150/96 mm Hg and pulse rate was 110/min with multiple ectopics. She also had evidence of malar rash and bilateral pitting edema. There was no pallor, cyanosis, clubbing or oral ulcers. Her cardiovascular examination revealed

presence of grade 3/6 pansystolic murmur at apex along with pericardial rub in the parasternal region. Abdominal examination revealed mild hepatomegaly. Neurological examination was unremarkable. There was no joint involvement.

Her ECG showed multifocal ventricular ectopics and non-specific ST-T changes. 2D echocardiogram showed thickened mitral valve leaflets, no discrete vegetation, and mild mitral regurgitation. There was no pathology involving the subvalvular apparatus or papillary muscles. Pericardium was normal with minimal pericardial effusion. Septal hypokinesia was persisting, however troponin levels remained normal. Her coronary angiogram was normal with no evidence of thrombosis that would explain her regional wall motion abnormalities. Left ventricular ejection fraction was 40% with evidence of bilateral ventricular dilatation.

Various causes of cardiomyopathy were excluded. In view of presence of malar rash, pericarditis and absence of infective etiology, possibility of autoimmune disorder was considered and patient was further evaluated by autoimmune markers.

Laboratory Investigations

CBC: Hemoglobin 9.1 gm/dl, Total leucocyte count 11,000/mm3, Differential leucocyte count P90,L6,M2,E2, Platelet count 2.5 lakhs/mm3, Peripheral smear - Normocytic normochromic anemia.

ESR 69 mm 1st Hr, CRP 8 mg/dl

Blood Sugar 90 mg/dl, HbA1c 5.4%

Blood Urea 48 mg/dl, Serum Creatinine 1.5 mg/dl

Serum Sodium 132 mEq/l, Potassium 4.1 mEq/l

Urine routine: Albumin +++, RBC 10-12/hpf, granular cast +

24 hours protein: 4.8 grams

Troponin I : 0.12 ng/ml

Serum bilirubin : 1.0 mg/dl, SGOT 44 IU/ml, SGPT 40 IU/ml

Total protein : 5.4 gm/dl, Albumin 2.4 gm/dl

ECG nonspecific ST-T changes, sinus tachycardia, ventricular ectopics

Ultrasound of abdomen revealed bilateral normal sized kidney with mild increased echogenicity and maintained cortico-medullay differentiation.

Chest X ray: Blunting of bilateral CP angles

Urine culture and Blood culture –Sterile

Antinuclear antibody (ANA): Positive (1:320, Fine Speckled)

Anti-double stranded DNA (anti-dsDNA): Positive (1:10 dilution)

Anti-neutrophil cytoplasmic antibodies (cANCA and pANCA) : Negative

Complement C 3, C4 levels: Low

Antiphospholipid antibodies: Negative

Thyroid stimulating hormone : 2.1 mIU/L

Management

Based on clinical presentation & laboratory results, diagnosis of systemic lupus erythematosus (SLE) was made. The predominant involvement of heart in the form of pericarditis, myocarditis and valvular thickening was evident on echocardiogram. Renal involvement was suggested by nephrotic range proteinuria along with active urinary sediment. Also, serum complement level was low. SLE being a multi system disease with predominant dysfunction of both heart and kidney caused cardiorenal syndrome Type 5 in this patient.

USG guided renal biopsy was done, which

showed diffuse proliferative glomerulonephritis with mesangial and endocapillary proliferation (Class IV lupus nephritis) with full house (IgG, IgA, IgM, C3 and C1q) on immuno-fluorescence. The interstitium had focal infiltrates of lymphocytes and plasma cells. Arteries were showing intimal hyperplasia.

In view of her rapid cardiac and renal involvement, she was started on intravenous pulse methyl prednisolone therapy for 3 days followed by daily maintenance doses of oral steroids (1 mg/kg/day). She was also started on monthly cyclophosphamide therapy (750 mg/m2) as induction therapy. Steroids were gradually tapered off and she completed 6 cycles of monthly cyclophosphamide therapy and put on azathioprine (2 mg/kg/day) as maintenance therapy. Immunosuppression helped her in achieving the remission. Her proteinuria decreased to less than 500 mg/day and her cardiac functions stabilized with disappearance of pericardial rub and improvement in left ventricular ejection fraction. At last follow-up, she was clinically well, though still hypertensive requiring therapy. The 2D Echo showed a decrease in mitral valve thickening with no evidence of pericardial thickening. Her other medications included telmisartan, metoprolol and torsemide. (Fig 1.)

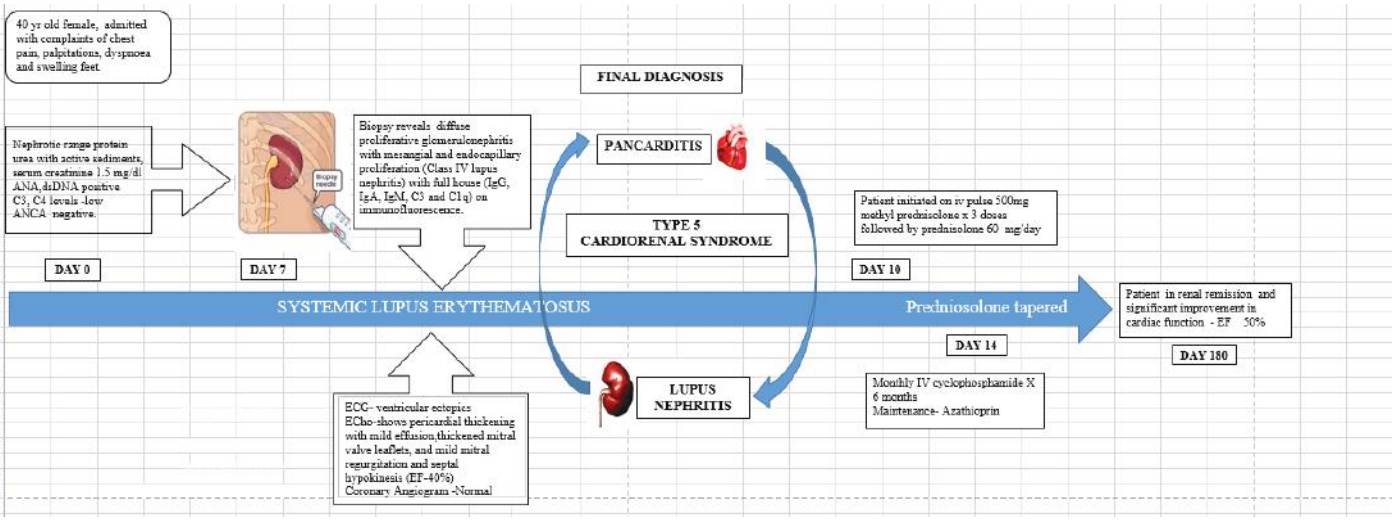

Fig 1: Timeline of clinical course of patient with Cardiorenal Syndrome Type 5 in a patient with SLE

Discussion

This patient had cardiorenal syndrome type 5- reflecting concomitant dysfunction of heart and kidneys in the setting of systemic condition i.e. systemic lupus erythematosus, which primarily affected both the organs. This patient with active lupus nephritis developed acute deterioration in myocardial function. SLE is one of the most common multisystem autoimmune disorder characterized by development of auto antibodies directed against self-antigens, leading to inflammatory damage of various target organs. Diagnosis of SLE is typically based on the revised criteria of 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus, which require positive antinuclear antibody (ANA) at a titer of ≥ 1:80 on HEp-2 cells, and presence of other criteria, which are scored; namely constitutional features, hematologic, neuropsychiatric, mucocutaneous, serosal, musculoskeletal, renal disorders and

presence of immunological criteria based on presence of Antiphospholipid antibodies, low complement proteins and SLE specific antibodies. A total score of ≥ 10 and ≥ 1 clinical criterion are required to classify SLE (Figure 2). [2] This female had only evidence of serositis at initial presentation, however subsequently; she had proteinuria along with micro hematuria, malar rash along with positive ANA and Anti-dsDNA. Anti-dsDNA antibodies are highly specific for SLE but they are present only in 70% of cases.

The prevalence of cardiac involvement is > 50% in patients with SLE. [3] SLE may affect all parts of the heart, including pericardium, conduction system, myocardium, valves, and coronary arteries. Pericarditis is the most common manifestation occurring in 11-54% of patients. Acute pericarditis can be fibrinous or sero-fibrinous and can lead to cardiac tamponade, constrictive pericarditis & purulent pericarditis. Corticosteroids and non-steroidal anti-inflammatory drugs are first line drugs for severe cases of acute pericarditis. Clinically myocardial involvement is seen in 7-10% of cases. Myocarditis can lead to ventricular dysfunction, cardiomyopathy & heart failure, which can be aggravated by presence of renal failure, hypertension & coronary artery disease. Endomyocardial biopsy is the investigation of choice for diagnosing myocarditis, though it is not frequently required in clinical practice. [4]

The classical valvular abnormality is the verrucous Libman-Sacks lesion. Valvular abnormalities have been documented in up to 35% of patients with lupus; most frequently in patients with anti-phospholipid syndrome. Libman-Sacks endocarditis most commonly involves mitral and aortic valves even though all four valves can be involved. Valvular abnormalities occur as masses, diffuse leaflet thickening, valvular regurgitation, and, infrequently, stenosis. Distinguishing vegetation of infective endocarditis from those of Libman-Sacks endocarditis may be difficult. [5,6]

The risk of coronary artery disease is also increased in patients with SLE. Patients of anti-phospholipid syndrome suffer from increased rate of myocardial infarction and cerebrovascular accidents. [7] Conduction abnormalities with bundle branch block and AV blocks also been described, particularly in children with anti-Ro/SSA antibodies.

Renal involvement is a major cause of morbidity in patients with SLE, leading to chronic kidney disease. 61-81% of patients with SLE have renal involvement. [8] A renal biopsy is necessary to confirm the diagnosis and classify the stage of lupus nephritis and hence to guide treatment. Our patient had nephrotic-nephritic urinary sediment with hypertension. Renal biopsy showed features of class IV -G (A) (Active diffuse global proliferative lupus nephritis) disease with full house on immuno- fluorescence. Anti-dsDNA was also positive. Anti-smith antibodies have been shown to have significant association with lupus nephritis. Complements, both C3 and C4 are depressed, reflecting preferential activation of the classical complement pathway.

The clinical features of lupus nephritis (LN) depend on the histological class of the disease, classified as per the International Society of Nephrology/Renal Pathology Society 2003 classification. (Table 1) Class I LN; has only minimal mesangial involvement; has no or mild clinical disease. Class II LN; mesangial proliferative LN, with proteinuria <1gm/day, low complements

and normal renal functions. Class III LN; focal proliferative LN, with nephrotic range proteinuria, hypertension and renal dysfunction. Class IV LN; diffuse proliferative LN, with active sediments, renal impairment and hypertension and low complement levels. Class V LN; membranous LN, with nephrotic range proteinuria and may develop thrombotic complications. Class VI LN; advanced sclerosing LN with sclerotic and fibrotic lesions leading to irreversible renal impairment. [9]

The treatment of LN depends upon the class of the disease. Patients with proliferative LN require aggressive immunosuppressive therapy with steroids and cytotoxic agent i.e. either with cyclophosphamide or mycophenolate mofetil. [10] Resistant cases may require rituximab therapy. The long term outcome depends upon response to therapy and frequency of relapses. 8-15% of patients with LN progress to end stage renal disease.

Our patient responded to immunosuppressive therapy and achieved remission with decrease in proteinuria and improvement in renal functions. Her cardiac functions improved dramatically with disappearance of pericarditis and Myocarditis.

Conclusion

SLE is frequent cause of chronic type 5 cardiorenal syndrome, leading to concomitant renal and myocardial dysfunction with obvious clinical manifestations. Timely diagnosis and appropriate immunosuppressive therapy along with measures to counter heart failure is required for active lupus nephritis with cardiac involvement. The mortality and morbidity depends upon the outcome of the primary condition.

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Table 1:

Abbreviated International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (2003)

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosing lupus nephritis

Figure 2
Classification criterion for systemic lupus erythematosus

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		*Antiphospholipid antibodies*	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	*Complement proteins*	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	*SLE-specific antibodies*	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Manipal Hospitals Logo Launch - Ghaziabad

Cervical Metastasis in a Case of Glioblastoma Multiformae

Jaskaran Singh[A], Jasleen Kaur[B]

[A] Consultant Neurosurgery, Manipal Hospitals, Patiala

[B] Senior Consultant Pathology, Manipal Hospitals, Patiala

Introduction

Glioblastoma multiformae (GBM) is the most common primary brain tumor in adults with an overall poor prognosis. In spite of its aggressive nature, extracranial metastasis of Glioblastoma multiformae are extremely rare having an incidence of 0.2-2% in literature. [1,2,5] These are generally seen post-surgery or when there is breach of the blood brain barrier due to local extradural spread. The possible mechanism of metastasis suggested are phatic spread, venous invasion and direct invasion through dura and bone. [1-5] Most common sites of metastasis are lungs/pleura, lymph nodes, bones and liver. [1,2]

Case Report

Here we present a case of 45 years old female patient who was operated for recurrent left temporal glioma (first biopsy was low grade glioma WHO grade 2, operated 1.5 years back). The histopathology was consistent with GBM (WHO grade 4). Immunohistochemistry revealed GFAP positive, IDH-1 mutant with 40% Ki-67 index. After second surgery, she received chemo-radiotherapy but developed a neck swelling six months after the second surgery (while on temozolomide). MRI showed a T1 hypointense, T2 hyperintense neck tumor with heterogenous contrast enhancement.

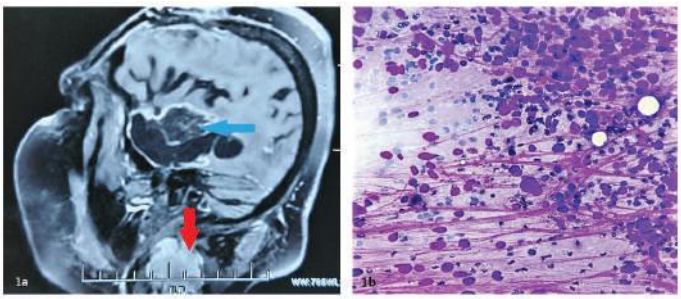

Figure 1 : Figure 1a shows sagittal section of contrast MRI with blue arrow pointing to the primary resection site having peripheral enhancement (? recurrent lesion), red arrow showing the metastatic mass in the posterior triangle of neck having heterogenous contrast enhancement. Neck mass was subjected to FNAC which revealed highly pleomorphic malignant cells with high nuclear: cytoplasmic ratio along with fibrillary processes (40 x magnification, H&E stain) consistent with GBM metastasis. (Figure 1b) Patient continued radiotherapy and chemotherapy (temozolomide) but succumbed to the disease 2 months after diagnosis.

Conclusion

Thus, metastasis should be kept as a differential for cervical lymphadenopathy in a case of glioblastoma multiformae. The treatment for extracranial metastasis in GBM is radiotherapy and chemotherapy (Temozolomide) but overall prognosis remains dismal with median survival being 6 +/- 0.8 months. [5]

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Manipal Hospitals Logo Launch - Jaipur

Infant with Hypotonia with Rare Disorder: A Case Report

Sachin Jain
Consultant Neonatologist, Department of Pediatrics & Neonatology, Manipal Hospitals, Gurugram

Introduction

Hypotonia and weakness in early infancy may be sign of central nervous disorder, primary neuromuscular disorder or genetic syndrome. It represents a diagnostic challenge for the treating pediatricians and neonatologists. Here we present an evaluation of a case of congenital hypotonia with dysmorphic features delivered at Manipal Hospitals, Gurugram.

Case Report

Birth and Perinatal History:

A late preterm (35+4weeks) male baby was delivered by cesarean section in view of fetal distress. The parents were non-consanguinous with uneventful family history, mother being G2P1. The elder sibling was 5 years old male with normal for age milestones. Anthropometry at birth was: Weight 2380 gm (10th centile), length 43 cm (<10th centile), occipito-frontal circumference 32 cm (<50th centile) by Fenton preterm growth charts. Baby cried immediately after birth but had cyanosis & respiratory distress, so was shifted to Neonatal Intensive Care Unit (NICU) on free flow oxygen. He had tachypnea with grunting & desaturation (Downes score 6), thus was started on bubble CPAP support (FiO2 0.35, PEEP 6 cm H2O). He improved gradually & was shifted to Heated Humidified High Flow Nasal Cannula (HHHFNC) support at 48 hrs of life (FiO2 23% & flow 7 l/min). Baby had shallow respiration & required HHHFNC support for 7 days. Apart from USG scan done at 20 weeks which showed polyhydroamnios (AFI 17.5cm) with mild bilateral hydro-uretronephrosis and bilateral club feet, no other prenatal screening tests were done. Maternal perception of fetal movements was normal.

On examination baby had severe hypotonia with extended arms and slightly flexed legs. There was no attempt to raise head in sitting position for the assessment of flexor and extensor tone. Complete head lag was there on pull to sit and curved back with head and limbs hanging on ventral suspension. Baby had broad root of nose, high arched palate, low set ears, long philtrum, widely spaced nipples (Figure1), open mouth, bilateral talipes equinovarus deformity of both feet (Figure 2), cortical thumb, single simian crease and flexed index finger (Figure 3). Baby was having bilateral undescended testis with hypospadias with normal phallic length. Baby was accepting breast feeds well with good rooting and sucking reflexes and had stable hemodynamics.

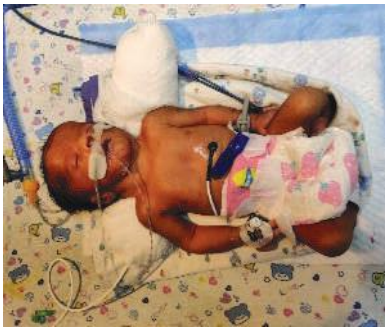
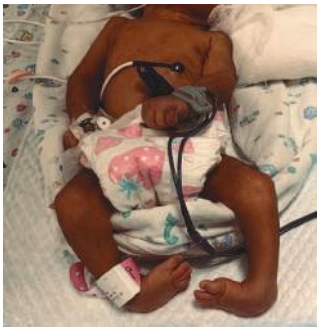


Figure 1 :
Bilateral Talipes Equinovarus Varus deformity

Figure 2 :
Extended Posture, Broad Neck, wide spaced Nipples, Low set ears



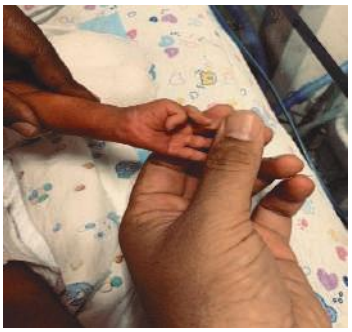
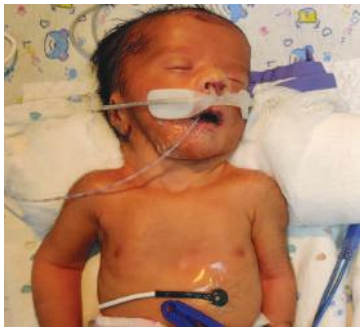


Figure 3 :
Extended Posture, Broad Neck, wide spaced Nipples, Low set ears

Figure 4 :
HHHFNC Support



Investigations

Septic screen, kidney function tests & plasma sugars were normal. Venous blood gas showed respiratory acidosis with normal lactate levels. Post-natal USG done at 48 hrs of life showed grade 1 bilateral pyelectasis. X-ray chest, 2D echocardiography & USG cranium were normal.

