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Competency Based Medical Education

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As per the Times of India News, in December 2017, Union Health Ministry of India proposed an amendment bill draft for the national exit test (NEXT) after the completion of MBBS. A central government official said, NEXT would improve the quality of medical education in the country and help benchmark students. It is also said that will bring about standardization.[1] This news provoked a debate about the need of such an examination.

Over the years, a perceptibly increasing gap between the health professionals' education, health care delivered, and societal health needs has raised global concerns. Medical schools are increasingly facing the question, 'Are they producing graduates who are competent to cater to health needs of the society?' – Perhaps, not in entirety.[2] Such exit examination like NEXT can be one of the corrective actions for reducing the gap as officials have added that NEXT will be outcome based test. [1] But only such exit examination is not sufficient. We have to work our way backwards from first defining the expected roles of a physician that best serve the healthcare requirements of the community and also to clearly state the characteristics and abilities of doctors graduating from medical schools that enable them to perform these roles well. The curricula then need to be designed towards achieving these outcome requirements steered by appropriate assessment methods. Herein lies the origin and essence of Competency-Based Medical Education (CBME).[2] In 'Vision 2015' document of Medical Council of India (MCI), the outcomes of graduate medical education were expressed as the competencies that an 'Indian Medical Graduate' would develop so as to function as a 'Basic Doctor' or physician of first contact to the people of India and the world. The five roles of a Basic doctor were stated as: Clinician, Leader and Team member, Communicator, Lifelong learner, and Professional (who is ethical, responsive and accountable to patients, community and profession). The competencies to be developed to perform the above roles were also specified. The term competency was meant to imply 'desired and observable ability in the real life situation'.[3] Some experts consider CBME as another form of outcome-based education (OBE), where learning outcomes assume more importance than learning pathways or processes.[2]

Definitions

Frank and colleagues found out many definitions of CBME and therefore the international CBME collaborations proposed following definitions of CBME and related terms after reviewing of literature.[4]

Competence - The array of abilities across multiple domains or aspects of physician performance in a certain context. Statements about competence require descriptive qualifiers to define the relevant abilities, context, and stage of training. Competence is multi-dimensional and dynamic. It changes with time, experience, and setting.

Competency - An observable ability of a health professional, integrating multiple components such as knowledge, skills, values, and attitudes. Since competencies are observable, they can be measured and assessed to ensure their acquisition. Competencies can be assembled like building blocks to facilitate progressive development.

Competency - based medical education

An outcomes-based approach to the design, implementation, assessment, and evaluation of medical education programs, using an organizing framework of competencies.

Competent - Possessing the required abilities in all domains in a certain context at a defined stage of medical education or practice.

Competency - based approaches to preparing professionals go back 60 years. Within medicine, CBME has been proposed for over 50 years but has only recently come to the fore. A number of forces and trends have given rise to a particular interest in CBME. From recent arguments in favour of CBME, four overarching themes

have emerged: a focus on outcomes, an emphasis on abilities, a de-emphasis of time-based training, and the promotion of learner-centeredness. [4]

How CBME differs from contemporary process based curricula is well discussed. A traditional program may begin with the question, "what do learners need to know?" or "How shall we teach our learners?", CBME begins with outcomes. CBME is organized around the question, "what abilities are needed of graduates?". The answer to this question can come from educational needs assessments, such as practice profiling, task analysis, defining population health needs, or identifying Entrustable Professional Activities (EPA) for the specialty or subspecialty. The identified abilities are organized as competencies for a curriculum, and are further delineated in terms of their building blocks. Working backward, educators can then identify milestones that trainees will need to reach as they acquire the required competencies. Instructional methods and assessment tools can then be selected to facilitate the development of learners for these abilities.[4]

Following are the steps described in the planning of CBME curricula: [4]

1. Identify the abilities needed of graduates.

2. Explicitly define the required competencies and their components.

3. Define milestones along a development path for the competencies.

4. Select educational activities, experiences, and instructional methods.

5. Select assessment tools to measure progress along the milestones.

6. Design an outcomes evaluation of the program.

Teaching- Learning Methods in CBME [5]

Since CBME is learner-centred, offers flexibility in time, and focuses on all the three domains of learning together; the teaching–learning activities would need a change in structure and process. Since it focuses on outcomes and prepares students for actual professional practice, teaching–learning activities would be more skill-based, involving more clinical, hands-on experience. Some examples of teaching methods adopted in CBME by a couple of African medical colleges include problem-based learning in the preclinical years and case-based learning in the clinical years, clinical pathological conferences, clinical audits, and early clinical exposure. Skills' training was imparted in the laboratory and via practical sessions. Community-based research and service were also included. Information communication technology was additionally used to enhance learning. For significant learning to happen by a competency-based curricular design, novel instructional methods such as a “flipped classroom” approach and “team-based learning” have also been suggested. One of the competencies expected of an IMG by the MCI is “being a life-long learner.” Hence, students must be provided ample opportunities for self-directed learning. The inbuilt feedback process would help them be aware of their own lacunae in learning. The teacher's role would be to facilitate the student's progress.

Assessment in CBME

The international collaborators for CBME have enlisted six key features of effective assessment in CBME. First, it needs to be continuous and frequent. This is so that more formative assessments can take place to guide the student's progress. Second, it must be criterion-based, using a developmental perspective. Thus, a student would not be deemed competent, merely because he is better than the rest, but only if and only when his performance matches a certain minimum required a standard of care. Third, the assessment needs to be largely work-based. Although simulation can be used in the early phases for assessment and feedback, direct observation, and assessment of authentic clinical encounters would be an essential component of CBME. Fourth, the assessment tools themselves must meet certain minimum standards of quality in terms of validity, reliability, accept ability, educational impact, and cost-effectiveness. Fifth, more qualitative approach to assessment must be incorporated. Judgments and feedback from experts are more meaningful than numbers, scores, or grades. Moreover, sixth, assessment should draw upon the wisdom of a group, and the trainee should himself be actively involved in the assessment process. This means that a greater use needs to be made of multiple tools of assessment including work-place-based assessment tools such as mini-clinical evaluation exercise, direct observation, multisource feedback, and records of clinical work such as logbooks and portfolios.

Formative assessments with feedback, largely work-based, would form the backbone of CBME. [6] For CBME in post-graduate (PG) medical education, change is needed in all levels of PG training including intensive faculty development that addresses curricular design and the assessment of competency. [7]

Challenges in the implementation in CBME

The implementation of CBME in undergraduate education poses challenges for curriculum design, student assessment practices, teacher preparation, and systemic institutional change. [8]

Considering the fact that CBME is a relatively novel concept in India, sensitization and training of stakeholders and faculty would be necessary to enhance acceptance and also ensure uniform implementation of the CBME-based curriculum across all medical schools in the country. Bringing about a paradigm shift in our teaching–learning and assessment methods would be a difficult process. Finally, working out the logistics of implementation which includes procuring additional resources in terms of infrastructure, material, and workforce would be necessary. CBME de-emphasizes time-based training, but to manage a cohort of learners, wherein each one progresses at a different pace may be a challenge. [5]

Future Approach for CBME

We as a country still have a long road ahead towards implementing competency-based medical training. There is a need to review and revise our curriculum respecting the key role of assessment in achieving the deliverables. With the benefit of the existent curricular frameworks in use in different nations, we need to develop a competency framework suited to our needs and feasible in our settings and resources. [2] The MCI has been intent in gently moving toward a competency-based curriculum as described in its 'Vision 2015' document. However, to maximize the gains of CBME, a hybrid approach has been suggested wherein CBME should be inbuilt in the tenets of the conventional curriculum in the initial phases of the change, and then the conventional curriculum could be gradually replaced by CBME. This would ensure that the stakeholders would not be overwhelmed by a sudden change, while also providing an opportunity to measure and analyse the benefits of CBME. [5]

Considering these future prospects, this outcome based exit exam; NEXT, declared by the Union Health Ministry of India, would be a new beginning and small step towards the implementation of CBME.

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REVIEW ARTICLE

Antimicrobials - The End Of An Era ! : The Implications And The Solutions

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"The world is heading towards a post-antibiotic era in which common infections will once again kill. If current trends continue, sophisticated interventions, like organ transplantation, joint replacements, cancer chemotherapy, and care of pre-term infants, will become more difficult or even too dangerous to undertake. This may even bring the end of modern medicine as we know it."

-Dr Margaret Chan
Director-General WHO

The antibiotic story, which started with a fungal spore blowing on to a petri plate, seems to be coming to an end. The fungus inhibited the growth of Staphylococci on an agar plate and Sir Alexander Fleming named the inhibitory substance 'Penicillin', after the mould Penicillium notatum[(1)]Mankind celebrated its victory against microbes and there was a perception that the problem of bacterial infections had been solved for all times. Over the years many newer antimicrobials were discovered and extensively used in healthcare settings. All advances in medicine were possible due to support of antibiotics.

In 2013 Tom Friedan, the then, director of the Centers for Disease Control and Prevention (CDC) warned "If we're not careful, we will soon be in a post-antibiotic era."[(2)]Now a mere four year later, we seem to have arrived at the end of this magical era!

Last August, a woman in her 70s checked into a hospital in Reno, Nevada with a Klebsiella infection in her hip. The organism belonged to a class of particularly tenacious microbes known as Carpabenem resistant Enterobacteriaceae (CREs). However, in addition to Carpabenem, this organism was also resistant to Tetracycline, Colistin, and 26 other antimicrobials. A few weeks later she developed septic shock and died.[(3)] This was "a wakeup call" for the world!

How did we reach the end of the antibiotic era?

The overuse of antibiotics drives the evolution of resistance. As early as 1945, Sir Alexander Fleming raised the alarm regarding antibiotic overuse. He warned about the 'phenomenon of antibiotic resistance' in his Nobel Prize winning lecture saying that if antibiotics were used injudiciously, antibiotic resistance would develop.[(4)]

What is Antimicrobial resistance?

It is resistance of a microorganism to an antimicrobial drug OR a drug originally effective for treatment of an infection becomes ineffective. So, infections persist, increasing the risk of spread to others. Resistant microorganisms could include bacteria, fungi, viruses and parasites. In this review the focus is on antibacterial resistance.

The bacteria become resistant to antibiotics due to selective pressure exerted by antibiotics and the world has been awash with antibiotics.

How do bacteria get drug resistant? Bacteria acquire the capacity to develop drug resistance by mutation or transmission of genes into the bacteria by transformation, transduction or conjugation. Genes could be present on the chromosome of the bacteria or more often on plasmids and transposons. The latter are easily transmissible from bacteria to bacteria.[(5)]

The presence of the gene manifests as resistance by the following ways:

1. Enzymatic inactivation:e.g.-β-lactamases production by Staphylococci

2. Altered transport system/ permeability: e.g.-Reduced uptake of antimicrobials by the bacteria or increased efflux e.g. Fluoroquinolones

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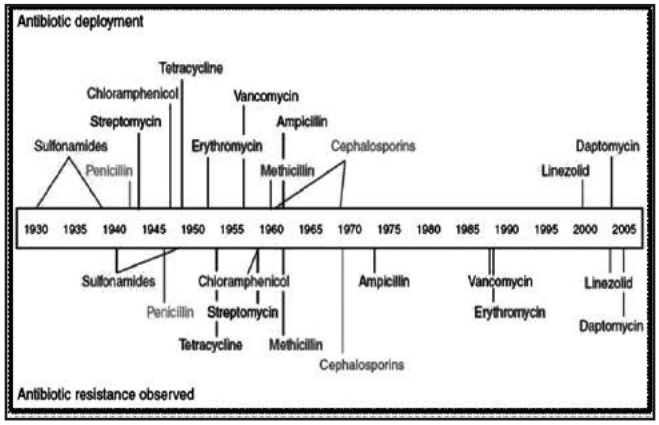
3. Alteration of antimicrobial target: e.g. –Conversion of Penicillin binding protein PBP to $PBP_{2a;}$ so Penicillin cannot bind

4. Synthesis of resistant metabolic pathways: e.g.Folate synthesis by Trimethoprim & sulphonamides

Evolution of Drug Resistance :

Introduction of every new class of antimicrobial drug has been followed by microorganisms developing resistance to it. (Fig 1)

Fig 1 : Summarizes the timeline in development of newer antibiotics and the emergence of resistance [6]



Gram positive organisms:

Penicillin was successful in controlling bacterial infections among World War II soldiers but by the 1950s, Penicillin-resistant S. aureus emerged as a major threat in hospitals and nurseries. This lead to the introduction of broad spectrum Penicillins i.e. Cloxacillin and Methicillin.[7] By the 1970s, methicillin-resistant S. aureus(MRSA) had emerged and spread. The epidemiology of MRSA was constantly changing, which resulted in variation in its drug-resistance patterns throughout regions and countries.[8]In India prevalence rate of MRSA varies from 30-85% in different parts and has now become endemic. A multi-centric study done in India involving 17 tertiary care Hospitals reported MRSA prevalence of 41% in 2008 -2009.[9]

Vancomycin was introduced into clinical practice in 1972 for the treatment of methicillin resistance in both S. aureus and Coagulase-negative Staphylococci.In the 1990s, Vancomycin-resistant Enterococci (VRE) emerged and rapidly spread; most of these organisms were resistant to other traditional first-line antimicrobial drugs. At the end of the century, the first S. aureus strains with reduced susceptibility to Vancomycin were documented, prompting concerns that S. aureus fully resistant to Vancomycin may be on the horizon[7,10]

Gram-negative pathogens:

E.coli producing β -lactamases were documented almost simultaneously with the introduction of Penicillin. Today there are 1,000 different types of β-lactamases documented in Gram negative bacteria which result in development of resistance to most of the commonly used β-lactam drugs. The introduction of the third-generation Cephalosporins into clinical practice in the early 1980s was a major breakthrough in the fight against β-lactamase-mediated bacterial resistance to antibiotics. However, in 1983, plasmid-encoded β-lactamases capable of hydrolyzing the extended-spectrum Cephalosporins i.e. ESBLs were reported.[11, 12, 13]

To overcome this problem the Carbapenems were developed and remained the treatment choice for such infections. In 1985, Imipenem became the first Carbapenem used in the treatment of such complex microbial infections. Later on, several novel Carbapenems (Meropenem, Ertapenem, and Doripenem) were identified.[14,15]

Arrival of NDM1 –the super bug!