Genetic Evaluation: Q-PCR for trisomy 13, 18, 21 X and Y chromosome were normal.

Case was discussed with clinical geneticist & possibilities of Smith Lemli Opitz Syndrome (Undescended testis, hypospadias), Ehlor Denlos Syndrome (contracture and laxity of joints), Arthrogryposis, Otopalatodigital type II (characteristic facial feature), Congenital Myopathy (abnormal respiratory rate and pattern) or Microdeletion/dupli syndromes were kept. Targeted Whole Exome Sequencing (WES) detected two heterozygous likely variations of uncertain significance in STAC3 gene, which causes congenital myopathy, Bailey - Bloch type, that correlated with the phenotype in this child. STAC3 related disorder results in congenital weakness, open mouth appearance of face, congenital contractures which all correlated well with the clinical features in our child. However, the variations/ mutations detected in STAC3 in the child were novel and had not been reported before in any patient. Hence, to further gather evidence for pathogenicity of these variations, it was advised that the parents undergo testing to demonstrate the presence of genetic variations in them.

Follow up advice

The child was advised for physiotherapy, early stimulation therapy and follow up for close monitoring of growth, developmental milestones and any respiratory issues.

Discussion

Hypotonia in a newborn poses a diagnostic challenge for neonatologists & pediatricians, as it is a clinical sign suggestive of both benign & serious conditions. The differential diagnosis for neonatal hypotonia is extensive but detailed history & complete examination is the key in

narrowing the differential diagnosis. The physical examination should include the assessment of relevant clinical signs including a detailed neurologic evaluation & an assessment for dysmorphic features. [1, 2] The presence of congenital malformations in other organ systems and dysmorphic features indicates a possible syndromic diagnosis. Important conditions to rule out are trisomy 21 where hypotonia is associated with short stature, [3] characteristic facies & cardiac anomalies, [4] Single gene testing & gene panels are used when specific disorder associated with small number of genes is suspected. WES was done in our case is helpful when disorders are genetically heterogeneous with complex neurological diagnosis & multiple congenital anomalies. [5]

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Manipal Hospitals Logo Launch - Gurugram

Role of Carbon Dioxide Angiography in Critical Limb Ischemia- A Case Report

Deepa Kizhakke Veetil[A], Nitish Anchal[B]

[A] Associate Consultant, Department of Surgery, Manipal Hospitals, Delhi

[B] Consultant & Head, Department of Vascular Surgery, Manipal Hospitals, Delhi

Introduction

Critical limb ischemia is chronic limb ischemia with rest pain with or without loss of tissue or ulceration. [1] It needs to be identified in time as it can lead to limb loss without specific treatments. Once diagnosed these patient usually undergo Digital Subtraction Angiography (DSA) which is still the gold standard to diagnose and treat these vascular lesions. But the standard angiography, angioplasty and stenting procedures require the use of iodinated contrast material which is associated with its risks of hypersensitivity reactions and nephrotoxicity.

In patients like diabetics and with borderline renal function it is usually a decision of risk to benefit while administering the contrast required for the intervention. These patients are at a higher risk of contrast induced nephrotoxicity and in this subgroup of patients carbon dioxide angiography is a good alternative that can be used. [2]

Carbon dioxide angiography for the peripheral vessels was reported by Funaki in 2008. [3] This has been further tested in specific patient subgroups by Diamantopoulos et.al, [4] and Abdelbary et.al. [2] in their studies. Carbon dioxide angiography is used as a diagnostic tool to aid the interventional radiological procedures of peripheral angioplasty and stenting of blood vessels.

Carbon dioxide is a colourless and odourless gas found naturally in the human body. It has unique properties like a high solubility, it's compressible, buoyant and has a low viscosity. Tapping these properties has helped develop it into a good alternative for iodinated contrast material. [5]

It behaves differently when compared to the iodinated contrast, it displaces the blood and therefore it is visualized as a negative contrast in digital subtraction angiography imaging. It is a soluble gas which dissolves in blood and gets excreted through the lungs. Therefore it can be used in patients with renal dysfunction who are not candidates for administration of the iodinated contrast material.

We report the usage of this novel technique at our hospital in the month of March 2021 which helped us to avoid the side effects of administering the iodinated contrast agents in this patient.

Case report

A 74 year old diabetic & hypertensive patient presented with history of right foot wound debrided elsewhere & was non-healing at presentation. On examination the right popliteal pulse was feeble & distal pulses were absent. On the dorsum of right foot there was a 6 x 5 cm ulcer with non-healing margins, unhealthy floor & an exposed tendon in the base. (Fig. 1)

She was evaluated with Arterial Doppler ultrasound which showed atherosclerosis of the Right Common Iliac Artery & External Iliac Artery without any stenosis. Right Superficial Femoral Artery (SFA) & Tibio-peroneal trunk (TPT) showed near total occlusion with monophasic flow in Peroneal and Anterior Tibial Artery (ATA).

Patient was admitted & after pre requisite investigations & informed consent, was taken up for procedure. In view of the age & comorbidities, patient was taken up for a carbon dioxide angiography. For optimum effect the leg was elevated by 10-150 by tilting the table. The procedure was done under general anaesthesia to avoid discomfort to the patient during the procedure. But studies have shown that it can be done under sedation alone. [4]

Carbon dioxide pressure relief valve was preset to 1.3 bar and pure medical carbon dioxide was used for the procedure. The accessories used for the procedure in addition to the regular standard ones were the carbon dioxide angioset, pure medical carbon dioxide, pressure reduction valve and carbon dioxide aseptic filter.

Carbon dioxide peripheral angiography revealed > 90% occlusion in the mid & distal part of the right superficial femoral artery, as depicted in the Fig. 2. The right tibio-peroneal trunk, anterior tibial and peroneal artery had multiple chronic total occlusion lesions as demonstrated. The superficial femoral artery lesion was managed with the carbon dioxide angiography followed by angioplasty and stenting. For the below knee lesions reduced amount of iodinated contrast (around 5ml) was used for doing a completion check angiography.

Using carbon dioxide as the medium of angiography helped us in saving the limb and enabling wound healing in this patient.

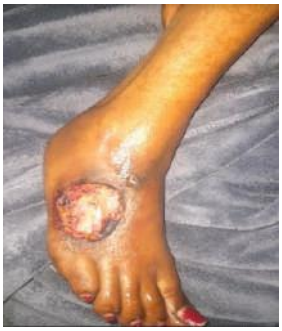

Figure 1 :
Right dorsum of the foot non healing wound

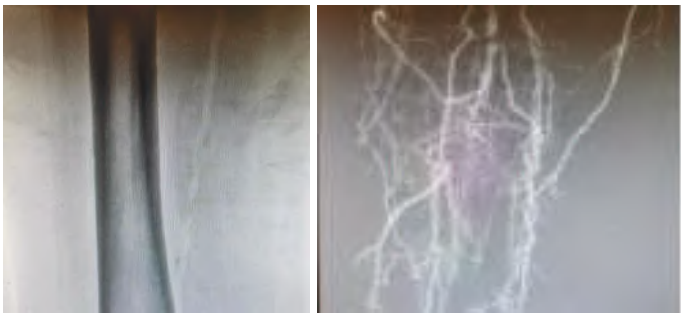

Figure 2 : Carbon dioxide angiography images of the patient showing right SFA mid & distal part >90% occlusion, tibioperoneal trunk, peroneal & Anterior tibial artery multiple CTO noted

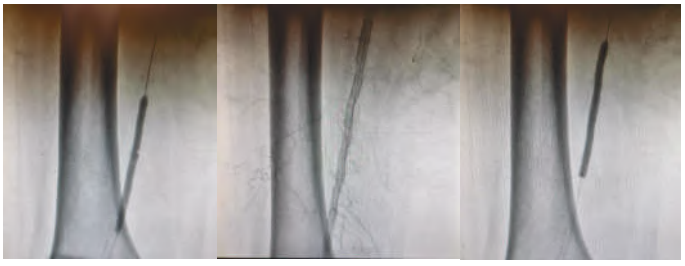

Figure 3 : Angioplasty of the mid and distal part of SFA done using 4 x 80mm balloon and stenting done using 5.5 x 100 mm supera stent

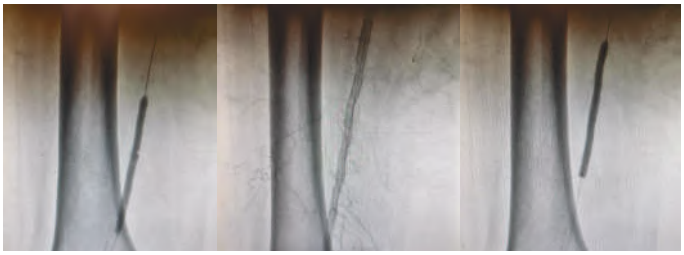

Figure 4 : Angioplasty of the tibio-peroneal trunk, anterior tibial artery and peroneal artery done using 2.5 x 120 mm balloon. Post angioplasty improvement in blood flow noted

Figure 5a : Post angioplasty skin grafting of the wound done within 10 days of angioplasty and improvement of blood flow

Figure 5b: Status of the wound at one month follow up

Post angioplasty the wound healed well with regular dressings & on post angioplasty day 10 patient was taken up for split thickness skin grafting of the wound as depicted in the Figure 5.

Discussion

Carbon dioxide angiography used in our patient helped in avoiding the nephrotoxicity of the iodinated contrast. We have been able to successfully demonstrate the advantage of this technique and believe that it would help the patients presenting with impaired renal function and peripheral vascular disease in the future.

Carbon dioxide angiography hasn't been approved for use in children and is contraindicated in patients with respiratory insufficiency. So patient selection for the procedure remains important.

This case also highlights the need to have a sequential treatment plan made for each patient to enable a favourable outcome, which was wound healing for our patient.

Identifying the vascular etiology in non-healing wounds or rest pain remains the first most important clinical diagnostic step for these patients. Once this is done then there is a whole armamentarium of diagnostic tests and interventions possible to give the patient pain relief and also wound healing by improving the blood flow to the tissues.

These patients already have multiple comorbid conditions by the time they present with this "leg attack" which is the critical limb ischemia i.e., stage III and Stage IV of chronic limb ischemia as per the Fontaine classification. [1] Diagnostic modalities and treatment offered should not contribute to an increase in the already existing comorbid conditions. Therefore making the diagnostic and treatment options safer for them to the extent possible remains the goal while managing these patients.

Using the novel technique discussed in this case report hopes to achieve this goal by opening venues for our patients with renal impairment and peripheral limb occlusive vascular disease.

Conclusion

Carbon dioxide angiography is a safe and useful alternative in patients with impaired renal function presenting with peripheral vascular occlusive disease. Using this technique we were able to avoid the nephrotoxicity of the iodinated contrast in our patient. Endovascular treatment for peripheral vascular disease in patients is

the first best option available especially for patients with multiple comorbidities and this modality can be made safer for them with the newer adjunct technologies.

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Running Marathons Post CABG

Dr. Ashu, a 51-year-old doctor from Delhi NCR underwent a routine cardiac health checkup including stress echo which showed minor changes. Following which a coronary angiography was done to rule out CAD. However, he was diagnosed with multiple blockage and was advised a coronary artery bypass graft (CABG) which was performed on 16th December 2020 by Dr Yugal Kishore Mishra, Chief Of Clinical Services, Head Of Cardiac Sciences And Chief Cardio Vascular Surgeon, HCMCT Manipal Hospitals and his team.

Dr. Ashu, a marathon runner who has participated in multiple marathons and is a frequent runner, came in for a routine health checkup at the hospital and had no prior symptoms. He was diagnosed with heart blockage despite participating in regular cardio vascular workout.

It's a myth that it will be difficult for patients who underwent CABG procedure to resume all their regular activities like running and strenuous activity, but breaking all the stereotypes. Dr. Ashu before a complete one year of his CABG procedure, ran a distance of 21.2 kms (half marathon) which he completed in 2 hr16 min on 12th December 21. He is doing absolutely fine and looking forward to running more marathons ahead.

Early Intervention with ECMO in Severe Celphos Poisoning: A Case Report

Vipin Jain[A], Ram Sharan Chaturvedi[B], Amit K Singh[C]

[A] Senior Consultant, Internal Medicine, Manipal Hospitals, Jaipur

[B] Consultant Cardiac Anesthesia/ ECMO Specialist, Manipal Hospitals, Jaipur

[C] DNB Resident, Internal Medicine, Manipal Hospitals, Jaipur

Abstract

Celphos (Aluminium phosphide) is a common mode of committing suicide in the country. The mortality rates after celphos ingestion are also very high. So, it is a rare occurrence that a patient is treated successfully and discharged in a stable condition subsequently. We report a case of Celphos ingestion by a young male who was treated successfully at Manipal hospital, Jaipur by the Internal Medicine department. This case highlights the importance of early intervention by means of ECMO (Extracorporeal Membrane Oxygenation) and its significant role in preventing mortality in celphos poisoning.

Introduction

Celphos (aluminium phosphide) is a common rodenticide in India and its ingestion as a means of suicide is a very commonly seen in the population. Here we present a case of a young male who had consumed 4 tabs of celphos, developed severe acidosis and global LV hypokinesia and had to be intubated, put on mechanical ventilation, IABP support and ECMO support for 4 days and was subsequently discharged in a healthy condition.

Case Report

A 25 year old male patient presented with alleged history of ingestion of 4 tablets of Celphos. The patients first ABG showed a ph of 7.29 and lactate levels of 9.9 with HCO3 of 13.6. He was immediately given a gastric lavage with sodium bicarbonate and coconut oil and was started on magnesium sulphate infusion. His baseline investigations were sent. His initial 2D ECHO revealed the EF to be 35% with Global LV hypokinesia.

The patient quickly deteriorated in the ICU, had severe acidosis and raised lactate levels on ABG and profound hypotension. He was put on multiple vasopressors (Noradrenaline, Adrenaline, Dobutamine) and had to be intubated and put on mechanical ventilation. The patient underwent a repeat 2D ECHO which showed global hypokinesia of the heart with an EF of 10-15%. His ABG had a pH of 7.002 with a lactate level of 18 and HCO3 of 9.8.

After discussion with the critical care team, a decision was made to put the patient on Intra-aortic balloon pump and subsequently ECMO support. ECMO was initiated (Veno-Arterial ECMO) by cannulation of right femoral vein by a 24F

venous cannula. The return cannula was a short arterial cannula of 18F inserted via the right femoral artery. Additional distal perfusion 7 F return cannula ("backflow cannula") was inserted retrogradely into the common femoral artery with a flow of 3.7 L/min & FiO2 of 100%. (Day 1)

After the procedure, S. Procalcitonin was found to be high with leukocytosis (TLC – 23610). Patient was put on Inj Meropenem & Teicoplanin. A 2D ECHO was performed to check the EF and position of the cannula. The EF was still 10-15% with global LV hypokinesia with cannula in situ with LVOT – VTI – 6cm. He also developed atrial fibrillation for which he was started on Amiodarone infusion along with the ongoing magnesium sulphate infusion.

He underwent multiple serial 2D ECHO and ABG analysis

	Day 1	Day 2	Day 3
	Severe global LV hypokinesia	Severe global LV hypokinesia	Global LV hypokinesia
EF	15-20%	25%	25-30%
LVOT- VTI	8.7cms	12.2cms	12.9cms
pCO2	51.1	36.9	48.3
pO2	225	153	130
Lactate	19	3.9	1.1
pH	6.95	7.47	7.37

As the patient was maintaining stable vitals, it was decided to wean him off ECMO & decannulate him. The patient was weaned off the mechanical ventilator & extubated along with IABP removal, the next day. His 2D ECHO after removal of all support showed mild global LV hypokinesia with LVEF of 50%. The patient was discharged in a stable condition.

Discussion

Celphos poisoning has always been a menace for the physicians due to non-availability of its antidote and near 100% mortality which makes it difficult to salvage the patients.[1] The fatal dose is around 0.5 g and acute poisoning with these compounds may be direct due to ingestion of the salts or indirect from accidental inhalation of phosphine generated during their use.

The treatment involves usage of gastric lavage with sodium bicarbonate & coconut oil. The rationale behind the use of a mixture of soda bicarbonate & coconut oil in our patients is guided by the chemical reaction of AlP with moisture and HCl, liberating phosphine gas which rapidly gets absorbed through gastric mucosa. As the poison itself causes a lot of gastric mucosal damage, it exposes lot of raw area for

phosphine absorption. The mechanism by which coconut oil reduces the toxicity of phosphides is unknown but most probably it forms a protective layer around the gastric mucosa, thereby preventing the absorption of phosphine gas. [1]

Some studies also suggest a beneficial effect of giving magnesium infusion to maintain stability of cardiac cell membranes. In various studies, the proportion of patients who received magnesium sulfate was significantly higher among survivors than among non-survivors. The role of magnesium sulfate as a treatment option has been described in various studies with ALP poisoning. [2,3] The possible mechanism of action of magnesium sulfate was its effect as a cell membrane stabilizing agent reducing the incidence of cardiac arrhythmias. This anti-arrhythmic action could probably result in improvement in myocardial functioning. [2]

Extracorporeal membrane oxygenation (ECMO) is a well-documented therapy for improving survival in patients with severe respiratory failure. Veno-venous ECMO is the preferred method in patients with isolated respiratory failure. However, veno-arterial (VA) ECMO should be used in patients with combined cardio-vascular and respiratory failure. The high risk subgroup can identified by the following two criteria: (1) severely reduced left ventricular ejection fraction (LVEF ≤ 35%) and (2) severe metabolic acidosis (pH ≤ 7.0) and/or refractory shock, i.e. systolic blood pressure <80 mmHg despite conventional medical therapies. [3]

The cannulation site is determined based on patient status. The majority of patients underwent percutaneous cannulation through femoral vessels. The ECMO cannulation was done in intensive care unit. A venous cannula was placed in the inferior vena cava or right atrium for drainage infusion. The usual size of venous cannula ranges from 21 to 25 F. The return cannula is a short arterial cannula inserted via the common femoral artery. This cannula is fully inserted to the taper, with the tip lying in the common iliac artery or lower aorta. The usual size of arterial cannula ranges from 17 to 21 F. Additional distal perfusion 9 F return cannula ("backflow cannula") is inserted antegradely into the common femoral artery and directed into the superficial femoral artery.[4]

The patients are maintained on a continuous heparin infusion to achieve an activated clotting time between 180 and 200 s. The goal for the activated clotting time is adjusted if there are issues with bleeding or coagulation. To maintain a hemoglobin level of ≥10 g/dL and a platelet count of ≥100,000 dL−1, patients receive a transfusion during the ECMO treatment. The patients are continuously monitored in terms of hemodynamic improvement, reversal of metabolic acidosis, and adequate oxygenation. [5]

Among AlP poisoning patients in the high-risk subgroup, the mortality rate is significantly lower in those treated with ECMO. There is significant improvement in LVEF during the hospital stay. Low baseline LVEF is an important predictor of mortality in AlP poisoning patients who receive ECMO therapy. [6]

ECMO is associated with the following complications: vascular access site hematomas requiring multiple blood

transfusions, the need for surgical correction of vascular complications, profound thrombocytopenia and acute renal failure with or without the need for renal replacement therapy. [3]

This case highlights that early presentation to the hospital and immediate referral to the tertiary care center with facility and experience to use ECMO can make a difference in mortality. The decision to start ECMO should be prompt. Future studies may further refine the clinical criteria for its indications.

Suggestions

Specific measures can be studied to reduce fatal episodes of AlP. These include Role of ECMO & its prompt usage in reducing mortality in celphos poisoning. Role of hyperbaric oxygen should be studied especially in the background of inhibition of mitochondrial respiratory chain. The gastroscope can be used to remove the undissolved pellet.

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Polyembolokoilamania: Urethral Self-inserted Electric Wire in a 20-year-old Boy

Yogesh Garg

Senior Consultant - Urology, Manipal Hospitals, Patiala

Abstract

Polyembolokoilamania is broad group of disorders in which patient inserts foreign bodies into his/her body orifices for any reason which may be psychological or non-psychological. Self-insertion of foreign bodies in urethra is rare especially in people without any pre-existing mental disorder. The presentation to the hospital is usually delayed as the patient is too shy and ashamed to seek medical advice. Treatment by minimally invasive procedures (endourological), if possible, is preferable as they minimize trauma to bladder and urethra. Once foreign body has been retrieved detailed psychiatric evaluation is needed to detect any underlying mental disorder. We herein report a case of urethral self-insertion of electric wire for self-gratification.

Introduction

Self-insertion of foreign bodies in the male urethra is a rare urologic emergency. It is a part of a broad group of disorders called as Polyembolokoilamania in which patient inserts foreign bodies into his/her body orifices for any reason which may be psychological or non-psychological. Amongst the non-psychological reasons, the usual cause is sexual self-gratification. When the foreign body has been inserted into genito-urinary system the presentation is usually delayed owing to the emotion of shame and embarrassment. We herein report a case of urethral self-insertion of electric wire for self-gratification.

Case Report

A 20 year old boy, with no past medical history came to our department for hematuria for 1 day. Detailed questioning revealed that he had himself inserted a wire into his urethra for autoerotic stimulation after watching some explicit video on internet. On examination, wire was palpable throughout the entire penile length. Plain X-ray of the pelvis revealed a jumbled up mass of wire overlying penile soft tissue shadow. (Figure 1) As the mass of wire was palpable in the entire penile shaft we feared the entry of wire into the cavernosa. Retrograde urethrogram was done which revealed that the wire was confined to urethra and there was no extravasation of contrast. (Figure 2)

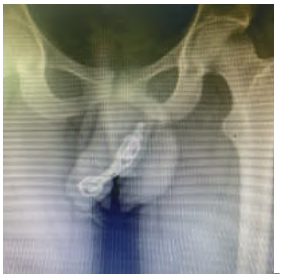
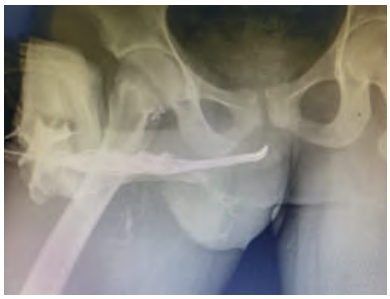


Figure 1: Plain X ray Pelvis showing wire inside the urethra

Figure 2 : RGU showing wire confined to urethral lumen with no contrast extravasation



Patient was taken up in for surgery, under spinal anesthesia. Urethroscopy was planned but could not be done as wire was tightly filling up the entire meatus. Meatotomy was done and the wire was reached and held with a hemostat. With gradual movements and traction the wire was pulled out. (Figure 3, 4) After removal of wire Urethroscopy was done which showed bulbar urethral injury. Foley catheter was placed and retained for 1 week. Postoperative period was uneventful; the patient was discharged after one day and referred to the psychiatric department. Patient and his family were counselled regarding the chances of development of urethral stricture due to the urethral injury caused by wire insertion.

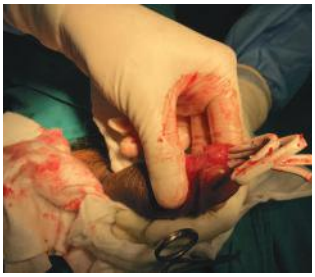
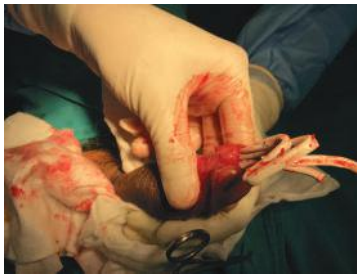


Figure 3 : Extraction of wire from urethra

Figure 4 : Retrieved knotted wire from urethra



Discussion

Cases of urethral foreign bodies have been described in medical literature quite often. [1] Though they are encountered in both sexes & all age groups, there is a male predominance. [2] The wide variety of self-inserted foreign bodies include needles, pencils, ball point pens, garden wire, copper wire, speaker wire, safety pins, telephone cables, straws, string, toothbrushes, Intrauterine Contraceptive Devices (IUCD), household batteries, light bulbs, marbles, cotton tip swabs, plastic cups, thermometers, plants and vegetables, & even parts of animals (leeches, squirrel tail, snakes, bones). [3] Almost every household item which can be physically inserted into the urethra has been described in literature. [4]

Patients with a foreign body stuck up in urethra usually delay seeking medical advice due to embarrassment & shame. It also depends on the degree of discomfort experienced as clinical presentation varies from minor to moderate signs such as dysuria, urinary frequency, strangury or hematuria to grave infectious complications like Fournier's gangrene. [5] Fortunately in our case there was no such delay & the patient presented to our hospital in less than 24 hours. In some cases the diagnosis is made after several years with no significant symptoms.

Causes of foreign bodies in lower urinary tract include self-insertion in patients with underlying (mental illness, borderline personality disorder, & drug abuse), iatrogenic causes during urological intervention, traumatic causes & migration from other organs. However, the commonest motive is sexual variation gratification & is not always associated with psychiatric disorders or drug abuse. [6] Lack of sex education in third world countries where talking about sex is still a taboo, might explain this behaviour partly. One rare

cause of urethral self-insertion of foreign bodies has been described in which patient used radio antenna to relieve his urethral itch regularly till one day it migrated proximally & patient had to seek medical help. [7]

Diagnosis is made after careful history (nature of foreign body, duration of insertion), physical examination (that may reveal a hard urethral mass or complication e.g. infection, gangrene) & radiologic evaluation. Plain X-ray pelvis is the first investigation & often sufficient in most cases. However, radiolucent foreign bodies can be missed & it does not give any information on the soft tissue damage. In those cases, ultrasonography, contrast urethrography or cystoscopy are helpful.

Removal of a urethral foreign body may be demanding & many means can be used, including non-operative means (using a basket or forceps), endoscopy, or surgery, including urethrotomy and/or cystotomy if necessary. Extraction method would depend upon the characteristics of the foreign body (namely size, shape, consistency, edges), location of foreign body (distal urethra or proximal urethra or intra vesical) and the time elapsed since insertion. In our case the wire was insulated which to some extent avoided soft tissue injury & facilitated retrieval as we were able to pull out several loops of the wire after de knotting. Uninsulated metal wire would have caused greater soft tissue damage and would have been more difficult to remove. Minimally invasive procedures, are preferred to minimize bladder and urethral injuries and are usually successful. Delayed complications such as urethral stricture can occur, so close follow-up is recommended if possible.

Conclusion

Urethral foreign bodies are rare in daily practice, especially in adolescents with no evident history of mental illness. Psychiatric evaluation is mandatory to detect an underlying mental disorder & to avoid repeat insertion.

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Osteochondral Autograft Transfer System (O.A.T.S.) for an Osteochondral Lesion of Talus- A Case Report

Gurdeep Singh Ratra[A], Pranshul Bishnoi[B]

[A] Senior Consultant, Department of Orthopedics, Manipal Hospitals, Gurugram

[B] Consultant, Department of Orthopedics, Manipal Hospitals, Gurugram

Abstract

Osteochondral autograft transfer is a relatively newer joint preservation procedure that has allowed orthopedic surgeons to treat patients with osteochondral lesions of joints esp. knee and ankle with relatively good outcomes. It's a technically demanding procedure using special instrumentation. We present here an interesting case report of a 33 year old male patient, an avid volleyball player, who had persistent ankle pain and difficulty in daily activities leading to restricted lifestyle due to an osteochondral lesion of talar dome.

Introduction

Osteochondral lesions of the talus (OLT) are characterized by aseptic separation of a fragment of articular cartilage, with or without attached subchondral bone. The causes for OLTs remain controversial. Biomechanical studies have shown that the talar cartilage is softest at the posteromedial part, whereas the maximum thickness is found at the posterolateral corner. Lateral lesions are most commonly caused by acute trauma with a dorsiflexion and inversion injury causing impaction on the fibula. Medial lesions are mostly associated with a single or repetitive supination trauma (microtrauma). Medial lesions are more common and occur most commonly in middle and posterior third of talus. The most important distinction to make is if the lesion is acute or chronic. Surgical management of OLTs is needed for pain relief in select chronic lesions and large acute lesions. [1] McCullough and Venugopal in a study found that in five of six patients treated conservatively for OLTs, radiological assessment at a mean follow-up of nearly 16 years showed that the lesions had failed to heal. [2] In most cases, patients complain of chronic ankle pain, more common with or after sports activities. Swelling and stiffness are accompanied in more advanced cases with constant pain. Occasionally, mechanical symptoms are present including catching, locking, and giving way.

Only 50% to 66% of osteochondral defects can be visualized by plain film radiographs alone. [3] MRI is an ideal screening tool and the method of choice for all patients with suspected OLTs. T2 mapping sequences provide increased sensitivity for cartilage architecture and quality. Dipaola et al developed an MRI classification system based on Berndt and Harty's original radiographic classification, [4] where they classified OLTs as stages I to IV depending upon cartilage health with stage IV signifying a loose body.

Nonoperative treatment is recommended for children and adolescents with small OLTs by partial weight bearing and anti-inflammatory drugs and only allow low impact exercises like biking and swimming for about one year. Immobilization and partial weight bearing has healing potential only for fresh traumatic osteochondral lesions. [5]

The preferred surgical management for stage II to IV OLTS is microfracture to stimulate fibrocartilage formation. Several studies indicate that a defect size greater than 1.5 cm2 results in inferior defect fill and inferior clinical findings after microfracture alone. [6] Osteochondral autograft transfer (OATS) or mosaicplasty is an option in the repair of severe osteochondral lesions with a significant lack of subchondral bone or in cystic lesions. Medium sized OLTs not amenable to other joint-sparing procedures are also indication for primary osteochondral transfer as arthroscopic debridement and microfracture may not be effective. [7]

Potential graft harvest sites are usually ipsilateral knee (supero-lateral femoral condyle, intercondylar notch) or allograft talus. [8] Allograft talus offers nearly the same cartilage thickness and harvest from the exact location of the native talus defect, however, it is not the patient's own tissue.

Surgical approach to the site depends on the location of the defect. Medial talar dome typically warrants a medial malleolar osteotomy. Lateral talar dome typically necessitates ligament releases with or without lateral malleolar osteotomy. The key is that exposure must allow perpendicular access to the OLT. [9]

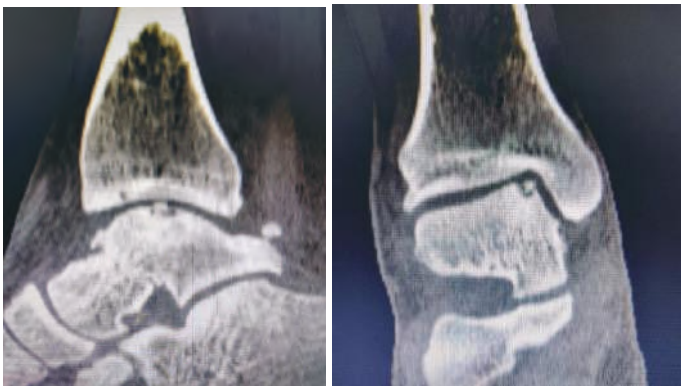


Figure 1 : CT images of the patient showing the osteochondral lesion of medial talar dome with associated loose bodies in the ankle joint

Case report

A 33 yr old male patient presented to us with a prolonged history of right ankle pain and stiffness after playing volleyball, causing swelling, stiffness and difficulty in weight bearing. His pre op x-rays were unremarkable other than few osteophytes. MRI done to rule out OLTs with CT correlation study which showed a significant OLT over medial talar dome classified as grade III along with multiple loose bodies. Ankle arthroscopy and microfracture/OATS with loose body removal was planned. He had an old left knee injury so plan for contralateral knee diagnostic arthroscopy and graft harvest from this knee. The procedure done under regional anesthesia with pneumatic tourniquet and single dose pre op prophylactic antibiotic. Initial arthroscopy of right ankle done using standard anteromedial and anterolateral portals. Multiple loose bodies removed.

Due to large size of the lesion and subchondral cyst, plan for microfracture was abandoned in favor of OATS. Medial approach to ankle with medial malleolar osteotomy for perpendicular access to OLT used.

OATS with 8mm Arthrex device chosen. Left knee diagnostic arthroscopy done initially and supero-lateral femoral condyle cartilage used for open harvest using lateral para-patellar approach.

Figure 2 :
OATS instruments (8 mm)

Figure 3 :
Osteotomy guide K wire for approach

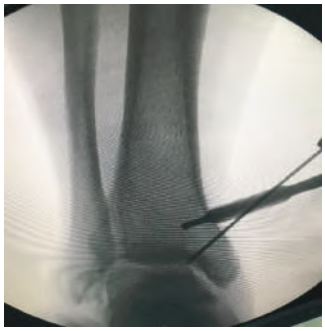


Figure 4 :
Post osteotomy lesion visible

Figure 5 :
Loose bodies removed arthroscopically

Recipient site prepared with Arthrex device compatible to 8 mm cylindrical donor to 11 mm depth. Graft harvest done to depth of 10mm and grafted to recipient site. The graft impacted with non-traumatic tamp to prevent donor cartilage damage. Graft impaction checked under image guidance to avoid any mismatch in subchondral bone. The excised tissue from OLT then grafted back to the donor site. Medial malleolar osteotomy closed and fixed with two partially threaded 4 mm cancellous screws with washer. Periosteal repair was done during closure. Short leg plaster splint given post op. Left knee compression dressing done. Limb elevation done in post-operative period to avoid post-op edema. Patient discharged after 48 hrs when adequate pain relief present.

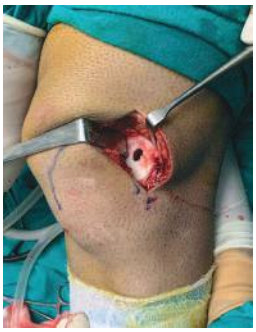
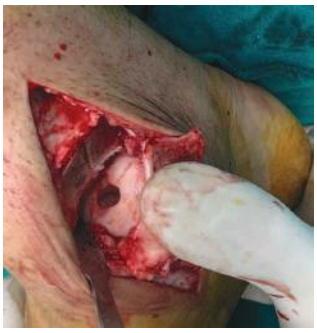


Figure 6 :
Donor site harvested

Figure 7 :
Recipient site prepared



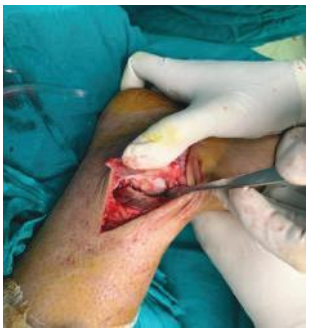
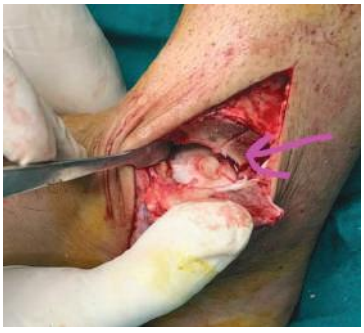


Figure 8 :
Post transfer picture

Figure 9 :
After tamping of graft



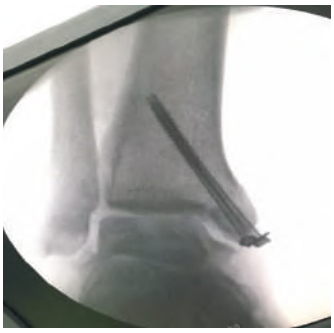
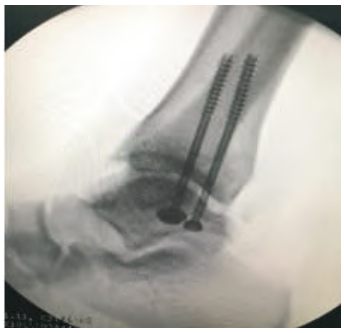


Figure 10 :
Post osteotomy fixation

Figure 11 :
Lateral view



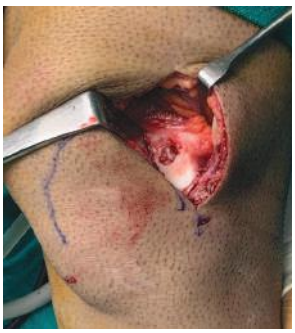
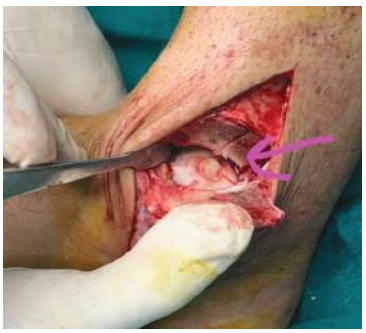


Figure 12 :
Excised bone grafted to harvest site

Figure 13 :
Follow up radiograph at 6 months



Post operatively, patient was kept non-weight bearing initially and allowed walker aided touchdown weight bearing walking after 6 weeks only. Plaster removed at 2 weeks with suture removal, to allow for progressively increasing ROM exercises. Left knee donor site had no pain after initial 2 weeks and ambulation improved thereafter.

Patient is ambulatory without any complaints at 6 month follow up and allowed brisk walks, cycling and swimming. His initial symptoms are no longer present and osteotomy has healed well without any complications.

Discussion

Osteochondral lesions of talus (OLT) may cause significant pain and mechanical symptoms in the involved ankle. There are limited treatment options including conservative management with off-loading of the ankle, microfracture and arthroscopic debridement. OATS offers a good option for such lesions which are grade II to IV, especially when allograft availability is limited. Good to excellent results at short to intermediate follow-up can be obtained in 90 to 94% of patients with excellent functional outcomes, improvement in ROM and much improved pain scores. [10] Best results for smaller defects (those that can be managed with single graft) are seen. Also results are not worse for osteochondral transfer performed as a secondary procedure after failed arthroscopic treatment compared to osteochondral transfer as a primary treatment. Possible complications are wound complications, infection, graft cartilage fissuring/ delamination, risk of developing degenerative change. Also donor site morbidity may be there, but this is rare to cause long term concern. As the talar cartilage is enclosed within the osseous structures of the ankle mortise, a good approach requires either medial malleolar osteotomy or lateral ligament release/osteotomy. Malleolar osteotomy may go to non-union but no such reported complications have been observed in studies especially for medial malleolar osteotomies. Overall OATS is a good primary treatment option for select OLTs which are not amenable for microfracture and also for failed arthroscopic treatment.