New Delhi metallo-β-lactamase (NDM) producing Klebsiella resistant to Carbapenems was first reported in 2008 from a patient operated in India.[16] The nomenclature of the organism was widely criticized in India.Subsequently similar mechanisms of resistance in diverse Gram-negative organisms were reported from many other countries including the U.S.A. and China.[17,18,19,20] This mechanism of resistance was detected in Pune in1.5% of the total clinical isolates & 2.2% of the Gram-negative isolates, essentially from Acinetobacter spp and Pseudomonas spp.[21]

Colistin was advocated as the drug of choice for these organism still the emergence of the new super bug: Total drug resistant (TDR) Bacteria. [22]Until recently, all Colistin resistance mechanisms was due to chromosomic mutations. In China in 2015, the plasmid-mediated Colistin-resistance gene was reported in animals and humans, which was named as named mcr-1. This was followed by descriptions of the variants mcr-1.2 and mcr-1.3[23]

Now we have these ugly superbugs prevalent in most

health care settings which is either MDR (multidrug resistant) or TDR.The CDC estimated that more than 2 million people develop an antibiotic resistant infection annually and 23000 die as a result of it.[10]

What drives antibiotic resistance?[6,24,25,26]

Antimicrobial resistance is a multifaceted problem.

1. Inappropriate use of antibiotics in hospitals and in the community provides favorable conditions for resistant microorganisms to emerge and spread. Use of broad spectrum antibiotics as an empirical therapy in the outpatients especially for any febrile illness leads to emergence of resistant strains. Availability of over the counter (OTC) antibiotics in many countries including India compounds the misuse in the community where they are often self-prescribed for viral infections also.[7]

Antibiotic overuse or misuse is thus a major driver of resistance. Evolution of antibiotic resistance is a consequence of selective pressure.Global sales of antibiotics of human consumption increased from 2000 to 2011 by 36%.Brazil, Russia, India, China, and South Africa accounted for 76% of this increase. Significant increases in consumption rates were noted for Carbapenems (45%) and Polymixins (13%).[24]

2. Inappropriate and irrational use of antibiotics in animal husbandry & veterinary practice. Antibiotics are used in animal husbandry and poultry farming as food adjuvants to increase yield of milk and prevent loss of livestock. These antibiotics are then ingested by humans in sub-therapeutic dosage with meat, milk and eggs. Selective pressure of these antibiotics results in the proliferation of resistant plasmids in the normal flora of individuals and these are subsequently passed on to the pathogens.[25]

The agricultural use of antibiotics also affects the environmental microbiome.Up to 90% of the antibiotics given to livestock are excreted in urine and stool and then widely dispersed through fertilizer and groundwater. This practice exposes microorganisms in the environment to these growth-inhibiting agents, altering the environmental ecology.[7]

3. Unsound practices in the pharmaceutical manufacturing industry.

The antibiotic content in individual preparations is compromised especially in countries where the regulatory authorities are not vigilant. Unscientific drug combinations also compounds the problem.

4. Lack of laboratory facilities in many parts of the country. Thus evidence based treatment is not available to the doctors and un-indicated use of antibiotics occurs. This also results in paucity of accurate Anti-Microbial Resistance data at the hospital level and national level making it difficult to plan antibiotic policies. Weak surveillance and regulatory systems are thus also an important determinant of antimicrobial resistance.[26]

5. Poor infection prevention and control practices in hospitals. This lead to transmission of resistant strains to vulnerable patients in the hospital scenario and subsequently to the community once the patients are discharged from hospitals.[26]

6. Depleted arsenals of medicines and vaccines. Pharmaceutical companies are reluctant to allocate resources for research and development of newer antibiotics. Since it costs millions of dollars to develop a single molecule and as soon as the drug is introduced into the market resistance begins to develop and the company may not recover the cost of the drug development. While money spent on anti-hypertensives and anti-diabetic medicines give a lifelong return.[7]

7. Growth of global trade and travel. This has resulted in the world becoming a global village and allowed resistant microorganisms to spread rapidly from country to country and across continents.[25]

8. Disparity in health care delivery. Provision of essential good quality medicines by the public sector is one of the measures to prevent antimicrobial resistance. However in many developing countries there is non-availability of some medicines because of irregular supply. There are also problems related to monitoring the drug quality. In India, around 5% of GDP is spent on health out of which public health sector contributes to 0.9% and a major portion of the remaining is by the private health sector.[26]

Implications of Drug Resistance

Antimicrobial resistance is an impending threat to humanity. We are in the midst of an antimicrobial apocalypse!

In a “post-antibiotic era", cost of health care will go up tremendously essentially due to prolonged

hospitalization. This increase in the cost of health care will place a tremendous burden on the patient and the governments of developing economies.

Mortality from simple infections &injuries that have been treatable for decades, will increase.Progress in medical sciences which has occurred by leaps and bound sover the last few decades will be hampered. Organ transplants, Implants and chemotherapy for malignancy will turn into high risk procedures. The control of infectious diseases will be hampered.[27]

Health-care gains to society will be jeopardized and there will be an overall increase in illness related mortality.

The solutions!

There is no single 'silver bullet' to address the demon of Antimicrobial resistance (AMR). We need an adaptive, multipronged approach involving many stakeholders. Though, AMR is inevitable because of continuous natural evolution of microorganisms, it can be kept in control with appropriate interventional measures.

It is envisioned that a three pronged approach would have to be taken to prevent the current crisis getting worse. This includes:

1. Optimizing the use of antibiotics and development of newer antimicrobials
2. Preventing infections
3. Preventing the spread of Drug resistance

Optimizing the use of antibiotics:

Rationalizing the use of available antimicrobial agents in both public and private sectors in health and animal health areas for rational therapeutic use of antimicrobials is required.[28]

To this end:

- Every hospital should have an Antibiotic steward who will monitor & guide selection of antibiotics. There needs to be promotion of deceleration of antibiotics based on antibiotic sensitivity reports. Monitoring of the usage of higher-end antibiotics by the pharmacy should be introduced.
- Improving antibiotic prescribing through the use of diagnostic tests, improved documentation of symptoms, and optimization of antimicrobial therapy.
- Prescribing antibiotics only when they are truly needed. There should be interdisciplinary consultations on AMR as well as prescription auditing for use of antibiotics.
- Over the counter sale of antibiotics should be stopped.
- The community can help by never sharing antibiotics with others or using leftover prescriptions.
- Effective and early diagnosis of infectious diseases by strengthening of laboratories would result in prompt rationale treatment being instituted. These will not only benefit the patient but also decrease the opportunity for development and selection of resistant microbes. Development of newer rapid test and encouraging quality accreditation of laboratories will result in decreased use of unnecessary antibiotics for viral and other infections.
- Each nation must develop and strengthen antimicrobial policy and standard treatment guidelines. A national plan for containment of AMR and research related to public health aspects of AMR at community and hospital level needs to be developed. India has now developed national treatment guidelines. [29]However appropriate legislation is not in place to enforce such guidelines.
- Stop the use of antimicrobials in animal husbandry and veterinary industry as growth supplements. Enforce appropriate antimicrobial use in the veterinary industry. Many European nations have already enforced a ban on the unnecessary use of antimicrobials in animals.
- Effluent from pharmaceutical industries needs to be appropriately treated before releasing into the environment to protect environmental bacteria from antibiotics.[30]
- Education and training programmes for doctors and veterinarians on rational use of antibiotics should be conducted as ongoing activities.[26]

Development of newer antimicrobials

It is imperative to give incentives to researchers to develop newer antimicrobials. Since pharmaceuticals are not interested in developing newer antimicrobial molecules, the state would have to promote and support development of these antimicrobials. [26, 28] The British

Government has declared a longitudinal prize toward this end amounting to 8 billion pounds.

Newer antimicrobial drugs working on different principles from the current ones need to be developed to try and bypass the current mechanisms of resistance of bacteria.[30] This could include:

- Newer synthetic compound

- Natural compounds from unusual locations e.g. under the ocean or in stalactites from deep caves Novel approaches to development of antimicrobials could include:

1. Bacteriophages: these bacteria-munching viruses could be the next weapon in the fight against infectious diseases[31].

2. Development of Gene – editing enzyme techniques to switch off genes that confer bacterial antibiotic resistance e.g.CRISPR[32]

3. Identification of plant based silver nano particles from various with antimicrobial activity[33]

4. Identifying enzymes which increase size of porins to facilitate better entry of antibiotics into the bacterial cell[34]

5. Development of efflux pump inhibitors[35]

Development of Antimicrobial Resistance Isolate (ARI)[36] banks :

These will be centralized repositories of microbial pathogens with well-characterized resistance profiles. A bank is maintained by CDC in collaboration with the Food and Drug Administration (FDA) USA .In Pune, we have an organism bank which is maintained at Microbial Containment complex (MCC), and Pashan. This repository can be used for research on resistance mechanisms and new drug developments.

Preventing infections

· Hands are the main pathway of transmission of bacteria. So, hand hygiene is the most important measure to be promoted in the community and health care settings[10]

· Improving vaccination strategies to prevent infections in humans and animals[26]

· Development of newer vaccines against infectious diseases.

· Public awareness campaigns on infection control need to be organised and hospitals held accountable for Health care associated infections.[30]

Preventing the spread of Drug resistance

· The implementation of infection control measures, such as screening and contact isolation to prevent the spread of drug resistant bacteria in health care settings. To this end, every hospital needs to have a functional hospital infection control committee[10,26]

· Instituting surveillance systems to monitor the emergence of novel resistance mechanisms, so they can be prevented from spreading to other areas[10,30,36]

· Prevention essentially includes monitoring the spread of drug resistance. The Global Antimicrobial Resistance Surveillance System (GLASS)[37]is the WHO supported system which supports a standardized approach to the collection, analysis and sharing of data related to antimicrobial resistance at a global level. This results in informed decision-making and drives local, national and regional action. GLASS developed in 2014 will continue to foster national AMR surveillance systems through harmonized global standards. It will monitor AMR trends, detect emerging resistance and estimate extent and burden of AMR.

The Indian Initiative:

The imminence of the crisis also resulted in the Indian government taking proactive initiatives to prevent the spread of resistance in the community.

A high level meeting to plan steps to tackle the crisis was held in Chennai followed by the release of the “Chennai declaration"- a document and an initiative to tackle the challenge of antimicrobial resistance from an Indian perspective. [36]Subsequently, A Ministry of Health and Family Welfare task [38] force announced a new national anti-microbial policy for Containment of Antimicrobial Resistance. Under the new Schedule H1 (now called HX), the use and sale of antibiotics over-the-counter was banned.

Certain antibiotics, including Carbapenems, would be available at only tertiary hospitals. These drugs could be sold only with a valid prescription of a registered medical practitioner. It envisaged that antibiotic use could be monitored by a pharmacist maintaining a separate register which should be retained for at least

three years and subjected to audit regularly.[36,38]

IIMAR (Indian Initiative for Management of Antibiotic Resistance)[26] was launched in March 2008, with WHO support, by a consortium of NGOs to promote prudent use of antimicrobials.

A national programme for surveillance of AMR[39] was developed under the 12th Five Year Plan, to be implemented throughout the country by National Centre for Disease Control (NCDC) which will also act as the nodal centre for AMR surveillance. A network of 10 labs was initiated and proposed to be expanded in a phased manner. Microbiology department; B.J.GMC is a part of this network since 2015.

Thus, to conclude we are currently near the end of the available antibiotic pipeline. We all need to be aware that antibiotics are a precious resource which we need to preserve for posterity. This can only happen if we all work together to prevent the spread of infection and resistance genes in the community and health care settings.

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Brain Death

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Traditionally a person is declared dead when his cardiorespiratory function ceases to exist i.e. we have always focussed on the heart function to declare somebody dead. This is the **CARDIAC DEATH .** With advances in medicine , a person can be kept alive by supporting the cardiovascular & respiratory system even when the brain has ceased to function. The artificial ventilation with a ventilator & cardiovascular support keeps the heart beating but as the brain function has ceased , the person is only technically alive , not alive in the real sense . This is another form of death i.e. **BRAIN DEATH .**

Historically , the new clinical state of "death of the nervous system" was first proposed by Wertheimer & collegues in 1959 [1] The first description of cessation of brain function using a concept similar to the modern definition of brain death was done by Mollaret & co – workers in 1959 [2] . He coined this state as coma depasse or irreversible coma. Much before that in 1902 Cushing had reported cessation of cerebral circulation when intracranial pressure exceeded arterial blood pressure in monkeys [3]

These historical reports prove that concept of brain death is independent of organ transplantation & came into existence much before the first organ transplant in 1967. Though concept of brain death preceded organ transplantation , the dicussion about brain death gained momentum after the first heart transplant. In 1968 the Harward Medical School adhoc committee published it's criteria for brain death & defined " irreversible coma as a new criterion for death [4] These criteria for irreversible coma included 1) Unreceptivity & unresponsiveness 2) Absence of reflexes 3) Flat EEG 4) All these tests were supposed to be repeated after 24 hours with no change in the findings 5) Hypothermia < 32.2 deg C / 90 def F & CNS depressants were recommended to be excluded, The committee focussed on whole brain formulation to define brain death.In 1981, the President's commission for the study of ethical problems in medicine & biomedical & behavioural reserach [5] defined the brain as primary organ & justified the application of a whole brain definition in USA. The Uniform Determination Of Death act (UDDA) was passed stating that " an individual who has sustained either 1) irreversible cessation of circulatory & respiratory functions or 2) irreversible cessation of all functions of the entire brain including the brain stem is dead . A determination of death must be made in accordance with accepted medical stamdards." This formulation is the one most commonly used in the world .[6]

Concept of brain death -

Brain death represents death of the organism & not merely death or necrosis of brain in living organism[7] The organism is aggregation of living cells & it exists only when the aggregation is under control of modulating system such as CNS. Brain oriented death can have 3 forms defined by the structures – 1) Whole brain death 2) Brain stem death & 3) Neocortical death

Whole brain death & brain stem death both are defined as the irreversible cessation of the organism as a whole. Brain stem has got a critical role to play to maintain life.

1) It is a thro' station for all cortical input & output

2) It is a center that generates arousal which is essential for consciousness

3) It is the center for respiration

Brain stem is usually the last structure to get damaged in the injured brain. So with brainstem death the person can be declared dead as the changes are irreversible & nothing can be done to bring the patient back to life.Therefore when there is loss of consciousness , loss of brain stem reflexes & apnea , this can be defined as the death of the human being. So really speaking , brain

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death should more precisely be called as brainstem death. In U.K. absence of clinical functions of the brainstem can be declared as brain death in spite of evidence of intact brain circulation as per UK criteria. Brain stem definition of brain death was first pronounced in 1976 by the conference of Medical Royal college & their faculties in the UK [8] In 1995 , the document entitled " criteria for the diagnosis of brain stem death " [9] encouraged the use of brain stem death rather than brain death. In UK , declaration of brain death dosn't require recording of an EEG for its diagnosis & same is followed in our country.

Neocortical death is also called as cerebral death. It is synonymous with persistent vegetative state.

Persistent vegetative state represents irreversible loss of consciousness but not irreversible loss of life. Patients in this state can survive for months or years. **This state should not be confused with brain death.** When we say it is brain death , it has to be brain stem death.

Mechanism of brain death -

Brain injury whether ischemic , traumatic or hypoxic leads to brain oedema. Brain oedema can be of 2 types – a) Vasogenic b) cytotoxic

In vasogenic oedema , there is dysruption of blood brain barrier. There is leakage of proteins in brain parenchyma. Chemical mediators like serotonin, histamine, angiotensin, prostaglandins & bradykinin can disrupt the BBB . Cytotoxic brain oedema occurs in ischemic & hypoxic insults. The oedema is the result of disturbances in cellular osmoregulation. There is increased entry of water into the cells. Though initially in cytotoxic oedema the BBB is intact , cytotoxic oedema disturbs the blood flow & leads to vasogenic oedema. Increase in intracranial presure (ICP) due to brain oedema causes decrease in cerebral perfusion pressure (CPP) . CPP = MAP – ICP When CPP falls below the critical value of 10 -20 mm of Hg , the cerebral perfusion is lost leading to brain necrosis. Within 3 – 5 days the brain becomes a liquid mass. The increased ICP compresses the entire brain including the brain stem & uncal & tonsillar herniation & total brain infarction [10] There is a second pattern of brain death where the brain tissue oxuygenation ($PbtO_2$) can fall to zero in spite of ICP not exceeding MAP & maintenance of CPP. This might be primary metabolic failure of the brain [11]

Role of brain stem in controlling various vital activities & their affection after brain stem death -

1) Arousal & consciousness -

Structures in the brain stem regulate the state of consciousness But ascending reticular activating system (ARAS) is not a monolithic unit & maintenance of wakefulness or control of sleep wake cycle doesn't depend on any single region of the brain. The wake promoting cells are scattered in various parts of the brain though mainly they are in the brain stem. In brain death there is no consciousness , no intellectual activity & therefore no true humanity. This state is defined as deep coma & is the basis for the concept of brain death.

2) Respiration -

As the respiratory centers are located in the reticular core of medulla oblongata , brain stem lesions result in various abnormal respiratory patterns like gasping , apneusis, irregular breathimg etc. After brain stem death , the spontaneous respiration is totally abolished & is not stimulated even after increase in the level of $PaCO_2$ to 55 – 60 mm of Hg in spite of CO_2 being a very potent stimulus for respiration, hence this fact becomes a diagnostic test of the brain stem death. This test is called **apnea test** which will be elaborated later in the text.

Another effect of brainstem death on the respiratory system is the development of pulmonary oedema. After brain death . There is a catecholamine surge due to autonomic storm & release of neuropeptide Y causing pulmonary vasoconstriction & increase in pulmonary capillary hydrostatic pressure. The lungs are also damaged by the loss of vasomotor tone & development of systemic inflammatory response initiated by brain death [12]

3) Circulation -

The central neurons controlling the circulation are distributed diffusely over the pontine & medullary reticular core. Activation of these cells increases the sympathetic outflow causing hypertension & tachycardia. With entire cerebrum becoming ischemic due to raised ICP, there is bradycardia. Compression of brainstem leads to bradycardia & hypertension (Cushing's phenomenon). When entire brainstem becomes ischemic, vagal vasomotor center becomes ischemic with unopposed action of sympathetic outflow resulting in *autonomic storm* with high levels of

catecholamines – *catecholamine surge* . At this stage the myocardium may get damaged affecting outcome of transplanted heart if this donor heart is used for transplantation. In humans , this period of hypertension & brdycardia is brief . So attempts to reduce it are not necessary [13] If with raised ICP , there is tonsillar herniation , there is a sudden fall in B.P. At this juncture , various inotropes have to be used to maintain the systemic blood pressure as circulation to the various organs to be transplanted has to be maintained optimally to preserve them in good condition Volume replacement with balanced salt soutions also may be required. Colloids are not preferred to protect the lungs for donation.

After establishment of brain death , various autonomic spinal cord reflexes may develop resulting in tachycardia & hypertension with stimuli like bladder distension , surgical stimulation etc. This necessitates use of vasodilators & general anaesthetic agents during organ retreival even after brain death.

4) Body temperature -

After brain death , neural connections between the temperature regulating center in hypothalamus & periphery are lost & the patient becomes poikilothermic. The patient tends to become hypothermic inspite of external warming . If infection develops, the warning sign of fever is lost. For performance of apnea test , one of the prerequisites is absence of hypothermia. Hence task of maintenance of body temperature becomes challenging in the care of the brain dead.

5) Hormonal effects -

After brain death levels of various hormones fall. There is a drastic fall in the level of vasopressin resulting in diabetes insipidus. In our experience almost 90 % brain dead patients develop this complication. There is a tremendous volume loss due to large amounts of dilute urine which has to be replaced with sodium free solutions a there is concomitant hypernatremia which is detrimental to the organs to be transplanted especially the kidneys & the heart. A heart donor management algorithm with four drug hormone therapy is suggested by UNOS – United Network Of Organ Sharing . Four drug therapy of T3, vasopressin, methyl prednisolone & insulin is shown to improve graft survival especially in patients with EF < 45 % & unstable hemodynamics [14] Organ Procurement & Transplantation Network OPTN / UNOS multivariate studies revealed increased 1 year survival of heart & kidneys after 4 drug therapy i.e. T3/T4 , arginine , vasopressin & insulin.[15].

6) Immune system -

It has been observed that the levels of inflammatory mediators like cytokines , interleukins & tumour Necrosis Factor (TNF) are increased in the blood & organs of the brain dead person[16,17]. The possible mechanisms involved are: *a*. Release of inflammatory mediators from the ischemic brain *b*. Catecholamine surge leading to anaerobic metabolism which induces nuclear factor kB (NF – kB) activation of the endothelial cells inducing ischemia of the gut. *c*. Metabolic changes after brain death modulate the inflammatory response. *d.* Neuropeptides are released from the nervous system, playing a role in inflammation [18]. As these inflammatory responses can affect the functioning of the transplanted organs, it is necessary to combat them. For this the patient is treated with methyl-prednisolone.

7) Various brain stem reflexes are used to determine brain death which are enumerated below :

Criteria and tests for brain death :

Determination of brain death is a very important step as that certifies that the brain is irreversibly damaged and the person is dead in-spite of the beating heart. It is ethically and legally very important as the organs of the brain dead donor can be retrieved only after the person is certified to be dead (Dead donor rule). It is conceptually impossible to evaluate all functions of the brain. The cessation of all functions of the brain is particularly determined by loss of consciousness (GCS -3) and unresponsiveness, loss of brain stem reflexes, apnea and ancillary tests for electrical silence/absent cerebral perfusion.

Prerequisites:

1. Cause of the coma must be identified - Organic brain damage must be confirmed by tests like CT and MRI.
2. Other confounding variables like drug intoxication, electrolye abnormalities, acid-base disturbances and hypothermia have to be ruled out. Hypothermia must be corrected as it may lead to mis-diagnosis due to CNS depression.

3. The blood pressure has to be supported by vasopressors if there is hypotension which is very commonly associated with brain death. Hypotension may decrease cerebral perfusion, affecting the EEG.

Check list for determination of Brain Death : [19]

Before performing the test for brain death, one has to ensure the following :

1. Irreversible coma with a known cause.
2. Neuroimaging explains coma
3. CNS depressant drug effect should be absent , If indicated, a toxicology screen can be used, If barbiturates are given serum level should be < 10mcg/ml
4. No evidence of residual paralysis with neuromuscular blockers which can be confirmed with peripheral nerve stimulator (PNS)
5. Absence of severe acid-base & electrolyte abrnomality
6. Normothermia or mild hypothermia (core temperature > 36 deg C should be ensured)
7. Systolic B.P. > 100mm Hg
8. Absent spontaeneous respiration

Actual examination

Pupils

Shape can be round / oval / irregular

Size may vary from 4 – 9 mm

Pupilary dilation due to intact cervical sympathetic flow

Absent Corneal reflex

Absent Vestibulo-ocular reflex which is elicited by moving the head from side to side with eyes open – doll's eye movement is absent. This test can be performed if there is no C-spine fracture

Oculo-vestibular reflex – Elicited by rinsing the middle ear with cold solution. This should be absent in brain death

No facial movements to noxious stimuli at supraorbital nerve and T-M joint.

Absent gag reflex – Elicited by stimulation of the posterior pharyngeal wall

Absent cough reflex – Elicited by stimulating trachea by suctioning

Absent motor responses in all four limbs

Spinally mediated reflexes

The following may be present

a. Lazarus sign [20]– bizzare seemingly purposeful movements of upper extremity in which the arms are flexed quickly to the chest from the patients sides, shoulders are adducted. Some patients may show hands crossed or opposed just below the chin

b. Other common spinally mediated movements can be – Finger jerks , undulating toe flexion sign, triple flexion response, pronation extension reflex and facial myokymia [21]

Apnea testing

1. Confirm haemodynamic stability
2. Normocapnea ($PaCO_2$ 34-45 mmHg attained by ventilation)
3. Preoxygenation with 100% FIO_2 for more than 10 minutes to achieve PaO2 above 200.
4. Patient well oxygenated with PEEP of 5cm H_2O
5. Provide oxygen via a suction catheter at the level of the carina
6. Watch for spontaeneous respiratory attempts
7. ABG at 8-10 minutes, patient reconnected to the ventilator
8. Ensure that $PaCO_2$ is above 60 mmHg or there is 20mm rise from normal baseline value before terminating the test

The level of $PaCO_2$ to be reached varies from place to place. American neurology recommendations are rise up to 60 mmHg or 20mm of Hg above baseline [22,23] whereas UK standard is a rise upto 50mmHg [24] If the patient destabilises during this testing in the form of hypotension below 90mmHg or decrese in O_2 saturation to less than 85 mmHg longer than 30 seconds, the test is abandoned.