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Kanavel's 5th Sign - High frequency Ultrasound in Pyogenic Flexor Tenosynovitis in Diagnosis and Management of Tenosynovitis in a post-Covid 19 patient.

Gaurav Malhotra[A], Gaurav Rastogi[B], Simran Singh[A]

[A] Consultant, Department of Radiology, Manipal Hospitals, Delhi

[B] Consultant, Department of Orthopedics, Manipal Hospitals, Delhi

Keywords – Tenosynovitis, ultrasound, Covid 19.

Abstract

Tenosynovitis is the infection of synovial sheath that surrounds the tendons. Infective flexor tenosynovitis is an orthopedic emergency. High frequency ultrasound is an easily available inexpensive and effective tool which can be used at bedside to confirm the diagnosis of this entity and can actually be termed as Kanavel's 5th sign. [1] This, in conjunction with MRI findings to determine the extent of disease, has significant role in early and prompt diagnosis and management of such cases.

Case Report

A 28 yr old young female patient presented to our hospital with sudden onset of pain, redness, tenderness and swelling of index finger of right hand. There were no known co-morbidities except for history of Covid-19 in July 2020. On clinical examination the 4 Kanavel's signs were positive. An urgent ultrasound was advised and diagnosis of flexor tenosynovitis was suggested. Following an unsuccessful trial of antibiotics, she was advised MRI to look for the extent of disease and was taken up for surgery. Incisional drainage was done. The patient recovered well after the procedure.

Observations

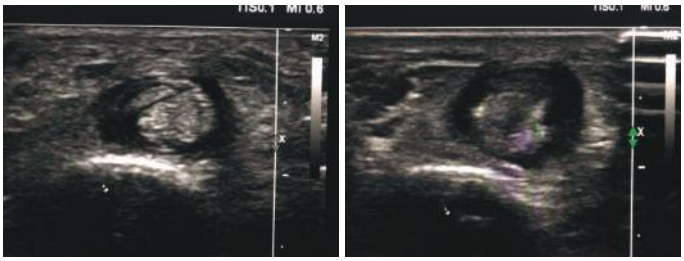

Figure 1 : Ultrasound comparing affected digit with corresponding digit of opposite hand. Significant amount of fluid is seen surrounding the flexor tendon and is absent in unaffected finger.

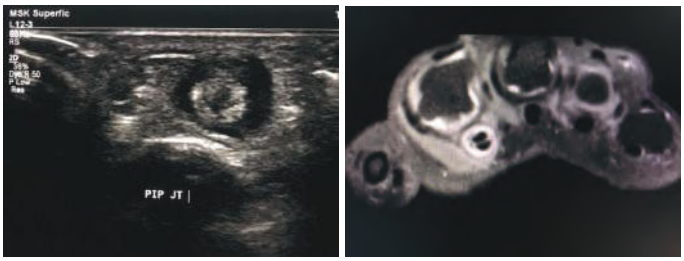

Figure 2 : Comparison between the ultrasound and MRI images demonstrating fluid around the flexor tendon sheath with tenosynovitis.

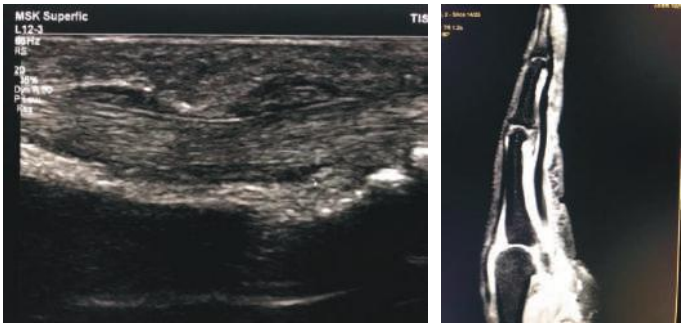

Figure 3 : Determining the extent of disease in longitudinal plane (i) ultrasound and (ii) MRI.

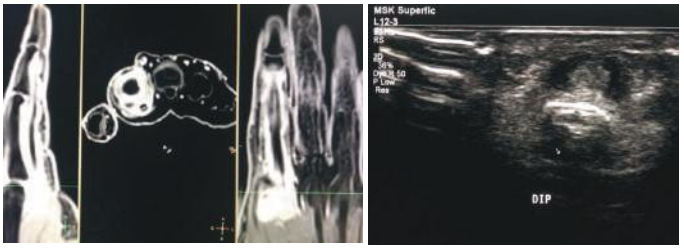

Figure 4 : Comparison between the ultrasound and MRI images demonstrating fluid around the flexor tendon sheath with tenosynovitis.

Discussion

Flexor tenosynovitis is an inflammation of the tendon sheath that results from either introduction of infection or various inflammatory conditions ranging from autoimmune arthropathies to crystal joint depositions. Flexor tenosynovitis caused by infection is an orthopedic emergency. [5] The incidence is 2.5 to 9.4% of all hand infections. The most common risk factors are diabetes, IV drug use and immunocompromised patients. [4] The clinical criteria for this diagnosis is based on Kanavel's Signs namely fusiform edema (often described as a "sausage digit"), PIP joint flexion, and pain with passive extension (most specific) and tenderness on palpation of the flexor tendon sheath. [4] In our case the patient had recovered from Covid -19 in recent past.

This purulent infection is the result of bacterial invasion of the flexor tendon sheath which is a closed anatomic space between the visceral epitenon layer and the outer parietal layer. The infection travels in the synovial sheath that surrounds the flexor tendon. The most common causative organism identified are Staph aureus (40-75%), MRSA (29%) in intravenous drug abusers and other common skin flora (staph epidermidis, beta-hemolytic streptococcus, pseudomonas aeruginosa). In immunocompromised patients, Eikenella and in human bites, Pasteurella multocida is the causative organism. [4]

A complication of infectious tenosynovitis is pyogenic flexor tenosynovitis (PFT) – formation of an abscess at the base of the digit. The abscess is classically described as being in the shape of a "horseshoe." [4]

The four signs commonly known as "Kanavel's signs" were first described by Dr. Allen B. Kanavel [2] –

1. Exquisite tenderness throughout the sheath, limited to the sheath

2. Flexion of the finger.

3. Excruciating pain on extending the finger, mostly at the proximal end, even with passive extension.

4. Fusiform swelling, sometimes termed sausage finger or sausage digit by clinicians.

PFT is primarily a clinical diagnosis. The specificity and sensitivity of these signs have not been established in literature; however, they remain a useful clinical tool for diagnosis of pyogenic flexor tenosynovitis because advanced imaging and laboratory data are often nonspecific. Although white blood cell count, erythrocyte sedimentation rate, and C-reactive protein level can aid in diagnosis, these tests are considered sensitive with a low negative predictive value and specificity. [3] Radiologically, Ultrasound and MRI are the modalities of choice for evaluating a swollen digit in which PFT is suspected. High frequency ultrasound although operator dependent, is an easily available inexpensive and effective tool which can be used at bedside to confirm the diagnosis of this entity. MRI cannot distinguish infectious flexor tenosynovitis from inflammatory but may help determine the extent of the disease process. [4]

PFT requires timely recognition and intervention by the clinician. Prompt treatment of PFT does not however, eliminate the potential for complications. Previous studies report a 10% to 25%

incidence of residual digital stiffness resulting from flexor tendon adhesions, joint capsular thickening, breakdown of the pulley system/flexor sheath, or surgical impediments. Further complications may include spread of infection, necrosis of tendon and tendon rupture, osteomyelitis, and amputation. Factors increasing the likelihood of amputation include delayed treatment, digital ischemia at presentation, subcutaneous purulence, age greater than 43 years, and comorbidities including diabetes mellitus, renal failure, and peripheral vascular disease. [3]

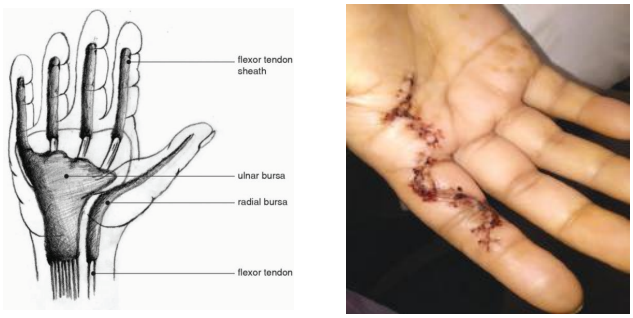

Figure 5 : Flexor sheath abscess – two weeks post op. Swelling & redness reduced considerably

Surgery was done using Modified Brunnelli Approach and the long flexor tendons were found to be encased in brownish necrotic tissue along with scant pus. There was considerable inflammation of the flexor sheath with areas of necrosis. The flexor tendon itself had lost its sheen and was soft in consistency suggestive of impending rupture. The surgical findings corroborated with the ultrasonographic diagnosis of Pyogenic Flexor Tenosynovitis. Thorough debridement was done along with pulsed fluid lavage all through the length of the flexor sheath. Capsulotomy of the joints of the finger revealed healthy proximal interphalangeal joints as well as metacarpo-phalangeal joints. Wound was closed in zig-zag manner over a number 12 Romovac Drain.

Post-operatively, the finger was immediately mobilized to decrease the chances of adhesion formation and satisfactory results in terms of pain relief and movements were achieved after a brief period of physiotherapy. Intra-operative cultures grew Staphylococcus Aureus and appropriate antibiotics were administered for 6 weeks

Conclusion

system /Finger is a simple, easily available and effective modality used at bedside in diagnosis of flexor tenosynovitis and is extremely accurate in urgent settings and may be termed as Kanavel's 5th sign.

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Anesthetic Management of Patient of Achalasia Cardia with Coronary Artery Disease for CABG

Rakesh Kumar Solanki[A], Naresh K Aggarwal[B], Yugal K Mishra[C]

[A] Consultant, Department of Cardiac Anaesthesia, Manipal Hospitals, Delhi

[B] HOD, Department of Cardiac Anaesthesia, Manipal Hospitals, Delhi

[C] HOD, Department of Cardiac Surgery, Manipal Hospitals, Delhi

Abstract

Achalasia of the esophagus is a rare condition with a reported incidence of eight cases per 100,000 population. [1] Achalasia is a disorder characterized by aperistalsis of the esophageal body and impaired relaxation of the lower esophageal sphincter. Dysphagia and regurgitation of undigested, retained food or accumulated saliva are common presenting symptoms. Recurrent aspiration pneumonia may also occur particularly in older patients. This is a report of patient with achalasia with coronary artery disease who underwent coronary artery bypass grafting (CABG) under general anesthesia which was induced using the rapid-sequence induction technique.

Case Report

The patient was a 75 years old female, ASA physical status III, with a Mallampati class III airway. She had recovered from COVID 19 infection three months back. She was a known case of achalasia cardia and underwent esophageal dilation twice. Her coronary angiography revealed coronary artery disease and was advised CABG surgery. Her HRCT chest confirmed esophageal lumen dilatation with dependent fluid density and air lucency.

Patient was kept nil orally for 12 hrs, rapid-sequence induction of general anesthesia using etomidate and succinyl choline with cricoid pressure was performed with the patient in the supine position. [2] Some difficulty in visualizing an anteriorly placed larynx was felt to be exaggerated by the cricoid pressure. Gradual release of the cricoid pressure to improve visualization of the larynx was immediately followed by regurgitation of milky fluid from the esophagus into the mouth. Immediate suctioning of the regurgitant fluid was followed by successful endotracheal intubation. The trachea was suctioned and was found to be clear of fluids prior to applying positive pressure ventilation. No evidence of aspiration was found following the procedure. Patient was extubated on postoperative day 1 and shifted to ward on 3rd post-operative day.

Discussion

Features of achalasia include degrees of dysphagia, regurgitation, chest pain and rarely polyarthritis. Respiratory complications due to aspiration of esophageal contents result in low-grade tracheo-bronchitis, pneumonitis or

pulmonary fibrosis. Aspiration of large volumes may lead to choking, lobar collapse, abscess formation or bronchiectasis, and in patients whose esophageal content is colonized with atypical mycobacteria, overspill may result in clinical and radiological features identical to tuberculosis. [3] Achalasia are clearly at a high risk for aspiration during general anesthesia. The rapid-sequence induction technique with endotracheal intubation and cricoid pressure is, therefore, indicated. [4] Gastric tube insertion and aspiration of esophageal contents is also recommended. [5]

Conclusion

In conclusion, although the rapid sequence induction technique may be intuitively indicated in patients with achalasia during anesthesia it may still be associated with the risk of aspiration. It is, therefore, prudent to take additional measures to minimize that risk including positioning the patient in head-up position and being prepared for the immediate suctioning of any fluids that regurgitates into the mouth.

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A Rare Case of Wandering Fibroid: Case Report

Arti Mahla[A], Neha Godara[B]

[A] Consultant, Department of Obstetrics and Gynecology, Manipal Hospitals, Jaipur

[B] Associate Consultant, Department of Obstetrics and Gynecology, Manipal Hospitals, Jaipur

Abstract

Wandering fibroids are exceedingly rare extra-uterine neoplasm in contrast with uterine fibroids which are the most common uterine masses. They present in unusual locations that can confound imaging and diagnosis. We present a case of a peri-conceptional woman, previous history of myomectomy, one live issue, planning for second pregnancy. USG and MRI were s/o multiple large fibroids in the uterus. Wandering fibroid diagnosed provisionally intra operatively, was confirmed on histopathology. Patient was managed successfully but these types of cases need revised protocols in fibroid management as their clinical presentation and unusual locations are big challenges for clinicians to reach correct pre-op diagnosis.

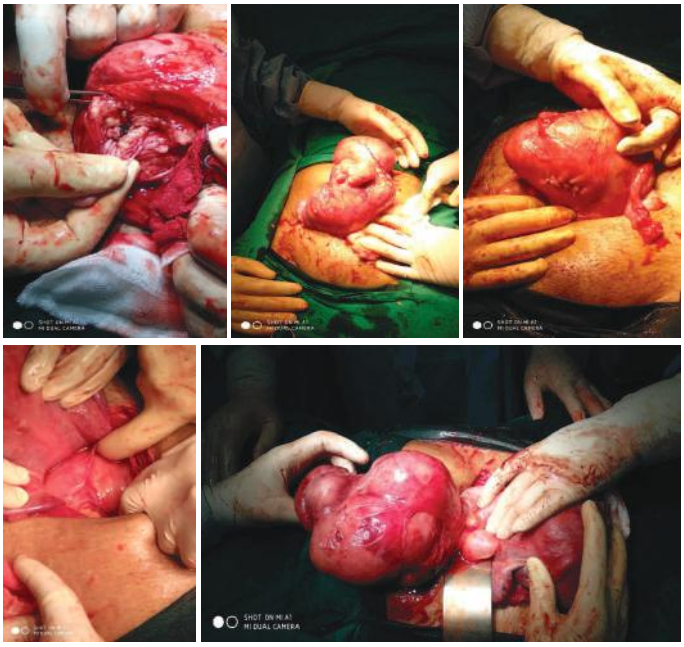
Introduction

Looking into parasitic myoma's infrequent occurrence, its diagnosis is very rarely done on imaging or on clinical examination of patient. In our case, history of laparoscopic myomectomy in past and imaging studies showed multiple myomas. After removing all myomas and reconstructing uterus towards near normal anatomy, it was an unusual finding that she had a huge mass still inside her abdomen. Multiple fibroids in uterus from seedling to 20cm size, along with huge mass related with intestine and mesentery and multiple seedlings in other sides in mesentery, all indicated strong tendency towards fibroid formation.

Case Report

A 31 yr old female presented in the OPD for myomectomy. She had been investigated and planned for myomectomy outside but came here for surgery. Patient had profuse but regular periods for many years along with pain lower abdomen and backache. She also gave history of laparoscopic myomectomy 10 yrs back at 21 yrs of age when she was unmarried. Later she got married, conceived spontaneously after 5 yrs of surgery and had vaginal delivery. She was planning to conceive again hence wanted conservative surgery that is myomectomy. On per abdominal examination there was a large lump present in abdomen reaching upto 3-4" above umbilicus which appeared arising from pelvis, more on left side, firm in consistency, non-tender, with restricted mobility. On per vaginal examination cervix was normal with grossly enlarged uterus, appeared incorporated in abdominal mass. On investigations, MRI was suggestive of markedly enlarged, lobulated and bulky uterus, superiorly reaching up to L3 vertebral level. Endometrial canal was

compressed and elongated, multiple intramural fibroids of various sizes were seen in fundus in anterior and posterior myometrium and also subserous fibroids, some fibroids showed calcification and hemorrhage. Bilateral ovaries were normal. No enlarged lymph nodes present. On blood investigation Hb was 10.4 gm/ dl, other pre operation investigations were normal so patient was taken for myomectomy after PAC fitness. Operative findings were uterus was grossly enlarged due to multiple fibroids of variable sizes from seedling to 10-12 cm size. Large bunch of fibroids was subserous arising from fundus, same enucleated out through one incision over fundus. Another 4-5 cm size fibroid taken out from anterior surface of uterus. Bilateral tubes and ovaries were normal, uterus was bulky due to adenomyosis. Multiple cystic collections of chocolaty fluid was present in myometrium. Hemostasis achieved, raw space obliterated. Uterus repaired back to normal shape but size was larger than normal. On peritoneal exploration there was a huge peritoneal mass completely separate from uterus and adenexa, found adherent over large intestine receiving its blood supply from mesentery, mass appeared to be fibroid as it was smooth, globular and soft in appearance with size 18-20 cm. Oncosurgeon was called for needful. Large mesenteric mass was enucleated out. Whole of intestines were explored for any other mass, there were few small fibroids of 2-3 cm adherent to omentum, same removed, hemostasis achieved, drain kept after peritoneal lavage, abdomen closed back, and patient withstood the procedure well. Post operatively patient was given IV iron therapy and injection Lupride depot 3.75 mg by intramuscular route. Her histopathology reports were consistent with fibroids and adenomyosis.



(1) Image showing uterus with multiple fibroids.

(2) Coexistent adenomyosis with fibroids.

(3 Reconstructed uterus afte myomectomy.

(4) Finding a large mass in peritoneal cavity after myomectomy.

(5) Large mass adherent with intestine.

Discussion

Parasitic fibroids have no uterine connection or myometrial participation. [1] Fibroids are the most common uterine masses and are one of the most common cause for gynecology OPD visit. A study by Baird et al. showed that approximate incidence of fibroid by 80 years of ages 70% of white and 80% for black women. [2] Their growth depends upon circulating estrogen levels and receptors for estrogen in myometrium. According to De La Cruz, fibroids account for 39% of all hysterectomies. [3] Adenomyosis is present along with fibroids in our patient which has been shown to have a high rate of coexistence with fibroids. [4] In contrast to uterine leiomyomas, wandering or parasitic fibroids are extremely

uncommon. [5] Typical characteristics of wandering fibroids are that they rarely cause symptoms and they are seldom diagnosed pre-operatively. Only symptoms they cause are due to mass effect.