All the tests have to be repeated after a gap of 6 hours and if again all tests are positive, the patient can be declared brain dead.

In case of children and neonates it might prove more difficult to apply the clinical tests. The child's brain, being a developing organ, changes in pattern of vulnerability and different responses to injury may occur. As the need for organ procurement in infants and children is on the increase, it was thought necessary to formulate criteria for determination of brain death in children. In 1987, the task force for the determination endorsed the Determination of Death Act and offered guidelines for determination of brain death in children [25] These were further revised by a multi-society task force, the major changes being age of exclusion and ancillary tests . In 1987, neonates under the age of 7 days were excluded and ancillary tests were mandatory under 1 year of age. In 2011, the exclusion was restricted to preterm infants below 37 weeks of gestation and the ancillary tests were made optional.

Main differences in children and adult protocol

1. Time interval between two tests – 24 hours for neonates (37 w gestations to term upto 30 days of age) & 12 hours for infants and children upto 18 yearsas against to 6 hours in adults
2. Both examinations to be conducted by two different physicians
3. Assessment of neurologic function unreliable, immediately after CPR – wait for 24 to 48 hours for testing.
4. In addition to other brain stem reflexes, absence of sucking and rooting reflex should be confirmed in neonates.

Ancillary tests for detection of brain death

Various tests exist to confirm loss of bioelectrical activity of the brain or cerebral circulatory arrest. They are : EEG, Brain stem auditory evoked potential, Cerebral angiography, Radionuclide angiography, Computed tomography and trans-cranial Doppler ultrasonography.

These are required only if clinical tests are inconclusive or apnea test has to be abandoned. They are not mandatory in our country.

Legal framework for brain death and organ donation

The rules for brain death and organ transplantation vary from country to country. In India, the transplantation of human organs act (THOA) was passed in 1994 and subesequently amended in 2011 and 2014 [26]. Because of this act, the brain stem death is recognised as legal death and organs can be retrieved and transplanted from the brain dead individual. In all , 37 different organs and tissues can be used for transplantation. By the amendment in 2011 the brain death certification board constitution is simplified. If a neurosurgeon or a neurophyiscian is not available, an anesthesiologist or intensivist can be a member of the board provided he/she is not a member of the transplant team. Initially brain death could be declared only in institutions recognised by the state appropriate authority leading to unnecessary transfer of brain dead patients from one hospital to other for organ retrieval. With the new amendment, organ retrieval centers have been recognised avoiding this transfer.

NOTTO – National Organ and Tissue Transplant Organisation is the apex body for coordination and networking for procurement and distribution of organs and tissues and registry of organ and tissue donation and transplantation in our country. NOTTO maintains the wait list and decides the recipient once brain death is informed to them. NOTTO has various ZTCCs (Zonal Transplant Coordination Committees) & SOTTOs (State Transplant coordination committes) under it. Sassoon General Hospital is a recognised retrieval as well as transplant center. Here a committe of four doctors is involved in the certification of brain death. The committe comprises of the following :

1. The treating physician
2. The superintendant
3. The neurosurgeon / the neurophysician
4. Any member of the brain death committee appointed by the institute

Once we have a brain dead patient, we have to obtain consent of a relative

(Husband/Wife/Son/Daughter) for donation. The consent has to be voluntary & without any monetary transaction. A social worker plays an important role in motivating the family for organ donation. The job is easier said than done. The dialogue with the relatives can not be initiated before unequivocal confirmation of brain death following both the apnea tests at an interval of 6 hours. A trasplant co ordinator also plays an important role of co ordination with the ZTCC

Once the donor is identified, the ZTCC swings into action. The donor is subjected to various tests a. To

identify the organs that can be retrieved and b. To maintain homeostasis in such a way as to preserve organs till retreival. The patient is screened by ECG, Xray Chest, Echocardiography, abdominal ultrasonography and a battery of biochemical tests like blood grouping, blood culture, liver function tests, kidney function tests and serial BGL , ABGs ,screening for infections like HIV and hepatitis A,B,C. The ZTCC coordinates the recipient according to the wait-list and blood group matching. First preference is given to the parent hospital wait list. then to the other hospitals in the same city & then within the state. Till all this is arranged, the donor has to be energetically managed

Care of the donor

Meticulous care of the brain dead donor is vital in maintaining the quality of the organs to be transplanted. As discussed above, there are many biochemical changes occurring in the body that need to be tackled.

1. Diabetes insipidus– This is very common . Even though books mention the incidence as 70 % , in our experience over the last two years, the incidence is above 90%. Vasopressin infusion is used to control this. The result of D.I is hypovolemia and hypernatremia. Hypernatremia is detrimental to the kidneys and heart to be transplanted. Maintaineance of serum Sodium in the range of 135-155mM. is the goal. To avoid hypernatremia Vasopressin and Sodium free fluids are to be used.
2. Hyperglycemia – Use of Dextrose in infusion fluids is unavoidable as Na free fluid has to be used. This leads to hyperglycemia which is worsened by the use of methylprednesolone which is required to counter immune mediators . Decrease in insulin secretion after brain death compounds the problem. The hyperglycemia has to be managed vigorously with insluin infusion to maintain BGL less than 150mg% for a better organ yield.
3. Maintenance of haemodynamics – Meticulous IV fluid management, judicious of vasopressors (First Dopamine and add NorAdrenaline if no response) along with Vasopressin and continuous monitoring of urine output and central venous pressure is necessary.
4. Prevention of hypothermia with warm IV fluids and forced air warming.
5. Maintenance of acid-base balance with frequent ABG estimation and necessary correction.
6. Maintenance of PaO_2 above 100mmHg
7. Good nursing care

Actually the donor management begins with impending brain death. Standardised donor management with specific goals increases the number of organs transplanted per donor. The objective of donor management goals (DMG) is to maintain cardio-vascular,pulmonary,renal and endocrine homeostasis. The goals vary from centre to centre. These can be 6 DMGs, 8DMGs or 10DMGs.[27] Specific values of MAP, CVP, serum Sodium, number of pressors, PaO_2 , PaO_2/FIO_2 ratio, ABG, blood Glucose, Urine output in ml/kg/hour, ejection fraction and haemoglobin % are the 10 goals. Analysis of individual goals showed terminal PaO2 > 100mmHg or > 80mmHg on FIO2 < 40% , low pressor use (< 1 pressor with a lesser dose), BGL < 150 mg % were independent predictors of high organ yield. Tight glucose control is a significant predictor for pancreas & lung transplant . Lungs are 10 times more likely to be trasplanted when the PaO2 is > 100 mm Hg.In studies with 10 DMGs , compliance with 8 or more goals increased likelihood of 4 organs per donar. Four individual goals were highly significant . They were

CVP between 8-10 mm of Hg

Ejection fraction > 50 %

PaO2 / FiO2 > 300 mm of Hg

Serum Na < 150 mmol/ lt

Anaesthesia for organ retreival -

There may be a general belief that no anaesthesia will be required for the brain dead donor but contrary to this belief , the anaesthesia can be quite challenging. Because of development of spinal reflexes resulting in movement , a neuromuscular blocker is needed. The spinal level autonomic reflexes may give rise to hypertension & tachycardia with surgical incision . This may necessitate use of vasodilators / general anaesthetic agents. The volume status & hemodynamic management has to be meticulous intraoperatively

Role of anaesthesiologist in brain death & organ donation -

1 . Knowledge of medical & legal definitions of death as well as ethical concepts behind them

2 . Diagnosis & certification of brain death

3 . Meticulous care of the donor right from impending brain death stage till organ retreival

4 . Anaesthetic management of the cadaveric donor

5 . Management of the recipient

To conclude, one can say that the concept of brain death & its legalisation has increased organ harvesting from a brain dead donor giving new lease of life to the enormous number of potential organ recipients . India has seen a rapid growth in organ donation rates going from a dismal 0.05 per million population to 0 .8 per million population in a span of few years . We have to catch up with the world figures which are as high as 35 per million population in counties like Spain .[28] It is a mammoth task accomplished only with good team work , perfect understanding of all members & a humane approach.

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REVIEW ARTICLE

Neuropathic Pain : Current Concepts In Pathophysiology And Management : An Update

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Neuropathic pain is usually chronic in nature[2]. It impairs patient's quality of life. Majority of patients fall into three broad classes:

1. Peripheral focal and multifocal nerve lesions: traumatic, ischemic, inflammatory

2. Peripheral generalised polyneuropathies: toxic, metabolic, hereditary, inflammatory

3. Central nervous system lesions: stroke, multiple sclerosis, spinal cord injury

The aetiology and pathogenesis may differ in many conditions but clinical presentation may remain the same. The advances in the knowledge of pathophysiology are many and have provided clues about useful therapeutic approaches, treatment has remained mostly empirical.

A physician can outline a systematic approach to the management of neuropathic pain based on knowledge of its pathophysiology and data from controlled clinical trials.

Pathophysiology of neuropathic pain is complex and arises from changes in peripheral nervous system, central nervous system or both.

Aetiology based classification of painful peripheral and central neuropathies:

1. Peripheral nerve lesion

Focal or multifocal

i. Entrapment syndromes

ii. Complex regional pain syndromes

iii. Phantom limb pain: stump pain

iv. Post traumatic neuralgia

v. Diabetic mononeuropathy

vi. Ischemic neuropathy

vii. Polyarteritis nodosa and other vasculitic neuropathies

Generalized

i. Diabetic polyneuropathy

ii. Alcoholic neuropathy

iii. Amyloid

iv. Plasmacytoma

v. Hypothyroidism

vi. HIV induced neuropathy

vii. Drug induced neuropathies

2. Central nervous system lesion

- Post stroke pain
- Multiple sclerosis
- Spinal cord injury

Wolf CJ et al[3] in Lancet in 1999 described the current theories about peripheral neuropathic pain and insisted that the management should focus at the mechanisms that operate to produce the symptoms. The authors suggested that we require progress in our understanding of the pathophysiology of neuropathic pain, the development of accurate diagnostic tools to discover the mechanisms which contributed to the pain syndrome.

Pasero C[4] in his article in 2004 highlighted the fact that neuropathic pain is not self limited and is not as easily treated.Varied aetiological factors were discussed. He also suggested discovering the cellular mechanisms which contributed the pain transmission.

Wasner G et al[5] in 2004 investigated the mechanisms of cold pain by studying the effect of menthol on pain, temperature perception, touch sensation and skin perfusion. The authors suggested that menthol acts to sensitize cold sensitive peripheral vasoactive C

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nociceptors and activates cold specific A delta fibres. The authors recommended topical menthol as a human model for cold pain.

Peripheral mechanisms can manifest as spontaneous pain, stimulus independent pain or as hypersensitivity to a particular stimulus after damage in sensory neurons (stimulus evoked pain) [3]. Peripheral sensitisation is an increase in response to thermal or mechanical stimuli. Allodynia is pain in normal silent nociceptors due to non painful stimuli. The vasomotor and sudomotor changes may be due to sympathetic nervous system involvement. Wide dynamic range WDR neurons in dorsal horn may become responsive to input from primary afferent nociceptors. Central sensitisation is a process through which central nociceptive neurons become abnormally hyperexcitable as a result of peripheral injury and release of neurokinin A and substance P and neurotransmitters.

Inflammatory mediators released from immune cells are also implicated in the development of neuropathic pain. Cold specific A delta fibres normally suppress the sensation of pain originating from C nociceptors[4]. Selective blockade of A fibres impairs innocuous cool sensation and unmasks cold induced pain in such a way that it is perceived as burning[5]. Investigations into excitatory ion channels identified a cold and menthol sensitive transient receptor potential channel (TRPM8) that is activated at temperatures of 8-28 degree celcius[6]. Cold pain is due to lack of C nociceptor inhibition or sensitisation of cold sensitive C nociceptors like trauma, CRPS.

Dynamic mechanical allodynia is characteristic of several neuropathic pain states such as postherpetic neuralgia PHN and complex regional pain syndrome. The two mechanisms may explain this phenomenon. Nociceptor hyperactivity after nerve injury is associated with the enhanced expression of certain voltage gated sodium channels. The accumulation of sodium channels would lower the action potential threshold and is the cause of spontaneous ectopic impulse generation in damaged primary afferents.[5]Mechanical allodynia in patients with irritable nociceptors is not transmitted by peripheral nociceptors[7]. Its occurrence depends on dramatic functional alterations in the central processing of nonnociceptive mechanoreceptive information. This nociceptor hyperactivity produces prolonged enhancement of responses to afferent stimuli in spinal cord dorsal horn neurons i.e. central sensitisation. Large A beta fibres become capable of activating central pain signalling neurons (dynamic mechanical allodynia).

Clinical features:

One symptom may produce several symptoms or one symptom may arise as a result of several mechanisms[3]. Important symptom is parasthesia (non painful abnormal sensation) and dysaesthesia (unpleasant abnormal sensation)[8]. Increased sensitivity to light touch and spontaneous non evoked pain, referred pain sleep deprivation are the other symptoms. Pain can be burning, tingling or aching. Diagnosis is a challenge as no single symptom is diagnostic and there is no single diagnostic test[9].

Physical examination should include physical and neurological evaluations and should determine whether pain is continuous or intermittent, spontaneous, other abnormal sensations, sensitivity to pin prick, touch, pressure, cold, heat or vibration, elicitation of dynamic allodynia, assessment of psychological state of patient. Neuropathic pain scale, neuropathic pain symptom inventory (NPSI) can be used[10].

Management:

No drug has proved effective for all patients from a given aetiology[11]. An approach that works well for one patient may not be effective for another patient. Primary aim of any pain management is only to reduce the intensity to a more tolerable level[12].

Pharmacological approach:

The drug is started at a low dose followed by a slow upward titration.

Anticonvulsants:

Carbamazepine has an effect on sodium channels and adenosine receptors. Gabapentin and pregabalin act on alpha delta 2 subunit of calcium channel. Lamotrigine acts on voltage gated sodium channels and on glutamate release. The drugs are effective in HIV sensitive neuropathy, postherpetic neuralgia and central post stroke pain. Side effects include somnolence, dizziness, fatigue and cognitive impairement, mild peripheral oedema. Dose adjustment of gabapentin is needed in renal insufficiency. If there is failure with one drug trial with other anticonvulsant should be done. Gabapentin is the drug of choice in elderly in doses of 1800-3600

mg/day. Pregabalin may reverse mechanical allodynia. Second generation anticonvulsants may be effective in neuropathic pain.

Antidepressants:

Blockage of sodium channels and NMDA receptors and inhibition of noradrenaline and serotonin reuptake are the mechanisms. Amytryptiline and duolexitene are most effective. They have effect on opioid and adenosine receptors[13]. All the components of neuropathic pain such as stimulus independent continuous burning or shooting pain and stimulus induced allodynia may be improved by this drug. The mean dose is 75-150 mg/day. But it can produce orthostatic hypotension due to alpha blocking action. It can cause sedation due to histamine receptor blocking properties which is effective with sleep deprived patients. It can cause urinary retention, memory loss and cardiac conduction abnormalities due to muscarinic anticholinergic actions. Elderly patients should be started on a low dose as 10 mg. Desipramine and nortryptiline block norepinephrine reuptake are as effective in treatment of post herpetic neuralgia and painful diabetic neuropathy[5].

Opioids:

These are considered if first line options fail. The fear of addiction or tolerance or side effects limits their use. Tramadol is well tolerated and beneficial in management of neuropathic pain[13]. Tramadol inhibits noradrenaline and serotonin reuptake. It is effective in post herpetic neuralgia[7]. It can be used to a maximum dose of 400 mg/day. Oxycodone titrated to a maximum dose of 60 mg/day can be used. Morphine can also be used to a maximum of 240 mg/day. Caution with patients with history of chemical dependence or pulmonary disease. It is advisable to use sustained release preparations or transdermal applications to decrease the side effects.

Local anaesthetics:

Intravenous lignocaine 2-5 mg% over a number of hours may give pain relief up to weeks. This can be done with use of disposable elastometric infusion devices. Topical lignocaine as a 5 % patch can be used[14].

Topical capsaicin:

It is an agonist of the vanilloid receptor which is present on the sensitive terminals of primary nociceptive afferents. On initial application it has an excitatory action which produces burning pain and hyperalgesia but with repeated application it inactivates the receptive terminals of nociceptors. It desensitises skin by depleting levels of substance p in peripheral neurons. Capsaicin extracts 0.025% and 0.075% can be used.

Other agents:

Baclofen is useful in treatment of trigeminal neuralgia. Colecystokinin antagonists: CCK is a gut peptide located in CNS.[12] It has antiopioid effect, reduces antinociceptive tolerance to opioids and can reverse established tolerance. 5HT-3 antagonists may block the descending facilitatory serotonergic pathways. Adenosine receptors[12] are present in peripheral as well as central nervous system. Intravenous adenosine infusion may be useful in treatment of neuropathic pain. N type calcium channel blockers such as ziconotide can be used intrathecally. Non intrathecally administered drugs are under trial.

Sindrup SH et al[13] studied tramadol slow release tablets of 200 mg/day during two treatment periods of 4 weeks duration and evaluated pain relief. The authors concluded that tramadol relieves ongoing pain symptoms and key neuropathic feature allodynia. Galer BS et al[14] studied efficacy of topical lignocaine patch versus placebo. The study concluded that topical lignocaine patch provides more pain relief and does not cause systemic side effects and is simple to use. Tremont Lukats et al[15] in his review article on anticonvulsants demonstrated mechanisms of action of these drugs and need for more clinical trials. Various drug combinations have been tried for treatment as per Cochrane review[16]. The review suggests superior efficacy of two drug combinations[16]. Various articles as by F Nasirinez[17] and GJ McCleane[12] have proved efficacy of 5H-3 antagonists in management of neuropathic pain. Schroeder Cl et al[18] in 2006 had studied highly selective 2-2 voltage gated VGCC calcium channel as a new class of therapeutics.

Non pharmacological approach[19,20,21]

- Physiotherapy
- Psychotherapy
- TENS
- Decreasing caffeine intake
- Regular exercise

· Acupuncture

Interventions[20]:

Sympathetically maintained pain can be blocked by a ganglion or intravenous use of guanethedine. But response is variable and unpredictable. Nerve blocks may temporarily interrupt the cycle of pain and spasm, allow patients more normal movement, decrease the amount of analgesia used, improve functionality.

Practical approach to neuropathic management:our experience: If a patient presents with any chronic pain, one must decide if it is neuropathic pain. We take detail history and do neurological examination to ascertain the same.

In cases of neuralgia, antiepileptic medications (carbamazepine, gabapentin and pregabalin) are used as first line agents. Combination of two antiepileptic drugs (carbamazepine + gabapentin) can also be tried if suboptimal response is obtained with individual drug. The average doses of these drugs are: carbamazepine 400-800 mg/d, gabapentin 900-1800 mg/d, pregabalin 150-300 mg/d. In our experience, doses above these are not tolerated by Indian patients.

In cases of pain associated with neuropathy, both antidepressants and antiepileptics are effective. Amitriptyline 10-50 mg/d, duloxetine 30-60 mg/d, pregabalin and gabapentin are first line agents. Combination of antidepressant and antipileptic drugs is also used regularly.

Conclusion

As more than one pathophysiological mechanism is responsible for neuropathic pain, early use of combinations of two or three drugs from different classes is preferable to a stepwise approach of successive monotherapies in majority of patients. Drug related adverse effects are common as many patients are older with co morbid illnesses. These factors should be kept in mind when selecting the drugs of first choice. Phenotype typing based treatment is the latest advance under trial[21].

Role of interventional and non pharmacological approaches for management has been discussed by Molton IR and Dworkin RH [19,20]. He suggested that simple treatment like epidural steroids should be used early and spinal cord stimulation or IDDS should be used only after conservative therapies have been tried. Hypnosis, acupuncture and TENS have been used with limited usefulness.[19]

There are significant gaps in the literature for evaluation of drugs. Majority of health workers have evaluated drugs against placebo. There are very few comparisons among two drugs. No review till date has systematically evaluated all evidence for management of chronic neuropathic pain.Alll the existing reviews focus on specific therapies or selected syndromes.

The guidelines suggest starting any drug at a lower dose, increase every 3 days until relief, unacceptable side effects or maximum allowable dose is reached.[7,12,16]

We recommend an early combination of two or more agents covering multiple types of pathophysiological mechanisms to obtain greater pain relief and few side effects.

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ORIGINAL ARTICLE

Clinical Profile, Vascular Lesions And Stroke Mechanisms In Posterior Circulation Stroke

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ABSTRACT

Objective: To study clinical profile of patients with posterior circulation stroke including risk factors, various infarct locations, stroke mechanisms, clinical findings and vascular lesions

Methods: We prospectively analyzed 128 patients with posterior circulation stroke including clinical presentation, lab parameters, cardiac evaluation and MRI brain with angiography. In all patients risk factors, infarct sites, vascular lesions and stroke mechanisms were studied.

Results: Total 128 patients; 94 males and 34 females were studied with average age of 51 years. Hypertension(58%), Diabetes mellitus (33%), tobacco use (38%) and dyslipidemia (19%) were significant risk factors. Arterial territories involved in infarct were Posterior Cerebral artery 34 (27%), Cerebellar 40 (31%) , Brainstem 52 (40.6%) and 38 thalamic infarcts. The most common stoke mechanism embolism in 72 (56%) with source of emboli in large proximal artery in 46 (36%) patients, Cardiogenic emboli 14. Other stroke mechanisms were large artery (hemodynamic) 32(25%) , Branch artery disease (14). Most commonly involved artery was intracranial vertebral artery.36 (28%) with 14 patients (11%) had simultaneous involvement of basilar artery. Isolated basilar artery involvement was seen in 12 patients. Vertebral artery involvement at origin was seen less frequently in 6 patients.Posterior cerebral artery was next frequently involved; total 26 patients (20%) out which 6 were bilateral.

Conclusions: Embolism is most common stroke mechanism in our patients with bilateral PCA infarcts most common site. The source of emboli was diseased artery due to intracranial atherosclerosis. Control of risk factors and identification of source of emboli is of paramount importance for secondary prevention

Keywords: Posterior circulation stroke, stroke mechanisms, vascular lesions.

Introduction

Posterior circulation strokes (PCS) account for approximately 20% of all strokes[1]. Posterior circulation ischemia can range from intermittent insufficiency of the posterior circulation (so-called VBI), to the "locked-in syndrome".

Clinical information about posterior circulation ischemia has lagged behind that for anterior circulation ischemia. Posterior circulation ischemia was initially reported to have high mortality and morbidity. Basilar artery occlusion (BAO) represents 8-14% of all posterior circulation strokes and carries mortality of over 90%[2]. Before MRI was widely available, imaging of posterior territory and vessels was not easily possible. Lack of treatment modalities lead to further disinterest in vascular evaluation in posterior territory ischemia as compared to anterior circulation.

However, in the New England Medical Center Registry of Posterior Circulation Strokes, the overall mortality among 407 patients was reported at only 4%, with 79% having minor or no disability[3]. With wide spread availability of MR angiography and CT angiography lead to easy, quick and non-invasive evaluation of vertebro-basilar system. This allowed safe and accurate definition of posterior circulation infarcts and cervico-cranial vascular lesions. Echocardiography has helped define cardiac and aortic embolic sources and identify coexistent heart disease.

The etiology of posterior circulation ischemia has been thought to be primarily due to local arterial atherosclerosis (large artery disease) and penetrating artery disease (lacunas) [4]. However, there is increasing evidence that cardiogenic embolization is more common than previously suspected and is responsible for 20-50% of posterior circulation strokes[13].

New England Medical Center Registry of Posterior

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Circulation Strokes[3] is one of the largest registries of patients with posterior circulation ischemia. This registry and various studies prior have shown significant differences in intracranial vascular lesions amongst different races and Asian patients.

Data regarding vascular lesions and stroke mechanisms amongst Asian patients is scarce[7]. There are only few studies of posterior circulation ischemia in Indian population[5,6]. We now report the frequency of risk factors, various infarct locations, stroke mechanisms, clinical findings and vascular lesions in 128 Indian patients. A comparison of these findings has been made with other similar studies in Western and Indian population.

Material and Methods

This 128 consecutive patients with posterior circulation ischemic stroke were enrolled in this study. Hemorrhagic strokes were excluded from study. Ethics approval was obtained from the institute committee on human research.

In all patients a detailed clinical history of symptoms, known risk factors etc was taken and neurological examination was done.

All patients underwent routine biochemistry investigation and serum lipid profile.

All patients underwent cardiological evaluation including a 12 lead ECG and transthoracic 2D echocardiography with color Doppler. Selected patients underwent 24 hours Holter monitoring and Trans-esophageal Echocardiography.

All patients under went MRI Brain on 1.5 T MRI machine.

All patients were subjected to 2D TOF MR Angiography of neck vessels including arch of aorta.

All MRI scans were discussed in Neuroradiology meet with radiologist.