All fibroids are benign spindle cell tumours which arise from smooth muscle of myometrium under influence of estrogen and progesterone. Fibroid cells have more hormonal receptors on their cell membrane.

There are different theories about development of parasitic fibroids. They can be divided into primary or secondary. Basically they all originate from uterus. Primary parasitic fibroids originate as sub-serous pedunculated fibroids but these growing neoplasms start taking their blood supply from other adjacent organs and detach from their primary site. Second type of wandering fibroids are rare late complication of laparoscopic hysterectomy or myomectomy where fibroids have been delivered through morcellation. It is likely that these small fibroid fragments get attached anywhere in abdomen in very strange locations like vaginal wall, pelvic wall, intestine, mesentery, anterior abdominal wall, rectum or even port site. [6,7,8]. They may remain in abdominal cavity and become implanted with development of blood supply, resulting in subsequent growth. [6,7,9]

Gaspara et al concluded morcellation during hysterectomy as a risk factor in developing parasitic fibroid in retrospective studies. [10] Our case has concomitant uterine as well as parasitic fibroids. Lu et al presented six cases of post morcellation parasitic fibroids. [11] Our case has strong likelihood of developing parasitic fibroids due to morcellation as she had history of large fibroid at age of 21 years for which laparoscopic myomectomy was done. She had concomitant occurrence of multiple fibroids in uterus as well as multiple seedlings over omentum and mesentery. This probably was the reason of her not being diagnosed pre-operatively as uterine and extra-uterine fibroids were overlapping. In view of origination theory of wandering fibroids and increasing number of laparoscopic myomectomy and hysterectomy, it is likely that we encounter many more parasitic fibroids in coming years. We as gynecologists, need to review the management of fibroid especially while doing laparoscopic surgery for fibroid. Morcellation needs to be done more carefully to avoid spillage of any fibroid fragments in abdominal cavity which could implant anywhere in abdomen, start taking their blood supply by neovascularization and start growing. [6,7,9] Parasitic leiomyomas form a late sequele of laparoscopic myomectomy with incidence of 0.2-1.25% and median diagnostic interval of 48months. [12] Despite better patient outcome following minimally invasive surgery, caution should be applied to prevent the spread of occult sarcomas which would significantly lower patient survival. [13,14]

In our case as there is a history of laparoscopic myomectomy followed by power morcellation 8 years back when she was unmarried, she likely had started developing multiple fibroids in uterus. There are chances that fibroid fragments during previous surgeries had implanted over intestine and mesentery but possibility of these parasitic myomas as being of primary type cannot be denied completely .She again wanted laparoscopic surgery, but

refused this time by surgeons outside due to multiple huge fibroids.

Conclusion

Parasitic or leiomyomas are rare, primary spontaneous parasitic fibroids are still rarer. Diagnosis seldom done on radiology. Nowadays, minimally invasive myomectomy or hysterectomy are becoming important cause of wandering fibroids. Careful pre-op workup necessary for diagnosis as well as careful morcellation preferably in endobag and peritoneal wash to remove all fibroid fragments so that this rare entity does not become a common iatrogenic complication.

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Rare Refractory Multisystem Inflammatory Syndrome in Children (MIS-C): Case Report

Pranajli Deshpande[A], Ganesh Badge[B], Abhishek Zanwar[C], Prabhat Kumar[D]

[A] Consultant Pediatrician, Department of Pediatrics, Manipal Hospitals, Pune

[B] Consultant Pediatric Intensivist, Department of Pediatrics, Manipal Hospitals, Pune.

[C] Consultant Pediatric Neurologist, Department of Pediatrics, Manipal Hospitals, Pune.

[D] Consultant Pediatric Cardiologist, Department of Pediatrics, Manipal Hospitals, Pune.

Introduction

First case of Multisystem Inflammatory Syndrome in Children (MIS-C) was reported from UK in April 2020. The surge of MIS-C cases followed the surge in COVID-19 cases by a month. Overall MIS-C is uncommon: 1% of all COVID-19 in children and adolescents and <10% of children hospitalized with COVID-19 related conditions. [1] Here we describe a case of refractory MIS-C – a rare case.

Case Report

A 5 year old female child was brought to the emergency room with complaints of high grade fever on and off since 4 days, vomiting and loose motions since 2 days. She had erythematous maculopapular rashes all over body since 1 day. Rash was associated with non-purulent conjunctival congestion. There was H/o Covid 19 infection in the family a month back, during which both parents were symptomatic while the child was asymptomatic.

The child was managed with i.v. fluids and antipyretics. Since fever was high grade and continuous, all investigations including blood culture & sensitivity, urine routine & culture, Dengue profile, D-Dimer, S. Ferritin, S. LDH, S. IL-6, S. Troponin, PT/INR and NT ProBNP were sent. On 2nd day, high grade fever persisted, rashes progressed to all over body. She had tachypnea with resp distress and her room air saturation was 88%. Her BP was below 50th percentile (80/40 mm of Hg), so she was shifted in PICU for respiratory and inotropic support. After shifting to PICU:

Day 1: in view of hemodynamic instability, decreased saturation and high levels of inflammatory markers in lab results suggestive of MIS-C, she was started on high flow oxygen (HFNC) 23/40. Femoral line was put and i.v Noradrenaline, i.v Immunoglobulins (IVIG) @ 2gm/kg over 48 hrs, inj Methylprednisolone (MPS) 30 mg/kg/day was started for MIS-C and antibiotics were upgraded after culture. Diagnosis of MIS-C with respiratory distress with compensatory shock was made.

Day 2: Child was not maintaining BP more than 50th percentile on Inj Noradrenaline,

therefore, Inj Dobutamine was added in view of cardiogenic shock. Chest X-Ray bedside was s/o mild B/L pleural effusion and bilateral patchy opacity. 2nd Echo was s/o LV dysfunction with MR and TR, LVEF of 45-50% and RCA dilatation. Later the child was intubated for persistent respiratory distress on HFNC. Inj Dobutamine was stopped once BP was maintained and Inj Milrinone added. Inj Noradrenaline was continued at higher rate along with inj milrinone for cardiogenic shock.

Day 3: Fever persisted even after administration of IVIG 2 gm/kg over 48 hrs and MPD 2nd doses of 30 mg/kg/day.

Day 4: Fever continued with tachycardia. I/v/o refractory MIS-C continuous fever and failure to respond of IVIG and steroid first line therapy with increased Inflammatory markers and lL6 level 533 pg/mL, as well as worsened cardiac function. IL6 inhibitor was given, later 20% Inj Albumin was given slowly for hypoalbuminaemia and 3rd space fluid loss. Along with Inj Furosemide infusion and target negative fluid balance. Tab enalapril and Furosemide was added for CCF due to worsened LVF and MR on follow up 2D-ECHO.

Day 5: Fever spikes continued, rashes were reduced, Inj Noradrenaline was tapered off as the BP was maintained above 50th percentile, Inj Milrinone continued. Due to anemia and CHF, 1 PRBC transfusion was given.

Day 6: Fever persisted with thrombocytopenia, blood culture for aerobic, anerobic and fungus along with ET Tube culture were sent. Antifungal was started prophylactically. Inj Noradrenaline was further tapered off and stopped. Since the child was maintaining well her vitals and O2 requirement reduced so, she was put on SIMV mode.

Day 7: Inj Milrinone was stopped. Fever reduced, SBT given to child and then extubated under all aseptic precautions. She was able to maintain vitals well on HFNC for 24 hrs after extubation. Baby was maintaining saturation on room air, and also able to take oral feeds so shifted in ward .Oral feeds upgraded, limb physiotherapy given .Baby was conscious and oriented, afebrile, alert and interactive at the time of discharge. On last 2 follow up child is stable, no fever, steroid tapered over 4 weeks, aspirin continued along with anti-failure medicine as follow up Echo suggestive of diastolic dysfunction and tachycardia with no deficit.

Investigation Chart

Date	16/5	17/5	18/5	19/5	20/5	21/5	22/5	24/5	4/6 Follow up
CBC	Hb 10.8 TLC 8.3 Plt 2.58	Hb 10.6 TLC 10 Plt 2.01		Hb 8.5 TLC 44.1 Plt 1.21	Hb 7.9 TLC 23.9 Plt 63	Hb 8.1 TLC 9.9 Plt 44	Hb 8.3 TLC 12.2 Plt 1.05	Hb 9.4 TLC 12.6 Plt 1.26	Hb 12 TLC 17600 Plt 12.56
CRP	>25								1.25
ProBNP	6008				>25000				
Ferritin	477.2			807		465		464.6	172
Procal					58.34				
D Dimer	3620			6301	>9482	5032	3620	3280	170
LFT			SGPT 82 SGOT 52			SGPT 64 SGOT 56		32 35	
RFT		Na 133 K 3.91 Creat 0.26		Na 135 K 3.09	Na 145 K 3.09	Na 149 K 3.11	Na 135 K 3.26		
IL6	336				513			25	
LDH	284								
Fibrinogen	519								
PT/ INR	1.49	1.63	1.29			1.39	1.35		
Albumin				2.1		2.1			

Case discussion

Pathogenesis of MIS-C is incompletely understood. The condition is diagnosed in children who have had Covid infection previously and also among those with active infection. Possible mechanisms:

- Immune dysregulation
- Antibody enhancement
- T-cell mediated damage or enhancement of inflammation.

Management

- Supportive care
  - Empirical antibiotics after obtaining blood culture for suspected or evident bacterial infection.
  - Intensive care support including vasopressor and ventilation where indicated.
- Specific Management – Depending on the MIS-C spectrum

Fever, raised inflammatory markers, No systemic features	**Febrile inflammation syndrome**	Observation Follow-up
MISC with no shock, well child	**Hyperinflammation phenotype MISC (mild)**	Methylprednisolone (MPS) Aspirin, IvIg if no response
MISC with shock without inotrope	**Moderate illness MISC**	IvIg & MPS, Aspirin
MISC - Kawasaki criteria	**KD phenotype MISC**	IvIg & MPS, Aspirin
MISC -Shock with inotropes, invasive ventilation, renal failure, coagulopathy, MODS, HLH	**Life threatening MISC (severe)**	IvIg & high dose MPS, Enoxaparin, Aspirin

Refractory MIS-C

Refractory MIS-C is defined as persistence of fever with high inflammatory markers 24 hrs after IvIg and Steroids. Usual first line of management for MISC is glucocorticoids with or without IvIg, depending on severity of disease. Similar to response in classic KD, IvIg also has been shown to be effective in MIS-C. It acts by pleotropic mechanism, which includes, neutralization of pathogenic antibodies, complement scavenging, B cell inhibition and up regulation of regulatory T cells. If child is unresponsive to steroid and IvIg then biologic should be tried. Till date three different biologics have shown to be effective for refractory MISC. [2] Tocilizumab is recombinant IL-6 receptor antibody that acts by inhibiting IL-6 pathway. It has been shown to be effective in other forms of cytokine storm (Post CAR-T cell therapy). [3] Various case reports have shown efficacy in MISC, especially when blood IL-6 levels were raised (Dose 8-12mg/kg). [4] Anakinra is IL-1 R agonist, which competitively blocks IL-1 binding thus inhibiting downstream pathway. There has been various case reports of successful treatment of refractory MIS-C with Inj Anakinra (Dose >4mg/kg/day IV or SQ). [5, 6] Recommended optimal time for use is before initiation of invasive ventilation. There has been reports of efficacy of anti-TNF agents like infliximab in MIS-C, especially in children with coronary artery aneurysm. Availability is one of the deciding factors in choice of biologics.

Conclusion

SARS-CoV-2 infection-related MIS-C is a rare but serious hyper immune response in children and adolescents that occurs 4-6 weeks after acute viral infection. Left ventricular dysfunction is the most common cardiac manifestation of MIS-C, followed by coronary artery aneurysm and electrical conduction abnormalities. Hemodynamic support and immunomodulatory therapies are the primary treatments. Most children recover from MIS-C, but medium-and long-term sequelae are unknown. Standardized approaches to cardiac monitoring and follow-up are vital for optimizing patient care and advancing understanding of outcomes in MIS-C. Due to multi-organ involvement in MIS-C, a multidisciplinary team approach is vital for diagnosis and treatment.

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JOURNAL SCAN

Dr Kunal Das

Consultant and HOD, Dept. of Gastroenterology, Manipal Hospitals, New Delhi

1. Efficacy and Safety of Itepekimab in Patients with Moderate-to-Severe Asthma

N Engl J Med 2021; 385:1656-1668 DOI: 10.1056/NEJMoa2024257

Michael E. Wechsler, M.D., Marcella K. Ruddy, M.D., Ian D. Pavord, M.D., Elliot Israel, M.D., Klaus F. Rabe, M.D., Ph.D., Linda B. Ford, M.D., Jorge F. Maspero, M.D., Raolat M. Abdulai, M.D., Chih-Chi Hu, Ph.D., Renata Martincova, M.D., Andreas Jessel, M.D., Michael C. Nivens, Ph.D., et al.

Abstract

BACKGROUND

Monoclonal antibodies targeting IgE, interleukin-4 and -13, and interleukin-5 are effective in treating severe type 2 asthma, but new targets are needed. Itepekimab is a new monoclonal antibody against the upstream alarm in interleukin-33. The efficacy and safety of Itepekimab as monotherapy, as well as in combination with dupilumab, in patients with asthma are unclear.

METHODS

In a phase 2 trial, we randomly assigned, in a 1:1:1:1 ratio, adults with moderate-to-severe asthma receiving inhaled glucocorticoids plus long-acting beta-agonists (LABAs) to receive subcutaneous itepekimab (at a dose of 300 mg), itepekimab plus dupilumab (both at 300 mg; combination therapy), dupilumab (300 mg), or placebo every 2 weeks for 12 weeks. After randomization, LABA was discontinued at week 4, and inhaled glucocorticoids were tapered over weeks 6 through 9. The primary end point was an event indicating a loss of asthma control, assessed in the itepekimab group and the combination group, as compared with the placebo group. Secondary and other end points included lung function, asthma control, quality of life, type 2 biomarkers, and safety.

RESULTS

A total of 296 patients underwent randomization. By 12 weeks, an event indicating a loss of asthma control occurred in 22% of the patients in the itepekimab group, 27% of those in the combination group, and 19% of those in the dupilumab group, as compared with 41% of those in the placebo group; the corresponding odds ratios as compared with placebo were as follows: in the itepekimab group, 0.42 (95% confidence interval [CI], 0.20 to 0.88; P=0.02); in the combination group, 0.52 (95% CI, 0.26 to 1.06; P=0.07); and in the dupilumab group, 0.33 (95% CI, 0.15 to 0.70). As compared with placebo, the forced expiratory volume in 1 second before bronchodilator use increased with the itepekimab and dupilumab monotherapies but not with the combination therapy. Itepekimab treatment improved asthma control and quality of life, as compared with placebo, and led to a greater reduction in the mean blood eosinophil count. The incidence of adverse events was similar in all four trial groups.

CONCLUSIONS

Interleukin-33 blockade with itepekimab led to a lower incidence of events indicating a loss of asthma control than placebo and improved lung function in patients with

moderate-to-severe asthma. (Funded by Sanofi and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT03387852.)

2. Clinical Features of Vaccine-Induced Immune Thrombocytopenia and Thrombosis

N Engl J Med 2021; 385: 1680-1689. DOI: 10.1056/NEJMoa2109908

Sue Pavord, F.R.C.Path., Marie Scully, M.D., Beverley J. Hunt, M.D., William Lester, M.D., Catherine Bagot, M.D., Brian Craven, M.B., B.Ch., Alex Rampotas, M.R.C.P., Gareth Ambler, Ph.D., and Mike Makris, M.D.

Abstract

BACKGROUND

Vaccine-induced immune thrombocytopenia and thrombosis (VITT) is a new syndrome associated with the ChAdOx1 nCoV-19 adenoviral vector vaccine against severe acute respiratory syndrome coronavirus 2. Data are lacking on the clinical features of and the prognostic criteria for this disorder.

METHODS

We conducted a prospective cohort study involving patients with suspected VITT who presented to hospitals in the United Kingdom between March 22 and June 6, 2021. Data were collected with the use of an anonymized electronic form, and cases were identified as definite or probable VITT according to prespecified criteria. Baseline characteristics and clinicopathological features of the patients, risk factors, treatment, and markers of poor prognosis were determined.

RESULTS

Among 294 patients who were evaluated, we identified 170 definite and 50 probable cases of VITT. All the patients had received the first dose of ChAdOx1 nCoV-19 vaccine and presented 5 to 48 days (median, 14) after vaccination. The age range was 18 to 79 years (median, 48), with no sex preponderance and no identifiable medical risk factors. Overall mortality was 22%. The odds of death increased by a factor of 2.7 (95% confidence interval [CI], 1.4 to 5.2) among patients with cerebral venous sinus thrombosis, by a factor of 1.7 (95% CI, 1.3 to 2.3) for every 50% decrease in the baseline platelet count, by a factor of 1.2 (95% CI, 1.0 to 1.3) for every increase of 10,000 fibrinogen-equivalent units in the baseline d-dimer level, and by a factor of 1.7 (95% CI, 1.1 to 2.5) for every 50% decrease in the baseline fibrinogen level. Multivariate analysis identified the baseline platelet count and the presence of intracranial hemorrhage as being independently associated with death; the observed mortality was 73% among patients with platelet counts below 30,000 per cubic millimeter and intracranial hemorrhage.

CONCLUSIONS

The high mortality associated with VITT was highest among patients with a low platelet count and intracranial hemorrhage. Treatment remains uncertain, but identification of prognostic markers may help guide effective management. (Funded by the Oxford University Hospitals NHS Foundation Trust.)

3. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH

N Engl J Med 2021; 385:1547-1558 DOI: 10.1056/NEJMoa2036205

Sven M. Francque, M.D., Ph.D., Pierre Bedossa, M.D., Ph.D., Vlad Ratziu, M.D., Ph.D., Quentin M. Anstee, M.D., Ph.D., Elisabetta Bugianesi, M.D., Ph.D., Arun J. Sanyal, M.D., Rohit Loomba, M.D., M.H.Sc., Stephen A. Harrison, M.D., Rozalina Balabanska, M.D., Lyudmila Mateva, M.D., Ph.D., Nicolas Lanthier, M.D., Ph.D., Naim Alkhouri, M.D., et al., for the NATIVE Study Group*

Abstract

BACKGROUND

Management of non-alcoholic steatohepatitis (NASH) is an unmet clinical need. Lanifibranor is a pan-PPAR (peroxisome proliferator–activated receptor) agonist that modulates key metabolic, inflammatory, and fibrogenic pathways in the pathogenesis of NASH.

METHODS

In this phase 2b, double-blind, randomized, placebo-controlled trial, patients with non-cirrhotic, highly active NASH were randomly assigned in a 1:1:1 ratio to receive 1200 mg or 800 mg of lanifibranor or placebo once daily for 24 weeks. The primary end point was a decrease of at least 2 points in the SAF-A score (the activity part of the Steatosis, Activity, Fibrosis [SAF] scoring system that incorporates scores for ballooning and inflammation) without worsening of fibrosis; SAF-A scores range from 0 to 4, with higher scores indicating more-severe disease activity. Secondary end points included resolution of NASH and regression of fibrosis.

RESULTS

A total of 247 patients underwent randomization, of whom 103 (42%) had type 2 diabetes mellitus and 188 (76%) had significant (moderate) or advanced fibrosis. The percentage of patients who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis was significantly higher among those who received the 1200-mg dose, but not among those who received the 800-mg dose, of lanifibranor than among those who received placebo (1200-mg dose vs. placebo, 55% vs. 33%, P=0.007; 800-mg dose vs. placebo, 48% vs. 33%, P=0.07). The results favored both the 1200-mg and 800-mg doses of lanifibranor over placebo for resolution of NASH without worsening of fibrosis (49% and 39%, respectively, vs. 22%), improvement in fibrosis stage of at least 1 without worsening of NASH (48% and 34%, respectively, vs. 29%), and resolution of NASH plus improvement in fibrosis stage of at least 1 (35% and 25%, respectively, vs. 9%). Liver enzyme levels decreased and the levels of the majority of lipid, inflammatory, and fibrosis biomarkers improved in the lanifibranor groups. The dropout rate for adverse events was less than 5% and was similar across the trial groups. Diarrhea, nausea, peripheral edema, anemia, and weight gain occurred more frequently with lanifibranor than with placebo.

CONCLUSIONS

In this phase 2b trial involving patients with active NASH, the percentage of patients who had a decrease of at least 2 points in the SAF-A score without worsening of fibrosis was significantly higher with the 1200-mg dose of lanifibranor than with placebo. These findings support further assessment of lanifibranor in phase 3 trials.

(Funded by Inventiva Pharma; NATIVE ClinicalTrials.gov number, NCT03008070. opens in new tab.)

4. Covid-19 Breakthrough Infections in Vaccinated Health Care Workers

N Engl J Med 2021; 385:1474-1484. DOI: 10.1056/NEJMoa2109072

Moriah Bergwerk, M.B., B.S., Tal Gonen, B.A., Yaniv Lustig, Ph.D., Sharon Amit, M.D., Marc Lipsitch, Ph.D., Carmit Cohen, Ph.D., Michal Mandelboim, Ph.D., Einav Gal Levin, M.D., Carmit Rubin, N.D., Victoria Indenbaum, Ph.D., Ilana Tal, R.N., Ph.D., Malka Zavitan, R.N., M.A., et al.

Abstract

BACKGROUND

Despite the high efficacy of the BNT162b2 messenger RNA vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), rare breakthrough infections have been reported, including infections among health care workers. Data are needed to characterize these infections and define correlates of breakthrough and infectivity.

METHODS

At the largest medical center in Israel, we identified breakthrough infections by performing extensive evaluations of health care workers who were symptomatic (including mild symptoms) or had known infection exposure. These evaluations included epidemiologic investigations, repeat reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assays, antigen-detecting rapid diagnostic testing (Ag-RDT), serologic assays, and genomic sequencing. Correlates of breakthrough infection were assessed in a case–control analysis. We matched patients with breakthrough infection who had antibody titers obtained within a week before SARS-CoV-2 detection (peri-infection period) with four to five uninfected controls and used generalized estimating equations to predict the geometric mean titers among cases and controls and the ratio between the titers in the two groups. We also assessed the correlation between neutralizing antibody titers and N gene cycle threshold (Ct) values with respect to infectivity.

RESULTS

Among 1497 fully vaccinated health care workers for whom RT-PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The B.1.1.7 (alpha) variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (Ct value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented.

CONCLUSIONS

Among fully vaccinated health care workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers during the peri-infection period. Most breakthrough

infections were mild or asymptomatic, although persistent symptoms did occur.

5. Ozanimod as Induction and Maintenance Therapy for Ulcerative Colitis

N Engl J Med 2021; 385:1280-1291 DOI: 10.1056/NEJMoa2033617

William J. Sandborn, M.D., Brian G. Feagan, M.D., Geert D'Haens, M.D., Douglas C. Wolf, M.D., Igor Jovanovic, M.D., Stephen B. Hanauer, M.D., Subrata Ghosh, M.D., AnnKatrin Petersen, M.D., Steven Y. Hua, Ph.D., Ji Hwan Lee, M.S., Lorna Charles, M.D., Denesh Chitkara, M.D., et al., for the True North Study Group*

Abstract

BACKGROUND

Ozanimod, a selective sphingosine-1-phosphate receptor modulator, is under investigation for the treatment of inflammatory bowel disease.

METHODS

We conducted a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of ozanimod as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis. In the 10-week induction period, patients in cohort 1 were assigned to receive oral ozanimod hydrochloride at a dose of 1 mg (equivalent to 0.92 mg of ozanimod) or placebo once daily in a double-blind manner, and patients in cohort 2 received open-label ozanimod at the same daily dose. At 10 weeks, patients with a clinical response to ozanimod in either cohort underwent randomization again to receive double-blind ozanimod or placebo for the maintenance period (through week 52). The primary end point for both periods was the percentage of patients with clinical remission, as assessed with the three-component Mayo score. Key secondary clinical, endoscopic, and histologic end points were evaluated with the use of ranked, hierarchical testing. Safety was also assessed.

RESULTS

In the induction period, 645 patients were included in cohort 1 and 367 in cohort 2; a total of 457 patients were included in the maintenance period. The incidence of clinical remission was significantly higher among patients who received ozanimod than among those who received placebo during both induction (18.4% vs. 6.0%, P<0.001) and maintenance (37.0% vs. 18.5% [among patients with a response at week 10], P<0.001). The incidence of clinical response was also significantly higher with ozanimod than with placebo during induction (47.8% vs. 25.9%, P<0.001) and maintenance (60.0% vs. 41.0%, P<0.001). All other key secondary end points were significantly improved with ozanimod as compared with placebo in both periods. The incidence of infection (of any severity) with ozanimod was similar to that with placebo during induction and higher than that with placebo during maintenance. Serious infection occurred in less than 2% of the patients in each group during the 52-week trial. Elevated liver aminotransferase levels were more common with ozanimod.

CONCLUSIONS

Ozanimod was more effective than placebo as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis. (Funded by Bristol Myers Squibb; True North ClinicalTrials.gov number, NCT02435992)

6. Global, regional, and national mortality among young people aged 10–24 years, 1950–2019: a systematic analysis for the Global Burden of Disease Study 2019

The Lancet 2021; 398: P1593-1618

Summary

BACKGROUND

Documentation of patterns and long-term trends in mortality in young people, which reflect huge changes in demographic and social determinants of adolescent health, enables identification of global investment priorities for this age group. We aimed to analyse data on the number of deaths, years of life lost, and mortality rates by sex and age group in people aged 10–24 years in 204 countries and territories from 1950 to 2019 by use of estimates from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019.

METHODS

We report trends in estimated total numbers of deaths and mortality rate per 100 000 population in young people aged 10–24 years by age group (10–14 years, 15–19 years, and 20–24 years) and sex in 204 countries and territories between 1950 and 2019 for all causes, and between 1980 and 2019 by cause of death. We analyse variation in outcomes by region, age group, and sex, and compare annual rate of change in mortality in young people aged 10–24 years with that in children aged 0–9 years from 1990 to 2019. We then analyse the association between mortality in people aged 10–24 years and socioeconomic development using the GBD Socio-demographic Index (SDI), a composite measure based on average national educational attainment in people older than 15 years, total fertility rate in people younger than 25 years, and income per capita. We assess the association between SDI and all-cause mortality in 2019, and analyse the ratio of observed to expected mortality by SDI using the most recent available data release (2017).

FINDINGS

In 2019 there were 1·49 million deaths (95% uncertainty interval 1·39–1·59) worldwide in people aged 10–24 years, of which 61% occurred in males. 32·7% of all adolescent deaths were due to transport injuries, unintentional injuries, or interpersonal violence and conflict; 32·1% were due to communicable, nutritional, or maternal causes; 27·0% were due to non-communicable diseases; and 8·2% were due to self-harm. Since 1950, deaths in this age group decreased by 30·0% in females and 15·3% in males, and sex-based differences in mortality rate have widened in most regions of the world. Geographical variation has also increased, particularly in people aged 10–14 years. Since 1980, communicable and maternal causes of death have decreased sharply as a proportion of total deaths in most GBD super-regions, but remain some of the most common causes in sub-Saharan Africa and south Asia, where more than half of all adolescent deaths occur. Annual percentage decrease in all-cause mortality rate since 1990 in adolescents aged 15–19 years was 1·3% in males and 1·6% in females, almost half that of males aged 1–4 years (2·4%), and around a third less than in females aged 1–4 years (2·5%). The proportion of global deaths in people aged 0–24 years that occurred in people aged 10–24 years more than doubled between 1950 and 2019, from 9·5% to 21·6%.

INTERPRETATION

Variation in adolescent mortality between countries and by sex is widening, driven by poor progress in reducing deaths in males and older adolescents. Improving global adolescent mortality will require action to address the specific vulnerabilities of this age group, which are being overlooked. Furthermore, indirect effects of the COVID-19 pandemic are likely to jeopardise efforts to improve health outcomes including mortality in young people aged 10–24 years. There is an urgent need to respond to the changing global burden of adolescent mortality, address inequities where they occur, and improve the availability and quality of primary mortality data in this age group.

FUNDING

Bill & Melinda Gates Foundation.

7. Implantable loop recorder detection of atrial fibrillation to prevent stroke (the loop study): A randomised controlled trial

Prof Jesper H Svendsen, MD , Søren Z Diederichsen, MD, Søren Højberg, MD, Prof Derk W Krieger, MD; Claus Graff, MSc; Christian Kronborg, MSc

Volume 398, Issue 10310, P1507-1516, October 23, 2021

Summary

BACKGROUND

It is unknown whether screening for atrial fibrillation and subsequent treatment with anticoagulants if atrial fibrillation is detected can prevent stroke. Continuous electrocardiographic monitoring using an implantable loop recorder (ILR) can facilitate detection of asymptomatic atrial fibrillation episodes. We aimed to investigate whether atrial fibrillation screening and use of anticoagulants can prevent stroke in individuals at high risk.

METHODS

We did a randomised controlled trial in four centres in Denmark. We included individuals without atrial fibrillation, aged 70–90 years, with at least one additional stroke risk factor (ie, hypertension, diabetes, previous stroke, or heart failure). Participants were randomly assigned in a 1:3 ratio to ILR monitoring or usual care (control) via an online system in permuted blocks with block sizes of four or eight participants stratified according to centre. In the ILR group, anticoagulation was recommended if atrial fibrillation episodes lasted 6 min or longer. The primary outcome was time to first stroke or systemic arterial embolism. This study is registered with ClinicalTrials.gov, NCT02036450.

FINDINGS

From Jan 31, 2014, to May 17, 2016, 6205 individuals were screened for inclusion, of whom 6004 were included and randomly assigned: 1501 (25•0%) to ILR monitoring and 4503 (75•0%) to usual care. Mean age was 74•7 years (SD 4•1), 2837 (47•3%) were women, and 5444 (90•7%) had hypertension. No participants were lost to follow-up. During a median follow-up of 64•5 months (IQR 59•3–69•8), atrial fibrillation was diagnosed in 1027 participants: 477 (31•8%) of 1501 in the ILR group versus 550 (12•2%) of 4503 in the control group (hazard ratio [HR] 3•17 [95% CI 2•81–3•59]; p<0•0001). Oral anticoagulation was initiated in 1036 participants: 445 (29•7%) in the ILR group versus 591 (13•1%) in the control group (HR

2•72 [95% CI 2•41–3•08]; p<0•0001), and the primary outcome occurred in 318 participants (315 stroke, three systemic arterial embolism): 67 (4•5%) in the ILR group versus 251 (5•6%) in the control group (HR 0•80 [95% CI 0•61–1•05]; p=0•11). Major bleeding occurred in 221 participants: 65 (4•3%) in the ILR group versus 156 (3•5%) in the control group (HR 1•26 [95% CI 0•95–1•69]; p=0•11).

INTERPRETATION

In individuals with stroke risk factors, ILR screening resulted in a three-times increase in atrial fibrillation detection and anticoagulation initiation but no significant reduction in the risk of stroke or systemic arterial embolism. These findings might imply that not all atrial fibrillation is worth screening for, and not all screen-detected atrial fibrillation merits anticoagulation.

FUNDING

Innovation Fund Denmark, The Research Foundation for the Capital Region of Denmark, The Danish Heart Foundation, Aalborg University Talent Management Program, Arvid Nilssons Fond, Skibsreder Per Henriksen, R og Hustrus Fond, The AFFECT-EU Consortium (EU Horizon 2020), Læge Sophus Carl Emil Friis og hustru Olga Doris Friis' Legat, and Medtronic

8. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial

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Prof Philippe Moreau, Cyrille Hulin, Aurore Perrot, Prof Bertrand Arnulf, Karim Belhadj, Lotfi Benboubker, et al

Summary

BACKGROUND

CASSIOPEIA part 1 showed superior depth of response and significantly improved progression-free survival with daratumumab, bortezomib, thalidomide, and dexamethasone (D-VTd) versus bortezomib, thalidomide, and dexamethasone (VTd) as induction and consolidation in patients with autologous stem-cell transplant (ASCT)-eligible newly diagnosed multiple myeloma. In part 2, we compared daratumumab maintenance versus observation only.

METHODS

CASSIOPEIA is a two-part, open-label, randomised, phase 3 trial of patients aged 18–65 years with newly diagnosed multiple myeloma and Eastern Cooperative Oncology Group performance status 0–2, done in 111 European academic and community practice centres. In part 1, patients were randomly assigned (1:1) to induction and consolidation with D-VTd or VTd. Patients still on study who had a partial response or better were randomly assigned (1:1) by an interactive web-response system to daratumumab 16 mg/kg intravenously every 8 weeks (a reduced frequency compared with standard daratumumab long-term dosing) or observation only for up to 2 years. Stratification factors were induction treatment and depth of response in part 1. The part 2 primary endpoint was

progression-free survival from second randomisation. This preplanned interim analysis of progression-free survival was done after 281 events and shall be considered the primary analysis of progression-free survival. Sponsor personnel and designees who were involved in the analysis were masked to treatment group until the independent data monitoring committee recommended that the preplanned interim analysis be considered the main analysis of progression-free survival in part 2. Otherwise, treatment assignments were unmasked. The interaction between induction and consolidation and maintenance was tested at a two-sided significance level of 0•05 by a stratified Cox regression model that included the interaction term between maintenance treatment and induction and consolidation treatment. Efficacy analyses were done in the maintenance-specific intention-to-treat population, which comprised all patients who underwent second randomisation. Safety was analysed in all patients in the daratumumab group who received at least one dose and all patients randomly assigned to observation only. This trial is registered with ClinicalTrials.gov, NCT02541383. Long-term follow-up is ongoing and the trial is closed to new participants.

FINDINGS

Between May 30, 2016, and June 18, 2018, 886 patients (458 [84%] of 543 in the D-VTd group and 428 [79%] of 542 in the VTd group) were randomly assigned to daratumumab maintenance (n=442) or observation only (n=444). At a median follow-up of 35•4 months (IQR 30•2–39•9) from second randomisation, median progression-free survival was not reached (95% CI not evaluable [NE]–NE) with daratumumab versus 46•7 months (40•0–NE) with observation only (hazard ratio 0•53, 95% CI 0•42–0•68, p<0•0001). A prespecified analysis of progression-free survival results showed a significant interaction between maintenance and induction and consolidation therapy (p<0•0001). The most common grade 3 or 4 adverse events were lymphopenia (16 [4%] of 440 patients in the daratumumab group vs eight [2%] of 444 patients in the observation-only group), hypertension (13 [3%] vs seven [2%]), and neutropenia (nine [2%] vs ten [2%]). Serious adverse events occurred in 100 (23%) patients in the daratumumab group and 84 (19%) patients in the observation-only group. In the daratumumab group, two adverse events led to death (septic shock and natural killer-cell lymphoblastic lymphoma); both were related to treatment.

INTERPRETATION

Daratumumab maintenance every 8 weeks for 2 years significantly reduced the risk of disease progression or death compared with observation only. Longer follow-up and other ongoing studies will shed further light on the optimal daratumumab-containing post-ASCT maintenance treatment strategy.

FUNDING

Janssen Research & Development, the Intergroupe Francophone du Myélome, and the Dutch-Belgian Cooperative Trial Group for Hematology Oncology.

9. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy type 1 (STR1VE-EU): an open-label, single-arm, multicentre, phase 3

Eugenio Mercuri, Prof Francesco Muntoni, Giovanni Baranello, Riccardo Masson, Odile Boespflug-Tanguy, Claudio Bruno

DOI:
https://doi.org/10.1016/S1474-4422(21)00251-9

Summary

BACKGROUND

Spinal muscular atrophy is a rare, autosomal recessive, neuromuscular disease caused by biallelic loss of the survival motor neuron 1 (SMN1) gene, resulting in motor neuron dysfunction. In this STR1VE-EU study, we aimed to evaluate the safety and efficacy of onasemnogene abeparvovec gene replacement therapy in infants with spinal muscular atrophy type 1, using broader eligibility criteria than those used in STR1VE-US.

METHODS

STR1VE-EU was a multicentre, single-arm, single-dose, open-label phase 3 trial done at nine sites (hospitals and universities) in Italy (n=4), the UK (n=2), Belgium (n=2), and France (n=1). We enrolled patients younger than 6 months (180 days) with spinal muscular atrophy type 1 and the common biallelic pathogenic SMN1 exon 7–8 deletion or point mutations, and one or two copies of SMN2. Patients received a one-time intravenous infusion of onasemnogene abeparvovec (1•1 × 1014 vector genomes [vg]/kg). The outpatient follow-up consisted of assessments once per week starting at day 7 post-infusion for 4 weeks and then once per month until the end of the study (at age 18 months or early termination). The primary outcome was independent sitting for at least 10 s, as defined by the WHO Multicentre Growth Reference Study, at any visit up to the 18 months of age study visit, measured in the intention-to-treat population. Efficacy was compared with the Pediatric Neuromuscular Clinical Research (PNCR) natural history cohort. This trial is registered with ClinicalTrials.gov, NCT03461289 (completed).

FINDINGS

From Aug 16, 2018, to Sept 11, 2020, 41 patients with spinal muscular atrophy were assessed for eligibility. The median age at onasemnogene abeparvovec dosing was 4•1 months (IQR 3•0–5•2). 32 (97%) of 33 patients completed the study and were included in the ITT population (one patient was excluded despite completing the study because of dosing at 181 days). 14 (44%, 97•5% CI 26–100) of 32 patients achieved the primary endpoint of functional independent sitting for at least 10 s at any visit up to the 18 months of age study visit (vs 0 of 23 untreated patients in the PNCR cohort; p<0•0001). 31 (97%, 95% CI 91–100) of 32 patients in the ITT population survived free from permanent ventilatory support at 14 months compared with six (26%, 8–44) of 23 patients in the PNCR natural history cohort (p<0•0001). 32 (97%) of 33 patients had at least one adverse event and six (18%) had adverse events that were considered serious and related to onasemnogene abeparvovec. The most common adverse events were pyrexia (22 [67%] of 33), upper respiratory infection (11 [33%]), and increased alanine aminotransferase (nine

[27%]). One death, unrelated to the study drug, occurred from hypoxic-ischaemic brain damage because of a respiratory tract infection during the study.