Digital Subtraction Angiography was performed if indicated.

Stroke mechanisms were defined according to New England Medical center stroke registry[3] criteria as follows.

1. Large artery occlusive disease hemodynamic mechanism (LAH)

Vascular tests showing occlusion or severe stenosis (>50% luminal narrowing) of the VA, BA or PCAs. Abrupt cutoff of vessels or branches was considered more likely embolic and not intrinsic disease.

2. Branch artery occlusive disease (Br A)

(1) **Penetrating arteries (lacunar or atheromatous branch disease) (BrAP).**

CT or MRI showing infarcts limited to single penetrating or circumferential branch territory.

(2) Circumferential branch arteries (BrA-C)

CT or MRI showing infarcts limited to territory of a single circumferential artery;

3. Embolism (Emb)

a) CT or MRI showing an infarct in the territory of a main intracranial artery or superficial branch (es) and

b) Vascular imaging showing abrupt cutoff of branch (es), or main artery (ies), or patency of arteries known to supply infarcts.

Clinical Supportive: sudden onset and course.

Cardiac (EmbC). cardiac studies showing,a cardiac embolic source.

Aorta (Emb-Aor) TEE or surgical inspection showing a >4 mm protruding mobile plaque or complex ulcerated plaques in the ascending aorta or aortic arch.

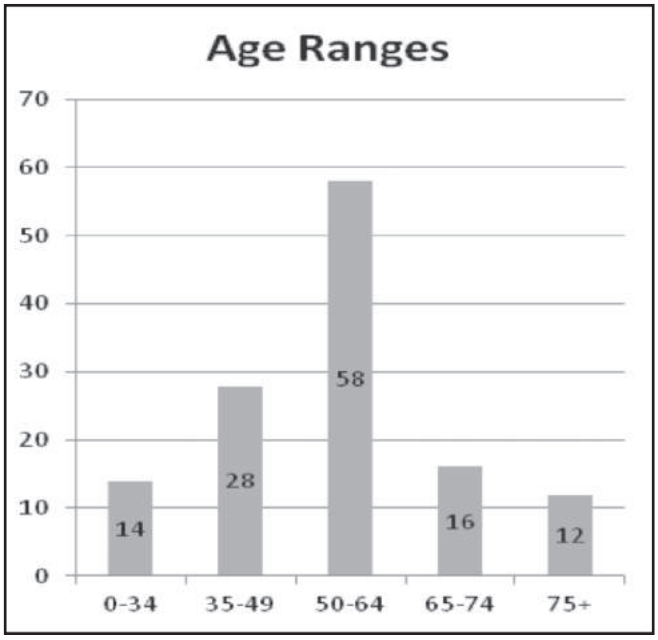
Artery-to-artery (EmbA-A).

Ultrasound, MRA, CTA or contrast catheter angiography showing occluded, severely stenotic (>50% luminal narrowing), or ulcerated proximal artery or an arterial dissection. Infarction in intracranial territories distal to occlusive lesions.

Results

Total 128 patients; 94 males and 34 females were studied in this study. The age distribution is shown in figure 1 with average age of 51 years.

Fig 1: Age ranges

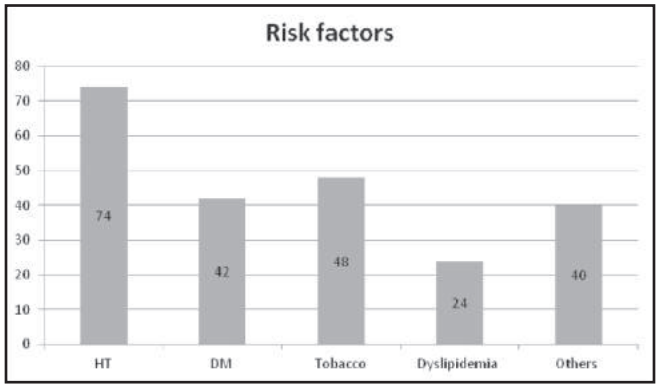


1. Stroke risk factors:

Hypertension was the commonest risk factor occurring in 74 patients (58%). Diabetes mellitus (33%), tobacco use (38%) and dyslipidemia (19%) were other significant risk factors. Coronary heart disease (n=18), Rheumatic heart disease (n=6), alcohol abuse (n=24) and family history of stroke (n=13) were other major risk factors noted.

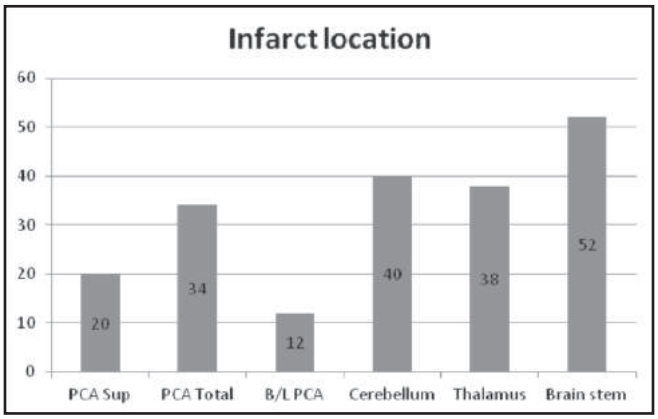
32 patients had more than 2 risk factors, 42 had two and 22 had single risk factors for stroke. 18 patients had none risk factors.

Fig 2: Risk factors



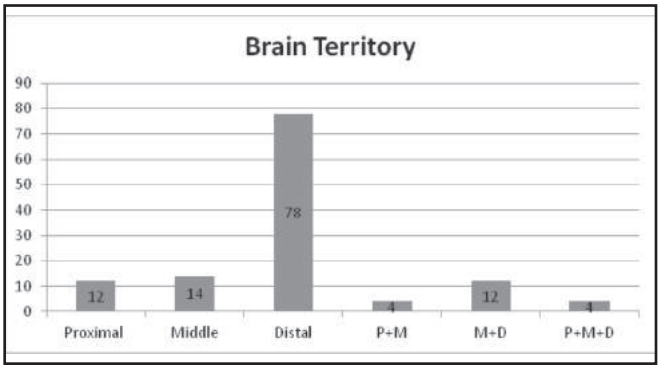
2. Topography of infarct location (Fig 3)

In our study the most common territory involved were



the Posterior Cerebral artery (PCA). 34 (27%) patients had total PCA territory infarcts involving parieto-occippito-temporal region along with thalamus and splenium. 20 (15.6%) patients had involvement of PCA branch mostly calcarine.12 patients had bilateral PCA infarcts. Cerebellar infarcts were seen in 40 (31%) patients with 16 being bilateral. Infarcts in superior cerebellar artery (SCA) territory were most common (n=16) followed by posterior inferior cerebellar artery (PICA) territory (n=12). 52 (40.6%) patients had brainstem infarcts with 22 in medulla, 20 in pons and 10 in midbrain. 38 thalamic infarcts were seen out of which 30 were along with deep PCA infarcts while 8 were restricted to thalamus.

Brain territory location according to NEMC-PCR[3] : (Fig 4)



In NEMC-PC registry[3] the vertebrobasilar territory is divided into three parts: proximal, middle, and distal territory. The proximal territory is fed by the intracranial vertebral arteries and the posterior inferior cerebellar arteries. This territory contains the medulla oblongata, and the postero-inferior part of the cerebellum. The middle territory is supplied by the basilar artery and its

branches, and by anterior inferior cerebellar artery. This territory is composed of the pons and cerebellum. The distal territory is fed by the superior cerebellar arteries, the distal penetrators from the basilar artery, and the posterior cerebral arteries. This territory contains the midbrain and thalamus, as well as the temporal, parietal, and occipital lobe supply zones.

Among patients with single territory involved, 78 patients (71%) had strokes in distal territory, 14 (11%) had in middle territory while 12 (9.3%) had proximal territory involved.

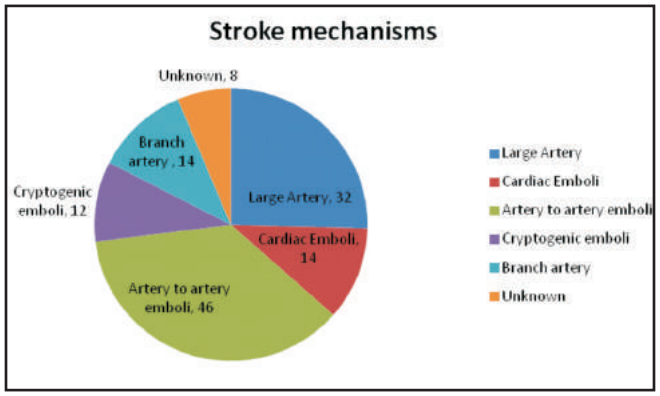
Among patients with more than one territory, middle and distal territory were involved in 12 patients while 4 patients had all the three territories involved.

3. Stroke mechanisms:

The most common stoke mechanism found in this study was embolism. Total 72 (56%) infarcts were thought be due to emboli. The commonest source of emboli was thought to be large proximal artery in 46 (36%) patients. Cardiogenic emboli caused infarcts in 14 patients while source of emboli could not be found in 12 patients.

The second most stroke mechanism was large artery (hemodynamic) in 32(25%) patients. Branch artery disease either thrombotic or atherosclerotic was found in 14 patients while in 8 patients cause of stroke remained undetermined.

Fig 5: Stroke mechanisms



4. Vascular occlusive lesions (Luminal stenosis > 50 %) (Fig 6)

ARTERY	N	%
Subclavian Artery	4	3
Vertebral artery origin	6	4.6
Intracranial VA	36	28
Basilar artery	26	20
Posterior cerebral artery	26	20
PICA	8	6
AICA	6	4.6
SCA	2	1.5

Fig 7: ICVA lesions

ICVA lesions	
Unilateral (u/L)	14
Bilateral (b/l0	8
U/L with basilar artery	10
B/L with basilar artery	4
Total	36

Most commonly involved artery was intracranial vertebral artery. Total 36 (28%) cases were noted out of which 14 were bilateral. 14 patients (11%) had simultaneous involvement of basilar artery. Isolated basilar artery involvement was seen in 12 patients. Vertebral artery involvement at origin was seen less frequently in 6 patients.

Posterior cerebral artery was next frequently involved; total 26 patients (20%) out which 6 were bilateral.

Anterior circulation also showed vascular lesions in 16 patients. Internal carotid was most commonly affected with critical stenosis in 4 patients.

One patient had Aorto-arteritis involving Subclavian artery while other developed Subclavian thrombosis after central catheter insertion.

Single artery lesion was found in were found in 22 patients while MR Angiography was normal in 18 (14%) patients.

5. PCA Infarcts:

Total 56 PCA territory infarcts were noted in this study out of which 12 had bilateral infarcts. 34 patients had

stem of PCA involved causing infarction of deep structures like thalamus, midbrain, splenium etc. 20 patients had branch involvement mostly calcarine causing occipital lobe infarct.

Most common symptoms were visual field defect seen in 40(65%) patients followed by motor deficits and imbalance in 22 (36%) patients' each. 18(29%) patients had sensory symptoms, most of whom had thalamic involvement. Language disturbances (n=8), agnosias (n=6), seizures (n=4), neurocognitive disturbances (n=8), color blindness (n=6) were other symptoms noted. 8 patients had cortical blindness.

Most common stroke mechanism was embolic stroke in 32 (52%) patients. In 8 patients the source of embolus could not be identified.16 patients had artery to artery embolism, mostly from vertebral artery with or without basilar involvement.4 patients had cardio-embolic stroke.

Large artery atherosclerosis stroke was found in 14(22%) patients. 10 had vertebral artery lesions and 2 each in basilar and PCA artery.

Penetrating artery disease was seen in 8 (13%) patients. In 8 patients stroke mechanism could not be determined.

6. Vertebral Artery lesions:

Occlusive lesions of > 50% luminal stenosis were noted in 36 patients of whom 14 were bilateral. 14 patients had simultaneous involvement of basilar artery of which 4 had bilateral vertebral lesions. Vertebral artery lesion at the origin as found only in 6 patients. Dissection was noted in 6 patients.

Hypertension was commonest risk factor identified in 28 (78%) patients followed by diabetes mellitus in 20 (56%) patients and smoking in 18 (50%) patients.

8 (25%) patients had transient ischemic attacks prior to stroke while 6 patients had prior strokes.

Most common symptom was giddiness/vertigo in 22(61%) patients while 18 (50%) patients had ataxia. Visual disturbances were seen in 18 (50%) patients. Sensory –motor symptoms were seen in 16 (45%) patients. 12 patients had cranial nerve deficits.

The site of infarction was most common in PCA territory in 22 (61%) patients followed by brain stem in 20 (56%) patients.12 patients had cerebellar infarcts. 10 patients had bilateral multiple infarcts suggestive of artery to artery embolism.

7. Basilar artery lesion:

26 patients had basilar artery lesions, 14 of which were with vertebral artery lesions.

12 patients had isolated basilar artery lesions. 5 patients had giddiness, 6 had cranial nerve deficits while 5 each had ataxia, sensory- motor and visual field deficits.

The infarcts were present in brainstem in 6 patients while in PCA territory and cerebellar in 5 each patients. 4 patients had multiple infarcts.

Discussion

1. RISK FACTORS:

In this study among Indian patients, the risk factors as compared with other studies were as follows

Fig 8:

Risk factor	Our study (n=128)	Caplan et al[3](n=407)	Huan et al[7](n=31)	Uma et al[6](n=76)	Mehndiratta et al[8](n=80)
Hypertension	58%	61%	71%	35.5 %	51%
Diabetes	33%	26%	22.6%	21%	24%
Tobacco	38%	36%	38.7%	47.3%	25%*
Dyslipidemia	19%	25%	NA	44.4%	17%
Others	32%	NA	NA	NA	18%
IHD	14%	35%	19.4%	17.1%	14%

On comparing with NEMC-PC registry, our study had significantly more diabetics 19% vs. 25%, while patients with IHD and dyslipidemia were less in our study if compared to western population. However on subgroup analysis of this registry, it was noted that Blacks, Asians and women had relatively high frequency of diabetes and intracranial occlusive disease. Our patients also differed from the Chinese population (Huan et al[7]) who had more hypertensive patients (71% vs. 58%) and fewer diabetics (33% vs. 22.6%). These observations underline significant differences in risk factors amongst different races. Our study population had less dyslipidemia as compared to other studies. However our data was similar to a study in North Indian population by Mehndiratta et al[8] .Another study from South India[9] also showed fewer patients with dyslipidemia among stroke patients as compared to western population. The incidence of ischemic heart disease was comparable to other Asian and Indian studies.

2. TOPOGRAPHY OF INFARCT LOCATION (Fig 9):

Location	Our study (n=128)		Lausanne registry[10](n=350)	Athens registry[11](n=259)	Kora et al[9] (n=19)	Mehndiratta et al[8] (n=80)
PCA branch	17%	48.37%	23.71%	27.4%	47.36%	53.75%
PCA total	22%					
B/L PCA	9.37%					
Cerebellum	31.25%		33.42 %	23.9%	26.31%	-
Thalamus	29.68%		NA	27%	10.5%	-
Brain stem	40.62%		32.28%	28.2%	15.78%	-

The present study showed a predominance of distal intracranial (48.37%) predominantly PCA territory infarcts, followed brain stem (40.62%) infarcts. This is significantly more if we compare data from western population[10,11,12]. However this data also states that intracranial disease is more common in Asian population which is further highlighted by our study[14,15]. Also other studies in Indian population show similar trends[8,9].

Compared to the NEMC registry data[3,12], a significantly lower representation of middle and proximal territory was seen in the present study **(Fig 10)**. This is because of large number of atherosclerotic lesion in proximal artery leading to distal embolus which preferentially lodged in distal territory viz distal brainstem and PCA territory.

Fig 10: According to NEMC-PCR classification

Territory involved	Our study (n=128)	NEMC PCR [3](n=407)	Uma et al[6](n=76)	Mehndiratta et al[8](n=80)
Proximal	9.37%	15.47%	27.63%	30%
Middle	10.93%	13.75%	14.47%	3.75%
Distal	60.93%	34.88%	44.30%	66.25%
Proximal + Middle	3.125	2.94%	NA	NA
Middle +Distal	9.37%	8.35%	NA	NA
Proximal +Middle +Distal	3.125%	2.21%	6.57%	NA

Mechanism	Our Study (n=128)	NEMC-PCR[3](N=407)	Lausanne stroke registry[10] (n=1244)	Mehndiratta et al[8] (n=80)
Large artery	25%	33%	11.25%	-
Cardio embolism	10.93%	24%	19.29%	10%
Intra-arterial embolism	36%	14%	15.27%	-
Cryptogenic emboli	9.37%	2%	12.45%	-
Branch artery	10.93%	14%	17.68%	3.75%
Undetermined	6.25%	13%	17.68%	7.5%

3. Stroke mechanisms (Fig 11)

4 Vascular occlusive lésions (Luminal stenosis > 50 %) Fig. 12 :

ARTERY	Our study (n=128)	NEMC PCR[3] (n=407)
Subclavian Artery	3	1.22%
Vertebral artery origin	4.6	32.18%
Intracranial VA	28	32.43%
Basilar artery	20	26.78%
Posterior cerebral artery	20	9.33%
PICA	6	3.43%
AICA	4.6	-
SCA	1.5	2.45%

In our study intracranial vertebral artery was most commonly involved followed by posterior cerebral artery and basilar artery. This in contrast to NEMC –PCR data[12] which shows almost equal frequency of ICVA and ECVA involvement and PCA was less frequently involved.In our study involvement of vertebral artery at origin was significantly less.

Prior studies have showed that extra cranial internal carotid artery lesions were more common in white race, male and hypertensive patients while intracranial lesions were more common in blacks, Asians and women[14,15]. Subsequently, angiographic and post mortem studies also proved that extra cranial vertebral artery was affected more severely in white while more severe and symptomatic intracranial branch disease was predominant in black patients[14]. A necropsy study in 114 Chinese patients found ICVA and basilar artery were frequently affected[17].

Also single artery lesion was found in 22 (17.18%) of our patients while in NEMC-PCR 161 (39.55%). Thus our patients had significantly more multiple lesions.

This difference in atherosclerotic lesions was further evident in stroke mechanism and infarct location. Embolism was the most common stroke mechanism found in our study. However the source of was more commonly artery to artery (36%) as compared to cardio embolism (10.93%). This is surprising as western data and some other Asian studies showed more cardio embolic strokes. However this finding is consistent with the vascular findings which show more severe intracranial atherosclerotic lesions. Also we had less number of IHD patients; hence the number of cardio embolic stroke was less.

These artery to artery emboli frequently lodged in distal territory like PCA territory and brainstem. As a result of distal embolism we noted more PCA infarcts (48.37 Vs 29.23%) in NEMC-PCR[3]. Other Indian studies also noted similar incidence of PCA infarcts. Also we had more deep PCA infarcts (45%vs 39) superficial PCA infarcts. Hence our patients had more frequent motor deficits and ataxia (36%vs 29%) and lesser visual field defects (65% Vs 84%).

Most common source of embolism was large artery mostly ICVA. Branch artery disease of PCA artery was rare in our study as with other studies.

Outcome of patients with embolism was poor in patients in NEMC-PCR[3] and they had highest frequency of death and disability. Vascular occlusive disease was found to cause more severe deficits when artery to artery embolism was present. Hence our study population was more likely to have poor outcome than western population. Also diffuse involvement of intracranial arteries would make vascular intervention difficult. Hence control of risk factors is of paramount importance.

Conflicts of interest- nil

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ORIGINAL ARTICLE

Comparative Study Of Propofol And Thiopentone Sodium As Intravenous Induction Agents On Haemodynamics, Seizure Duration And Recovery Characteristics In Patients Undergoing Modified Electroconvulsive Therapy

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ABSTRACT

Objectives: To compare the effects of Propofol and Thiopentone sodium as intravenous induction agents on haemodynamics, seizure duration and recovery characteristics in patients undergoing Modified Electroconvulsive therapy.

Methods : 100 patients with ASA grading I and II undergoing Modified Electroconvulsive therapy under general anaesthesia were divided into two groups of 50 each by computer randomisation. In group P (n=50), patients received propofol in the dose of 1.5mg/kg IV. and in group T(n=50) patients received thiopentone sodium in dose of 2.5mg/kg IV. Haemodynamic effects, seizure duration and recovery characteristics were observed.

Results : Heart rate, Systolic blood pressure and Diastolic blood pressure increased significantly after ECT till 30minutes in thiopentone group as compared to Propofol group. Duration of seizure was significantly reduced for propofol group as compared to Thiopentone group without affecting therapeutic outcome. Duration of recovery assessed by time to obey verbal commands was significantly shorter for propofol group as compared to thiopentone group.Incidence of side effects like nausea and vomiting was higher in thiopentone group as compared to propofol group.

Conclusion : Propofol was superior to Thiopentone as an induction agent in patients undergoing ECT because of its better haemodynamic stability, reduced seizure duration without affecting therapeutic efficacy and rapid and smooth recovery with antiemetic property.

Keywords : Modified electroconvulsive therapy, Propofol, Thiopentone Sodium,psychiatric patients

Introduction

Electroconvulsive therapy (ECT) is a psychiatric treatment in which seizures are electrically induced in an anaesthetized patients for therapeutic effect. For almost 30 years, ECT was performed without anaesthesia which resulted in complications like bone fractures, dental trauma and also adverse autonomic responsein form of bradycardia, tachycardia, arrhythmias and hypertension. Thus in 1951, with the use of succinylcholine and introduction of short acting intravenous induction agents, Modified ECT came into existence[1,2].There is always a need of an ideal anaesthetic agent that provides rapid smooth onset and short duration of action, attenuation of the adverse physiological effects of ECT, rapid recovery of consciousness, minimal side effects, minimal adverse effect on the seizure duration and minimal or no interaction with antipsychotic medications. The purpose of this study was to compare thiopentone and propofol as induction agents on haemodynamic effects, seizure duration and recovery characteristics in patients undergoing Modified ECT.

Materials And Methods

This study was a prospective randomized clinical study with a cross over design conducted in a tertiary care institute on 100 ECT patients after Ethics Committee approval.The patients between the age of 18 to 65 years with an ASA (American Society of Anesthesiologists) I or II status with no absolute contraindication were selected for ECT. 100 Patients were randomly divided into 2 groups of 50 each. Group T patients received Thiopentone (2.5%) 2.5mg/kg intravenously as induction agent and Group P patients received Propofol (1%) 1.5mg/kg intravenously as induction agent.

On arrival in the ECT room, the intravenous line was set up and multipara monitor was connected to the

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patients.All patients received pre-anaesthetic medications with Inj. Glycopyrolate 0.2 mg IV and were pre-oxygenated with 100% oxygen for 3 minutes. Baseline heart rate and blood pressure were recorded. General anaesthesia was induced with intravenousanaesthetic agent according to the group allocated and vital parameters were recorded again. The Blood pressure cuff was applied to the arm opposite to the limb where intravenous line was secured, needed to be isolated from the effect of muscle relaxation, for observing localized seizures and was inflated 100 mmHg above systolic blood pressure. Inj. Succinylcholine 0.5 mg/kg intravenously was administered after isolating the arm by a blood pressure tourniquet. All the patients were ventilated with 100% oxygen till fasciculation subsided and muscle relaxation was achieved. ECT was administered using a brief-pulse ECT BPE-891 machine (pulse of 60 Hz with 0.8msec duration with total stimulus time of 1 sec). The patients were ventilated with 100% oxygen till regaining of spontaneous respiration.

Heart rate, systolic and diastolic blood pressurewere recorded before induction of anaesthesia , after administration of the study drug , after succinylcholine, after applying ECT , at one minute, five minutes, 10minutes , 20 minutes and 30 minutes. Duration of seizure was recorded in seconds by isolated forearm technique from the start of electrical impulse to the end of the clonic contraction using a hand held stopwatch. Specific side effects like nausea and vomiting were recorded at recovery.Duration of recovery (Cognitive, orientation and neuromuscular co-ordination) was recorded from injection of intravenous anaesthetic agent to the time taken to obey verbal commands like opening the eye, protruding the tongue and moving the limbs.

Statistical analysis

2 independent sample t test, Chi square test and Fisher's exact test were used to investigate and model impact of various parameters like gender distribution, age, weight, hemodynamics, duration of seizure, duration of recovery and side effects. The data were expressed as mean, standard deviation and P<0.05 was considered significant.

Results

Demographic variables did not show any significant difference in age, sex, weight among the two groups.