INTERPRETATION

STR1VE-EU showed efficacy of onasemnogene abeparvovec in infants with symptomatic spinal muscular atrophy type 1. No new safety signals were identified, but further studies are needed to show long-term safety. The benefit–risk profile of onasemnogene abeparvovec seems favourable for this patient population, including those with severe disease at baseline.

FUNDING

Novartis Gene Therapies.

10. Efficacy of rituximab in patients with polymyalgia rheumatica: A double-blind, randomised, placebo-controlled, proof-of-concept trial

Diane E Marsman, Nathan den Broeder, Frank H J van den Hoogen, Alfons A den Broeder, Aatke van der Maas

ARTICLES| VOLUME 3, ISSUE 11, E758-E766, NOVEMBER 01, 2021

DOI: https://doi.org/10.1016/S2665-9913(21)00245-9

Summary

BACKGROUND

Glucocorticoids remain the cornerstone of polymyalgia rheumatica treatment, but their use has several drawbacks, such as long treatment duration and glucocorticoid-related adverse events. Effective glucocorticoid-sparing agents with a strong evidence base in polymyalgia rheumatica are absent. As B cells have been implicated in the pathogenesis of polymyalgia rheumatica, we aimed to evaluate the efficacy of rituximab for the treatment of polymyalgia rheumatica.

METHODS

We did a double-blind, randomised, placebo-controlled, proof-of-concept trial at Sint Maartenskliniek, Nijmegen, Netherlands. We enrolled patients with polymyalgia rheumatica according to the 2012 European League Against Rheumatism and American College of Rheumatology criteria, who were recently diagnosed or who had relapsed on prednisolone and were unable to taper their dose to less than 7•5 mg per day. Participants were randomly assigned (1:1) to a single intravenous infusion of rituximab 1000 mg or placebo, with a 17-week glucocorticoid tapering scheme. Participants and care and research personnel were masked to treatment assignment and randomisation sequence. The primary outcome was glucocorticoid-free remission at 21 weeks after infusion in patients who completed the study. This trial is registered with EudraCT (2018-002641-11) and the Dutch trial database (NL7414).

FINDINGS

Between Jan 14, 2019, and March 10, 2020, 116 patients were screened and 49 (42%) were enrolled. 47 patients (38 who were recently diagnosed, nine who had relapsed on prednisolone) completed the study: 23 (49%) in the rituximab group and 24 (51%) in the placebo group. Mean age (SD) in years was 64 (8) in the rituximab group and 66 (10) in the placebo group, the proportion of

women was 11 (48%) of 23 versus 13 (54%) of 24, and all participants were White. 11 (48%) of 23 patients in the rituximab group and five (21%) of 24 in the placebo group achieved glucocorticoid-free remission at 21 weeks (difference 27% [one-sided 95% CI 4]; relative risk 2•3 [1•1]; p=0•049). Ten infusion-related complaints occurred in the rituximab group versus three in the placebo group (relative rate 3•5 [one-sided 95% CI 1•3]). One serious adverse event occurred (pulmonary embolism; in the rituximab group), and there were no deaths.

INTERPRETATION

Rituximab was shown to be efficacious in combination with 17-week glucocorticoid treatment compared with glucocorticoid treatment alone in terms of glucocorticoid-free remission in patients with polymyalgia rheumatica. If these findings are confirmed by larger trials, rituximab could be a valuable glucocorticoid-sparing treatment for patients with polymyalgia rheumatica.

FUNDING

Sint Maartenskliniek.

5 STEPS IN CREATING YOUR DIGITAL MARKETING ECOSYSTEM

Dr Nishant Yagnik,
Neurosurgery, Manipal Hospitals Gurugram

Digital marketing is the number one upcoming tool in the hands of doctors to differentiate themselves and make their presence felt in the community they serve. While many doctors are hiring digital marketing agencies or educating themselves in this field, most doctors have no idea about what digital marketing includes. They pay huge fees for surface level work. Through this article I hope to educate the medical practitioners about the entire ecosystem of digital marketing- showing that digital marketing is not about a few trees, but an entire forest that is measurable, responsive, interconnected and automated.

I hope that this may be the first of many articles that will be published in our Journal to help doctors understand how to take their growth in their own hands through the Digital marketing workspace.

The 5 steps are as follows:

1) Copy-writing- the content of your advertisements / the content that is informative and attractive to your patients / SEO optimization of all content.

2) Digital marketing setup- Having active Google / Social media / Email marketing / Mobile marketing that is linked up to your website or even your Facebook page or Google business.

3) Automate the systems

4) Monitoring the digital ecosystem, assessment of results, cost analysis

5) Making changes to your digital marketing ecosystem – understanding the funnel system to gain insights through changes made.

Step 1: Data Collection

This is probably the most important part of the process. You need to understand your specific market very clearly. This includes answering some questions with as many specifics as possible. Remember, information is power.

- what is the profile (economic paying capacity of patients) that the hospital is catering to (and comparison with hospital cost packages)?

- which geographical areas are they coming from?

- who are the other doctors in your specialty in that region, who are competing with you and what is there level of experience in that region?

- what is unique in terms of your services or the operative procedures that you can offer patients as a selling point?

These answers will help form the content of your ads / videos / articles / infographics

They will also be the basis of your geo-economic-targeting of ads.

Step 2 :
Digital Marketing Setup

The next step is to setup your Digital marketing machinery. DM is not just a Google search ad or a few Facebook posts. Here is a stepwise plan to set things up.

- Preferably get a new phone number dedicated for DM and patient queries.

- Setup a Google business profile

- Setup your Facebook business page

- Setup your Whatsapp business manager app

- Create your website- including relevant content pages that are attractive and informative. Add contact forms to the website through your email client

- Setup your email / website query forms and contact forms for patients to be able to reach you.

- Interlink all these systems: Your Google business profile should lead people to your website / contact phone number / Whatsapp number. Your Facebook business page should lead people to your website / Whatsapp number. Your Website forms should allow people to ask you queries or leave their phone number / email id for contact and updates.

Step 3:
Automate The Systems

The above setup may take time, but once it's automated, you can achieve a lot with simple steps and automation to save time. Here are a few pointers to how this is achieved.

- Once you have the setup done, you need to spend 10 minutes a day, maybe more depending on your response, first checking your email client inbox for contacts / queries. Export this to an excel sheet where all your patient contacts should be stored.

- Spend one day a month scheduling created content to go to your contacts at a frequency of once per week- this includes emails that can be scheduled for the whole month and Whatsapp posts that are available on your desktop labelled before hand. They can then be sent on the morning of a set day.

- Run Google and Facebook / Instagram (my favorite) advertisements that should be setup once or twice a month with the right geo-targeting / right content and messaging for the economic strata that you want to cater to.

Step 4:
Monitor The Systems

The beauty of DM is that you can monitor your results unlike newspaper ads / pamphlets.

- Use Google site analytics to check the number of website visitors weekly.

- See how many people have left their contact numbers and what their queries are every week.

- See how many people has your google or Facebook ads reached

- Tally your costs with your earnings- based on the people in your excel sheet that have turned up in your OPD / Emergency.

Step 5: Funnel Strategy

A funnel is a marketing term used to define the process from the first time someone hears about you till the time they are discharged and recommend you to other people. For doctors, such processes are interesting to understand because they

mimic a lot of the systems we study about in the human body. We will cover the anatomy of a funnel in future articles, but here's some food for thought:

- Think constantly about the patient's journey from the first time they hear about you to after they go home post discharge and follow up.

- How are you targeting cold audiences (people who don't know you exist yet)- in terms of platforms used and content provided?

- Is your name showing up on google searches for doctors in your area- if not then develop website referrals through ads and back-links from other websites (eg doctors commonly write articles for online news agencies that link back to their website)

What can you change in your funnel strategy?- can you offer a free checkup? A free information booklet? Are you pricing yourself too high? Are you pricing yourself too low- only spending time on patients that won't convert? Are you thinking about a new USP (unique service proposition)?

The initial digital marketing setup (STEP 2) will take some time. But you'll get much faster at it as you do it more and more. You will also develop more advertisable content as you grow in your practice- including profile pics and graphics made on designing websites as taught in our previous lessons.

Your automation of messages to your patients and potential patients should take a few hours once a month, once you have the processes set up.

Your monitoring of results should be at least twice weekly.

A note of caution here- this can get very addictive- like checking the prices of stocks on a stock trading app. It'll give you a huge ecstatic kick when you see the numbers of your website visitors increase, you will end up checking the analytics multiple times in a day. Don't worry about analytics more than twice a week. Rome wasn't built in a day and digital marketing should be judged on the life-time referring value of a well treated patient. Slowly, your costs will reduce and returns will increase.

Conclusive Remarks

The maximum effort actually goes into developing original useful content- An article on a disease and treatment options in a local language, a video on a treatment etc. But diseases and treatment protocols don't change that rapidly, and yet new patients are found in the community regularly depending on the incidence of the disease, so most created content is valuable for a fairly long time.

I would like the reader to note that there is no better marketing strategy than treating your patients well, with scientific methodology, transparency, empathy and understanding. The above steps will help your name get into the minds of people in the area that don't know you exist to solve their problems and will help them come through your door.

But once people do come through your door, the real value lies in good treatment.

INFORMATION CORNER

List of Webinars done (January – June 2021)

- Sign N Symptoms N Second Wave Of Covid
- Infectious Diseases
- Variants Of Covid
- Myths N Facts About Vaccination
- Covid Vaccine
- Lifestyle Disease
- Chair Ergonomics
- Cancer Awareness
- High Bp And Anger
- Mental Health
- Diet And Lifestyle
- Work Life Balance
- Effects Of Covid On Mental And Physical Well-Being On Individual
- Ergonomics
- Aneuploidy Screening- Facts & Myths- What A Gynaecologists Should Know
- Diabetes Awareness
- Stress Management
- Know About Cancers

Convocation Ceremony of 1st Physician Assistant Batch 2021, at Manipal Hospitals Dwarka


Manipal Hospitals

Monthly CME Planner Year 2021-23

*Date is scheduled on 3rd Wednesday of every month

S.no	Department	Date
1	Anesthesia	23-Jun-21
2	Critical Care Medicine	21-Jul-21
3	CTVS/Cardiology Pacing and Electrophysiology /Interventional Cardiologist	18-Aug-21
4	Dental/ Derma	15-Sep-21
5	Emergency Medicine	20-Oct-21
6	ENT/Ophthalmology	17-Nov-21
7	Fetal Med/ Gynecology & Obstetrics	15-Dec-21
8	Gastroenterology	13-Jan-22
9	Internal Medicine/Infectious diseases/ Diabetes and Endocrinology	16-Feb-22
10	Lab -Transfusion medicine/Clinical Biochemistry/Clinical Hematology/Pathology/Microbiology	16-Mar-22
11	Liver Transplant & Hepat-Pancreatic & Biliary Surgery	20-Apr-22
12	Nephrology/Urology	18-May-22
13	Neurology	15-Jun-22
14	Neurosurgery	20-Jul-22
15	Nuclear Medicine	17-Aug-22
16	Orthopedics/Rheumatology/ Spine/ pediatric Ortho	21-Sep-22
17	Neonatology/Pediatrics &PICU/Pediatric Cardiology/Pediatric Orthopedics/Pediatric Gastro	19-Oct-22
18	Psychiatry/Pain Management/Psychology	16-Nov-22
19	Physical Therapy	21-Dec-22
20	Radio-Diagnosis & Imaging/ Intervention radiology	18-Jan-23
21	Respiratory Medicine	15-Feb-23
22	Surgery (Vascular Surgery/ Plastic surgery/ General/ Thoracic)	15-Mar-23
23	Oncology(Surgery/ medical/ radiation)	19-Apr-23

COVID 19

चीन वुहान से आया वायरस

सांस के जरिए फैला वायरस

श्वसन तंत्र की ले गया जान

सबकी ऑक्सीजन को पी गया वायरस

दिलो-दिमाग पर छा गया वायरस

अब देखो कितनों को पागल कर गया वायरस

लोगों के घर को उजाड़ कर देखो कैसे हंसता यह वायरस

अच्छे अच्छों की वाट लगा गया वायरस

अमीर—गरीब, छोटे —बड़े , ऊंच-नीच में नहीं बांटा इसने

किसी को दिया बड़ा झटका तो किसी को छूकर निकल गया

बहुत चतुर निकला यह वायरस ना ना जाने कितने रूप बदलकर

हम भी खड़े हुए लेकर अपना मास्क और पीपी किट

मेरा यह रूप देख कर कैसे सरपट भागा वायरस

एक हाथ में को वैक्सीन से दूसरे हाथ में कोविशील्ड से पंचर कर दिया सारा वायरस

देखो कैसे सरपट भागा वायरस

नहीं भेद पाया यह मेरा सुरक्षा कवच

घबराने की जरूरत नहीं है मित्रों अपना कवच नीचे नहीं करना, 2 सुई खाने से नहीं डरना

2 गज की दूरी रख कर इस वायरस को मार भगाओ, इस वायरस को मार भगाओ

Dr Vipin Jain
Consultant Internal Medicine
Manipal Hospitals, Jaipur

Match the following

Date	Day
07 April 2022	World Leprosy Day
03 May 2022	World Cancer Day
10 March 2022	World Kidney Day
14 June 2022	World Health Day
01 Dec 2022	World Malaria Day
10 Oct 2022	World Asthma Day
14 Nov 2022	World Blood Donor Day
28 July 2022	World Hepatitis Day
25 April 2022	World Mental Health Day
30 Jan 2022	World Diabetes Day
04 Feb 2022	World AIDS Day

Answer

Date	Day
30 Jan 2022	World Leprosy Day
04 Feb 2022	World Cancer Day
10 March 2022	World Kidney Day
07 April 2022	World Health Day
25 April 2022	World Malaria Day
03 May 2022	World Asthma Day
14 June 2022	World Blood Donor Day
28 July 2022	World Hepatitis Day
10 Oct 2022	World Mental Health Day
14 Nov 2022	World Diabetes Day
01 Dec 2022	World Aids Day

Instructions to Authors

Manipal Medical Journal (MMJ) is the official journal of the Manipal Hospital, Dwarka, New Delhi. The journal follows the International Committee of Medical Journal Editors (ICMJE) Recommendations for the conduct, reporting, editing and publication of scholarly work in medical journals. The journal gives priority to reports of outstanding clinical work, as well as important contributions related to common and topical problems related to all medical specialties, especially those relevant to developing countries.

Manuscript submission

MMJ will accept soft copies of the manuscript and will process it through a peer review process before being submitted to the Editorial Board for final selection & publishing. Presently all manuscript related queries will be through the official e-mail of the Department of Academics & Research. No hard copy manuscripts will be entertained. The online manuscript management and processing system would be adopted in future once the journal gets regularized and indexing is to be initiated.

Criteria for Acceptance

All manuscripts should meet the following criteria: the material is original, study methods are ethical and appropriate, data are sound, conclusions are reasonable and supported by the data, and the information is important; the topic has specialty specific interest; and the article is written in reasonably good English. The article should be submitted in the standard manuscript style, the details of which are given later in the instructions. Manuscripts conforming to ICMJE guidelines will also be accepted and enter the review process; however, if accepted, the final version would need to conform to the journal's style. All accepted manuscripts are subject to editorial modifications to suit the language and style of MMJ. After modifications, they will be sent to the corresponding author for approval.

Categories of Articles

Articles can be submitted as Original Research Papers, Research Briefs, Review Articles, Clinical Case Reports, Perspective, Update, Images, Clinical Case Letters and Correspondence.

Original Research

Manuscripts reporting original research may be submitted as Research Paper or Research Brief.

Research Paper

The submission should report research relevant to clinical specialty including randomized clinical trials, other intervention studies, studies of screening and diagnostic tests, analytical cohort and case-control studies, systematic reviews and cost effectiveness analyses. Descriptive studies, surveys, case records/series, pilot interventional studies, and secondary analyses of data are usually not preferred for this section.

Each manuscript should be accompanied with an 8-point structured abstract in not more than 250 words. The 8 subheadings of the structured abstract should be: background, objective, study design, participants, intervention, outcomes, results, and conclusion. The main text of the manuscript should be arranged in sections

on Introduction, Methods, Results and Discussion. The authors should take care to avoid use of sub-headings in the Results or Discussion section. However, Methods section should always include a subheading of 'Statistical analysis.' Key messages should be provided at the end of the manuscript in a box under headings: 'What is Already Known?' and 'What this Study Adds?.' As far as possible, authors should restrict to a one line answer for each of these two queries. Number of tables and figures should be limited to a maximum of 4 and 2, respectively. Extra tables and figures, will be subject to clearance by editorial review process. The typical text length for such contributions is 3000 words (excluding title page, abstract, tables, figures, acknowledgments, key messages and references). Number of references should be limited to 30.

Research Brief

Descriptive observational studies, epidemiological assessments, and surveys are published as Research Briefs. Knowledge, attitude, practice (KAP) studies are generally not preferred. Some of the manuscripts submitted as 'Research Papers' may also be considered for publication under this section at the discretion of editors. A reasonably large series of cases can also be considered for this section.

Abstract should be limited to 150 words, and structured using the following headings: Objective, Methods, Results, and Conclusions. The text should contain no more than 1500 words, up to 3 illustrations/tables and up to 20 recent references. The text should be arranged in order of Introduction, Methods, Results and Discussion. Also include a box entitled 'What this Study Adds?' highlighting the main result of the study. The distinction between Research Brief and Research Paper will be purely the journal's prerogative and will not reflect on the originality of the research submitted. The manuscripts will be finally published under the heading of Research Papers.

Clinical Material

Interesting Clinical observations may be shared through Clinical Case Reports or Images sections.

Clinical Case Report

Clinical cases highlighting some unusual or new but "clinically relevant" aspects of a condition are published as Clinical Case Reports. Such reports should highlight some new or unusual aspect regarding etio-pathogenesis, diagnosis or management of a condition that adds to the existing body of knowledge. Rarity of the reported condition alone will not be a criterion for acceptance.

The text should not exceed 2000 words and should be in running text with labelled paragraphs sequentially containing Introduction, clinical-description, and discussion. Include a maximum of 15 references. Only two very relevant figures are allowed. Photographs (either black & white/ colour should be of high quality, without any blurring. Colour images will be published only in the web-version of the journal; for print version, these will be converted to black and white (For details, see below under Figures and Illustrations). A maximum of seven authors are permitted. Whenever there is a clinical image, patient's written consent (or that of the next of kin) to

publication must be obtained, and the same must be affirmed/stated on the Title page. The editorial board may ask for such a consent form at any time during the manuscript review process.

Images

Only clinical photographs with/without accompanying skiagrams or pathological images are considered for publication. Images of radiographs/ histopathology slides alone (without accompanying clinical photograph) are not considered for this section. Image should clearly identify the condition and have the classical characteristics of the clinical condition.

A short text of about 250 words should be provided in two paragraphs; first paragraph having description of condition, and second paragraph discussing differential diagnosis and management. No references are needed. See guidelines for preparing and submitting Figures/images (vide infra). A maximum of three authors are permitted. Images of cases involving more than one department can have a maximum of six authors. The authors should ensure that images of similar nature have not been published earlier in MMJ. Authors must obtain signed informed consent from the patient/legal guardian, and the same must be stated on the Title page. Such form should also be attached as a supplementary material while submitting the manuscript.

Reviews

The journal encourages submission of review articles addressing recent advances/controversies. These may be submitted as either Review Articles or Update. Please note that as a routine all review articles submitted to MMJ will undergo a plagiarism check, and the articles will promptly be sent back for revision or rejected depending on the extent of similarity with the published literature.

Review Article

State-of-the-art review articles with systematic, critical assessments of literature will be published. The typical length for review articles is 2500-3000 words (excluding tables, figures, and references). An abstract of around 250 words with the following sections: Context (describing the clinical question or issue and its importance in clinical practice or public heath), Evidence acquisition (describing the data sources used, including the search strategies, years searched, and other sources), Results (major findings of the review with the greatest emphasis laid on the findings based on highest quality evidence), and Conclusions (emphasize how clinicians should apply current knowledge). The number of references should be limited to 50. Authors should take care to avoid excessive self-citation. The number of authors should usually be limited to eight.

Update

Short write-ups on recent modifications/ revisions of standard Guidelines, Classifications or Recommendations issued by Global organizations on topics of interest to clinicians will be published in this section. The word limit is 1500 words, author limit is six, and a maximum of 2 tables and 15 references are allowed. An unstructured abstract of upto 150 words should also be included. It is preferable that the most relevant changes from the

previous version are provided in a tabular form. The manuscript should preferably include an 'Introduction' detailing the current status of the disease/guideline and the need for the revision, important changes in the new version, and the implications of the changes.

Other Categories

Journal scan

Under this section, any good article, clinical guideline of special interest published in any reputed journal can be reviewed and submitted for publication. Important points for consideration here would be – relevance of the article to clinical practice, properly written and published article, learning points form the article relevant to clinical practice. The manuscript should consist of an Introduction (upto 250 words), Text (1000-1500 words), and Learning Points (upto 150 words).

Correspondence

Letters commenting upon recent articles in MMJ are welcome. Such letters should be received within 3 months of the article's publication. Letters commenting on 'Editorials', 'Case Reports' and 'Correspondence', are generally not preferred. At the Editorial board's discretion, the letter may be sent to the authors for reply and the letter alone or letter and reply together may be published after appropriate review. The manuscript must have a title that should be different from the title of the paper it intends to comment upon. Letters should not have more than 500 words, and 5 most recent references. The text need not be divided into sections. The number of authors should not exceed three, including the authors' reply in response to a letter commenting upon an article published MMJ. Names of additional persons who have helped in drafting the letter can be mentioned in the acknowledgment section.

Preparing the Manuscript

For reporting research, the authors are expected to comply with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations) prepared by the International Committee of Medical Journal Editors (ICMJE) (www.icmje.org).

Manuscripts not fulfilling the technical requirements shall be returned to the authors without initiating the peer-review process. A summary of technical requirements for preparing the manuscript is provided below:

- The manuscript is to be submitted in electronic format
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- Use 12-point font size (Times New Roman) and leave margins of 2.5 cm (1 inch) on all sides. The whole manuscript should be formatted in 'portrait' layout.
- Spacing: 1.5 times-space throughout, including title page, abstract, main text, key messages, references, figure legends and tables.
- Units of measure: Conventional units are preferred. The metric system is preferred for the expression of length, area, mass and volume.
- Use non-proprietary names of drugs, devices and other products. Proprietary

names, if given, should not have a superscript © or TM or R; just capitalize the first word.

• There should not be any discrepancy in names and sequence of authors, and the corresponding author details, as submitted in the title page.

• Abstract (wherever applicable) must be included in the main 'blinded manuscript.

Title Page

At the beginning, mention the category (i.e. Research Paper, Research Brief, etc.) for which the article is being submitted. The page should contain (i) the title of the article: which should be concise but informative; the type of study may be added in title after a colon; (ii) a short running title of not more than 40 characters; (iii) first name and surname (both are essential) of each author with the highest academic degree(s) and designation at the time when the work was done; initials will not be accepted for surnames. For example; 'Vidya K': here, 'K' will be considered as the Initial and 'Vidya' will be indexed as Last name; (iv) details of the contribution of each author; (v) name of department(s) and institution(s) to which the work should be attributed (This should mention the institution of affiliation at the time of conduct of the study, not your current affiliation); (vi) disclaimers, if any; (vii) name, address and e-mail of the corresponding author, (viii) source(s) of support in the form of grants, equipment, drugs or all of these; (ix) declaration on competing interests; (x) Status of ethical clearance for the study along with name of Ethics Committee clearing the research study, and the date and number of the clearance from the committee; (xi) Clinical trial registration number in cases of clinical trials; and (xii) word count (not including abstract, tables, figures, acknowledgments, key messages and references). A statement regarding ethical clearance and trial registration (if done) should also be provided in the methods section of the manuscript, without including any identifying details (Ethics committee name, Trial registration number etc.)

Authorship criteria

All persons designated as authors should qualify for authorship. The journal endorses the ICMJE requirements for authorship, which is based on the following four criteria: (i) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (ii) Drafting the work or revising it critically for important intellectual content; AND (iii) Final approval of the version to be published; AND (iv) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Conditions (i), (ii) (iii) and (iv) must all be met, for all authors, individually. One of the authors shall act as corresponding author of the paper and he/she should take the responsibility of co-ordinating the work as a whole, from its inception to published article. The name of the designated author who should be approached for access to raw data should also be stated in the contributors' details, along with e-mail (if different from the corresponding author). MMJD will not entertain requests for joint corresponding authorship or joint first authorship.

Competing interests

Competing interest for a manuscript exists when the author has ties to activities that could inappropriately influence his or her judgment, whether or not judgment is in fact affected. Financial relationships with industry – for example, through employment, consultancies, stock ownership, honoraria, grant, expert testimony, either directly or through immediate family, are usually considered to be the most important competing interests. If competing interest exists, the author(s) must disclose them while submitting the manuscript.

Funding

Authors are required to report all financial and material support for the research work, including grant number and funding agency

Abstract and Keywords

A structured abstract is to be sent in case of Research Paper (250 words), Research Brief (150 words) and Guidelines (250-300 words), Review Article (250 words), Update (150 words) and Research letters (50 words). For brevity, parts of the abstract may be written as phrases rather than complete sentences. No abbreviations should be used in the abstract. Four to five key words to facilitate indexing should be provided in alphabetical order below the abstract. Terms from the Medical Subject Headings (MESH) list of Index Medicus should preferably be used. Do not repeat words already included in the title.

Main Text

Introduction

The introduction must clearly justify and state the question that the author(s) tried to answer in the study. It may be necessary to briefly review the relevant literature. Cite only those references that are essential to justify the proposed study.

Methods

The methods section should describe, in logical sequence, how the study was designed (e.g. how randomization was done), carried out (e.g. how subjects were chosen or excluded, ethical considerations, accurate details of materials used, exact drug dosage and form of treatment) and data were analysed (e.g. an estimate of the power of the study, exact test used for statistical analysis). For standard methods, appropriate references are sufficient, but if standard methods are modified these should be clearly brought out. Authors should provide complete details of any new methods or apparatus used. Commercial names of the drugs/equipment may be used once at first mention, with the initial letter capitalized and manufacturer's name and address in parentheses. Subsequently the scientific/non-propriety name is to be used throughout. © or TM in superscript after the propriety name is not required.

Ethics: All studies involving human subjects must address ethical issues. When reporting experiments on human subjects, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional). The ICMR National Ethical

Guidelines for Biomedical and Health Research Involving Human Participants (https://icmr.nic.in/sites/default/files/guidelines/ICMR_Ethical_Guidelines_2017.pdf) is a helpful guide.

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Informed consent must be obtained in writing from all human participants of any study. MMJ reserves the right of seeking from the authors the details of the information given to participants about the deviations from the normal, the risks involved, and the potential benefits to the society. Authors should not use patients' names, initials, or hospital numbers, especially in illustrative material. Written consent must be obtained from patients or legal guardians for publication (in print or electronic form) of clinical details or/and clinical photographs in all 'Case Reports', 'Images' 'Clinical videos' and qualitative research reports.

This consent form need not be submitted with the manuscript but obtaining of consent should be confirmed on the title page. The identity of the patient in clinical photographs should be masked by suitable methods.

Statistics

Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Provide actual P values, rather than stating as just 0.05. References for statistical methods should be to standard works when possible (with pages stated) rather than to papers in which the methods were originally reported. Specify any general use computer programs used. Define statistical terms, abbreviations, and most symbols. The relevant guidelines may be consulted for appropriate reporting.

Results

This section should include only relevant, representative data and not all information collected during the study. Major findings should be presented clearly and concisely. It may also be useful to mention what the study did not find. Write units along with data at all places in the manuscript. Journal uses the format "mean (SD), median (IQR)" rather than "mean ± SD, median ± IQR" for reporting summary measures. Text, tables, and illustrations should be used judiciously. Avoid repeating in the text the data depicted in the tables or illustrations; emphasize or summarize only important observations. Restrict tables and figures to those needed to explain the argument of the paper. Cite the tables sequentially in the text, and provide each table on a new page after the reference section. Do not insert figures or tables in the main text of the manuscript.

Discussion

Ordinarily it should not be more than one-fourth of the total length of the manuscript. Do not attempt a detailed review of literature. This section should include (unheeded paragraphs in the order specified): (i) a summary of the major findings, (ii) limitations of the study, (iii) their relationship to other similar studies, and (iv) generalizability of the findings, and implications for practice/ policy/ research. Conclusions should be linked to the goals of the study. Avoid unqualified statements and conclusions not completely supported by the data. Authors should also refrain from making statements on economic benefits and costs unless their manuscript includes economic data and analyses.

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Authors need to be accurate in citing and quoting references. References should be numbered consecutively in the order in which they are first mentioned in the text.

• Identify references in text, tables, and legends by Arabic numerals in superscript. References cited only in tables or in legends to figures should be numbered in accordance with the sequence established by the first identification in the text of the particular table or figure.

• Use the style of the examples below. The titles of journals should be abbreviated according to the style used in PubMed. Do not use unpublished observations and personal communications as references.

• References to papers accepted but not yet published should be designated as "in press"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication.

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• The Uniform Requirements style (the Vancouver style) is based largely on an American National Standards Institute (ANSI) standard style adapted by the NLM for its databases. Please take care that citations are not directly copied and pasted from websites; remove the hyperlinks from the same. If the web version of a journal has been consulted instead of the print version, the same should be listed in the list of references. The manuscript may be returned to authors for re-typing, in case this is detected during the final page-setting.

• Article in journals: List all authors when six or less. When seven or more, list only first six and add et al.

o Gera T, Shah D, Sachdev HS. Impact of water, sanitation and hygiene interventions on growth, non-diarrheal morbidity and mortality in children residing in low- and middle-income countries: A systematic review. Indian Pediatr. 2018; 55: 381-93.

o Marwaha RK, Mithal A, Bhari N, Sethuraman G, Gupta S, Shukla M, et al. Supplementation with three different daily doses of vitamin D3 in healthy pre-pubertal school girls: A cluster randomized trial. Indian Pediatr. 2018; 55: 951-6.

• Personal author (book): Gupta P. Essential Pediatric Nursing, 2nd ed. New Delhi: AP Jain & Co.; 2010.

• Chapter in a book: Khilnani P, Singhal N. Respiratory failure. In: Choudhury P, Bagga A, Chugh K, Ramji S, Gupta P, editors. Principles of Pediatric& Neonatal Emergencies. 3rd ed. New Delhi: Jaypee Brothers; 2011.p.74-83.

• Conference proceedings: Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15-19; Kyoto, Japan. Amsterdam: Elsevier;1996.

• Conference paper: Mukherjee DK, Chowdhury BH, Das MM. Intrauterine growth of low birth weight babies and its relation to various placental and maternal factors - A multifaceted study. In: Choudhury P, Sachdev HPS, Puri RK, Verma IC, editors. 8th Asian Congress of Pediatrics; 1994 Feb 6-11; New Delhi, India. New Delhi: Jaypee Brothers; 1994. p.36.

• Newspaper article: City sees no respite from swine flu, 8 new cases reported. Hindustan Times 2015 Mar 08; New Delhi: p. 8 (col 4).

• Dictionary and similar references: Stedman's Medical Dictionary. 26th ed. Baltimore: Williams & Wilkins; 1995. Apraxia; p.119-20.

• Material published early on website but not yet published in print: Natarajan CK, Jeeva Sankar M, Agarwal R, Deorari A, Paul V. Performance on paladai feeding of preterm infants with bronchopulmonary dysplasia. Indian J Pediatr.2018 Dec 13.doi: 10.1007/s12098-018-2818-6. [Epub ahead of print]

• Material from the Internet: Website addresses must be in italics, and not underlined; give the date of accessing the website. Remove all hyperlinks.

o Equator Network. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials. Available from: http://www.equator-network.org/reporting-guidelines/consort/.Accessed January 01, 2019.

• Electronic material: Neonatal Resuscitation Program (NRP) Training Aids [on CD-ROM]. National Neonatology Forum, New Delhi, 2006.Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

Tables

Type each table with double-spacing on a separate sheet of paper. Do not submit tables as photographs. Number tables consecutively (Roman numerals) in the

order of their first citation in the text, and supply a brief but self-explanatory title for each. Tables with only two columns or those with more them 5 columns should be avoided. Also avoid tables with more than 20 Rows as these are likely to cross-over to the next page during printing. Detailed tables that cannot be adjusted in a single journal page will be incorporated as web-tables, at editorial discretion. Give each column a short or abbreviated heading in italic font style. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all abbreviations that are used in each table. For footnotes use the following symbols, in this sequence: *, #, $, ‡, ^, **, ##, $$, ‡‡, ^^, and so on. Identify statistical measures of variations such as standard deviation and standard error of the mean (Do not use ± sign). Be sure that each table is cited in the text. If data are used from another published or unpublished source, obtain permission and acknowledge them fully. The source of the table should be in the footnote in full, and not by reference number alone. Obtaining the permission from the original copyright holder for reproducing already published material is the responsibility of the author, and any relevant queries will be directed to the corresponding author.

Figures and Illustrations

Figures should be sent as separate files. Color photographs will be published only in the web-version of the journal. For print version, these will be converted to black and white except for images section. It is preferable to have the photograph in portrait form rather than in landscape form to fit easily into one column. Letters, numbers, and symbols in photographs should be clearly legible. The electronically submitted images should be of high resolution (>300 dpi). The following file types are acceptable: CDR, TIFF, EPS, and JPEG. Figures should be submitted separately from the text file. If photographs of individual/people are used, either they must not be identifiable or their pictures must be accompanied by written permission to use the photograph. It is advisable to cover the eyes unless specifically need to be shown. If a figure has been published, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. Figures should be numbered consecutively according to the order in which they have been first cited in the text. Legends for illustrations: Type or print out legends for illustrations using double-spacing, starting on a separate page, with Arabic numerals corresponding to the illustrations. When symbols, arrows, numbers, or letters are used to identify parts of the illustrations, identify and explain each one clearly in the legend. Explain the internal scale and identify the method of staining in photomicrographs. Legends should be a part of main manuscript, and should not be sent as supplementary material.

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Consent of Patient/Guardian for publication of material related to clinical images/videos In MMJ

Description of material (photograph or video): 1._____ 2._____ 3._____

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I understand that the material may depict my patient's medical conditions.

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Address: _____

_____

If you are not the parent, what is your relationship with the patient?

Witness Name: _____ Signed: _____

Date: _____

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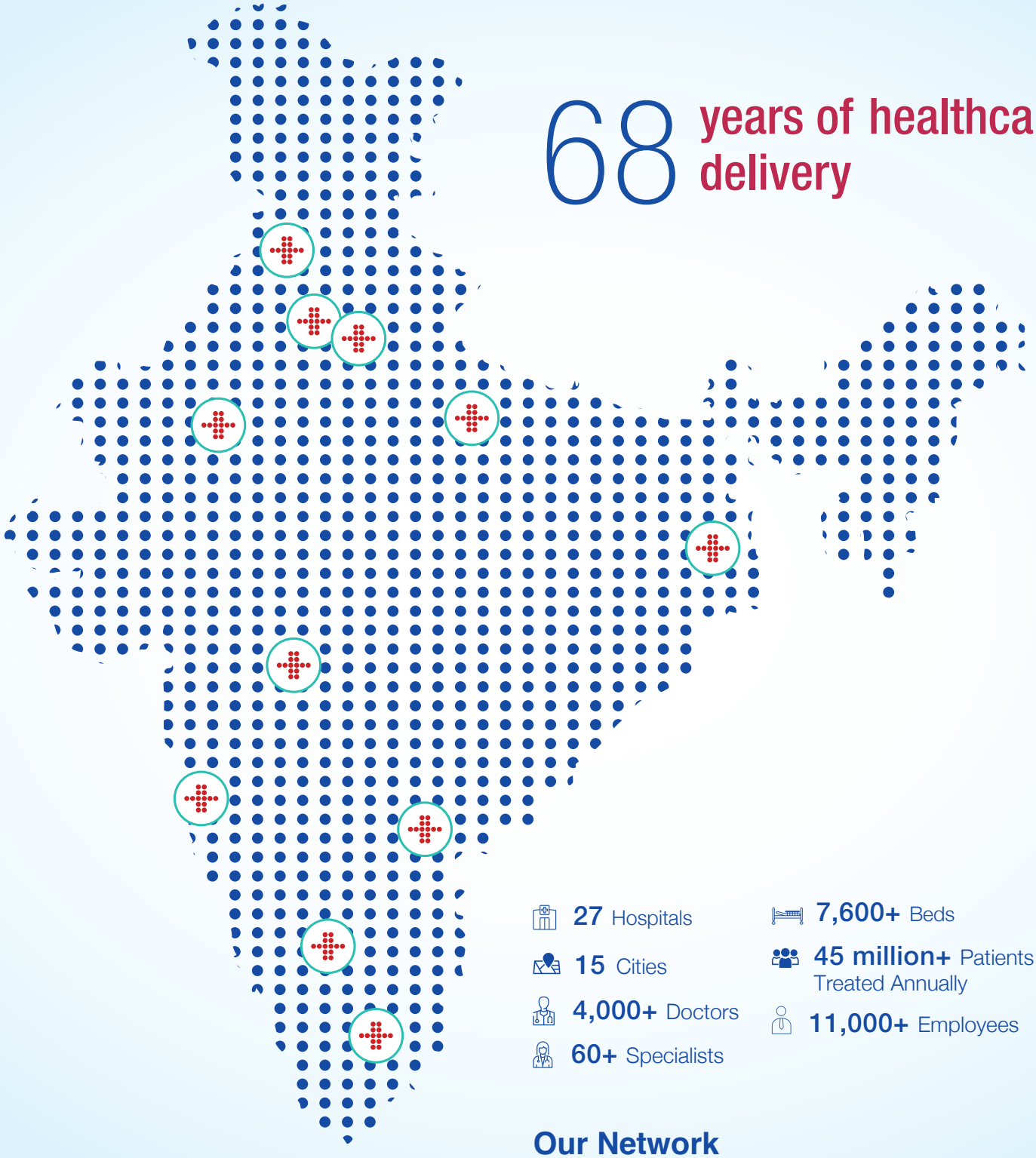

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