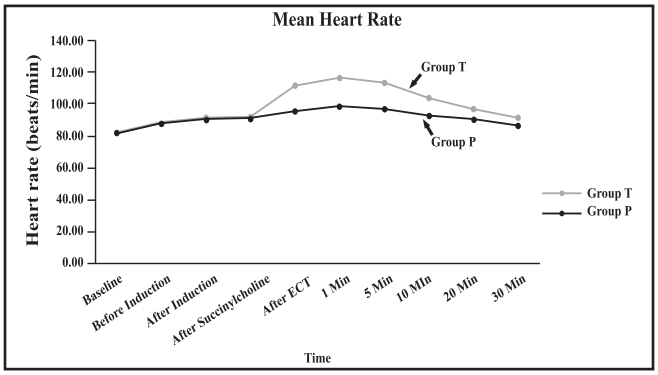
The mean heart rates increased in both groups after application of ECT till 30 minutes but it was significantly more in thiopentone group as compared to propofol group (p< 0.05). The maximum increase in both the groups was seen at the 1 minute from the application of ECT. The mean maximum increase in heart rate above pre induction levels in group T was 28.64 beats/min and 11.54 beats/min in group P. (Table I,graph 1)

Table no.I -Table showing comparison of heart rate in Group T and Group P

HR	Group T			Group P			p-value
	Number of patients	Mean	SD	Number of patients	Mean	SD	
Baseline	50	82.20	3.25	50	81.64	4.34	0.467
Before Induction	50	87.88	3.95	50	87.26	4.73	0.478
After induction	50	91.26	3.88	50	90.50	4.62	0.375
After Succinylcholine	50	91.98	3.76	50	91.18	4.66	0.347
After ECT	50	111.56	3.78	50	95.36	4.86	< 0.001*
1 min	50	116.52	3.35	50	98.80	4.52	< 0.001*
5 min	50	113.60	3.35	50	96.68	4.43	< 0.001*
10 min	50	104.02	2.92	50	92.84	4.97	< 0.001*
20 min	50	97.16	2.92	50	90.26	5.13	< 0.001*
30 min	50	91.74	3.03	50	86.44	4.77	< 0.001*

*P < 0.05 is significant

Graph no. 1- Graphical representation of comparison of Heart rate in Group T and P



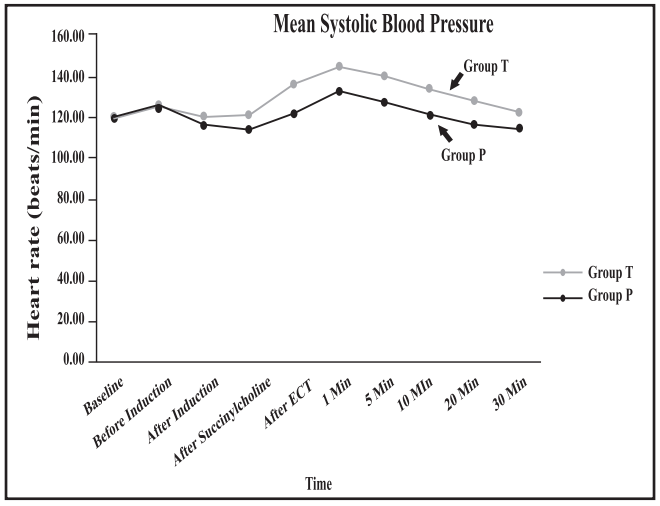
Systolic blood pressure from the time of induction till 30 minutes after application of ECT was significantly more in thiopentone group as compared to propofol group(TableII, graph 2).The maximum increase in systolic pressure with thiopentone group was 18.16 mmHg and 6.26 mmHg in propofol group was seen at the 1 minute from the application of ECT.

Table no. II -Table showing comparison of Systolic Blood Pressure in Group T and Group P

SBP	Group T			Group P			p-value
	Number of patients	Mean	SD	Number of patients	Mean	SD	
Baseline	50	117.04	3.32	50	117.84	4.46	0.311
Before Induction	50	121.84	3.38	50	122.74	5.11	0.302
After induction	50	117.14	3.10	50	114.02	5.48	0.001*
After Succinylcholine	50	117.96	3.10	50	111.52	5.44	< 0.001*
After ECT	50	132.68	4.51	50	118.90	4.96	< 0.001*
1 min	50	140.68	3.91	50	129.00	4.28	< 0.001*
5 min	50	136.18	4.06	50	124.58	4.24	< 0.001*
10 min	50	130.78	2.96	50	118.72	3.95	< 0.001*
20 min	50	124.88	3.01	50	113.70	3.48	< 0.001*
30 min	50	119.40	2.99	50	111.74	3.46	< 0.001*

*P < 0.05 is significant

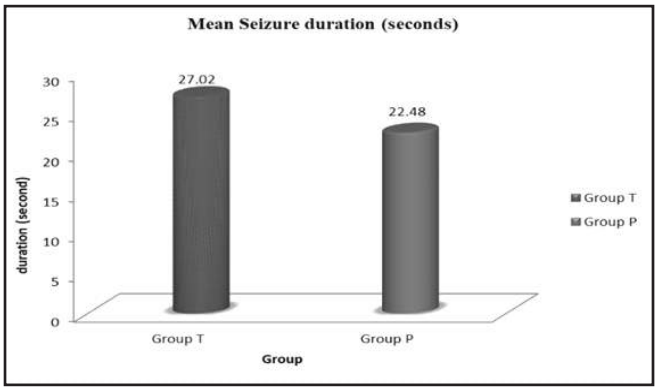
Graph no 2- Graphical representation of comparison of Systolic Blood Pressure in Group T and P



The mean diastolic blood pressure from the time when electrical stimulation was applied till 30minutes in significantly more in thiopentone group as compared to propofol group (p< 0.05).The maximum increase was 7.74 mmHg in thiopentone group from pre induction levels as compared to 2.8 mmHg in propofol group seen at the 1 minute from the application of ECT.

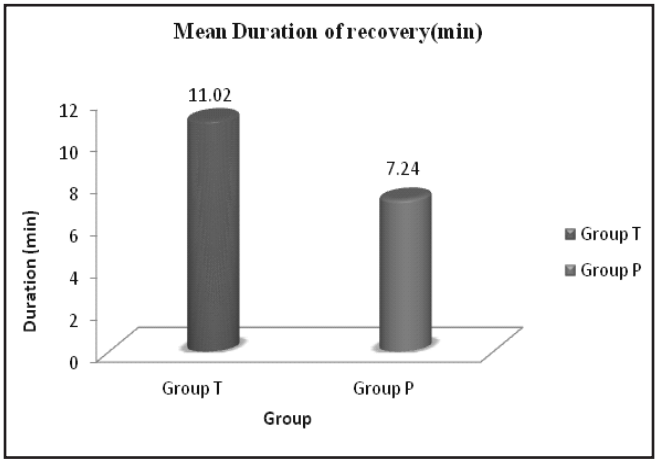
In our study, the mean seizure duration in group T was 27.02 ± 1.68 sec and 22.48 ± 2.18 sec in group P which is approximately 17% shorter in propofol group. The difference in mean seizure duration of both the groups was statistically significant (p < 0.001). (Graph 3)

Graph no.3: Graphical representation of mean seizure duration in Group T & Group P



Duration of recovery was 11.02 ± 1.86 minutes for group T and 7.24 ± 1.52 minutes in group P. The duration of recovery is significantly shorter for propofol group as compared to thiopentone group, p < 0.001. (Graph 4)

Graph no. 4: Graphical representation of duration of recovery in Group T & Group P



In our study, 4 patients developed nausea in thiopentone group as compared to one patient in propofol group and 2 patients developed vomiting in thiopentone group as compared to 1 patient in propofol group. The incidence of nausea and vomiting was more in thiopentone group as compared to propofol but the difference was not significant, p>0.05.

Discussion

To optimize the anesthetic management of patients undergoing ECT, it is important to understand the physiologic responses to the electrical stimulus, the effect of anaesthetic drugs on the ECT response, and the pharmacologic effects of the drugs used to attenuate the

side effects related to ECT[2].The duration of seizure is the main defining factor for treatment success during ECT while the general anesthesia applied can attenuate itseffectiveness[3]. The ideal anesthetic medication for ECT should provide arapid onset and recovery without altering the seizure duration while maintaining a stable hemodynamic state[4].

Because of its rapid induction and recovery profile, propofol was introduced for electroconvulsive therapy. The present study has compared propofolwith thiopentone, the drug most widely acceptable even today as an anesthetic agent for electroconvulsive therapy. We compared the two agents in terms of their haemodynamic effects, seizure duration and recovery characteristics in 100 patients undergoing Modified ECT.

In our study, the mean heart rates of Thiopentone and Propofol group were increased after ECT application but it was significantly more in thiopentone group as compared to Propofol group.This lower pulse rate with propofol is attributed to a resetting of baroreflexes to allow slower heart rates at lower arterial pressure. The reduction in heart rate with propofol may have a favorable effect on myocardial oxygen demand.

Saito et al in 2000[5] studied the comparative effects of thiopentone and propofol on systemic haemodynamic variables for 10 minutes post ECT. They concluded that the heart rate in thiopental group significantly increased after the application of electrical shock.

In our study, the mean systolic and diastolic blood pressure increased in both groups after ECT application but it was significantly more for thiopentone group as compared to Propofol group. Boey WK et al in 1990[(6)], demonstrated that there was significant increase in mean systolic and diastolic blood pressure after ECT with thiopentone group as compared to Propofol.

The mean seizure duration in group T was 27.02 ± 1.68 sec and 22.48 ± 2.18 sec in group P which is approximately 17% shorter in propofol group.Boey WK et al in 1990[6], Shah et al in 2010[7] also found significantly shorter seizure duration for propofol as compared to thiopentone.

Though significant shortening of seizure duration was observed in our study with propofol, it was above 20 seconds and thus it does not affect theefficacy of modified ECT. The APA task force advocates seizure lengths greater than 20 seconds and encourages the termination of seizures of 3 minutes or more for therapeutic efficacy[8]

Duration of recovery was 11.02 ± 1.86 minutes for group T and 7.24 ± 1.52 minutes in group P. Boey WK et al in 1990[6] concluded that the ability of the patients to walk 20 minutes after induction was significantly better after propofol.Due to short duration of procedure, unavailability of good recovery room facilities and inadequate number of trained staff nurses, rapid and smooth recovery from ECT is beneficial.

In our study, the incidence of nausea and vomiting was more in thiopentone group as compared to propofol but the difference was not significant, $p>0.05$.

Shah et al in 2010[7], reported that the incidence of nausea and vomiting was almost nil in propofol due to antiemetic property as compared to 23.33% in thiopentone, findings which are in accordance with our study.

Conclusion

Propofol was superior when compared to Thiopentone as an induction agent in patients undergoing ECT because of better haemodynamic stability, reduced seizure duration without affecting therapeutic efficacy, rapid and smooth recovery and antiemetic property. Thus Propofol in the dose of 1.5mg/kg can be safely used as an anaesthetic agent for induction of Electroconvulsive therapy.

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ORIGINAL ARTICLE

Study Of Maternal Factors Influencing Low Birth Weight Babies In A Tertiary Care Centre

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ABSTRACT

Objectives: 1.To estimate the proportion of low birth weight babies in a tertiary care centre. 2. To identify the maternal determinants of low birth weight babies in the study population.

Methods: Total of 1100 postnatal mothers who delivered a single baby in a tertiary care centre were included in the present study. Institutional Ethics Committee permission was obtained. After obtaining written informed consent, the interviews were conducted by the investigator with the help of semi-structured questionnaire and responses were recorded for each study subject. The data entered in Excel sheet and statistical analysis was done using software Epi Info version 7.1.4.0.

Results: The proportion of low birth weight babies was 24.54%. Mean birth weight of the babies was 2721± 448 grams. The mothers who were illiterate had 4.51 times higher odds of giving birth to low birth weight baby than one who had education above high school level. Mother from poorest socio-economic status (Class V) had 15.17 times higher odds of giving birth to low birth weight baby than one who belongs to upper socio-economic status (Class I).

Conclusion: The factors associated with low birth weight were maternal age, maternal height, maternal education, antenatal visits, consumption of iron and folic acid tablets during pregnancy, afternoon rest, anemia and diet during pregnancy, interpregnancy interval, associated co-morbid conditions during pregnancy, physical activity during pregnancy and socio-demographic factors like residence, socio-economic status.

Introduction

Low birth weight is one of the most serious challenges in maternal and child health in both developed and developing countries. Low birth weight is of public health significance because it is associated with a high rate of perinatal mortality, morbidity, human wastage and suffering.[1]

The infant mortality rate is about 20 times greater to all low birth weight babies. The lower the birth weight, the lower is the survival chance. Many of them become victims of protein energy malnutrition and infection. Low Birth Weight is an important guide to the level of care needed by individual babies. Low Birth Weight also reflects inadequate nutrition and ill-health of the mother.[2]

Prevalence of Low Birth Weight babies in India was 27 percent in year 2014.[3] Experts opine that the rates of Low Birth Weight babies could be reduced to not more than 10 percent in all parts of the world.[4]There are numerous factors contributing to Low Birth Weight, both maternal and fetal. The health statuses of the mother during pregnancy directly influence birth weight of baby. The maternal risk factors are biologically and socially interrelated; and most of them are modifiable.[5]

To identify the maternal risk factors influencing the birth weight of newborn babies and the proportion of low birth weight among the newborn babies the present study was carried out in a tertiary care centre.

Material & Methods

A Cross-sectional study was carried out in postnatal ward of tertiary care centre. Prevalence of LBW was 27% in India and by taking 10% allowable error sample size was calculated to be 1081.

So total of 1100 postnatal mothers who delivered a single baby in a tertiary care centre were included in the present study. Institutional Ethics Committee permission was obtained.

Study subjects were identified in the postnatal wards of a tertiary care hospital. All consecutive born babies excluding twins and those with congenital birth defects were included in the study from October 2014 to January

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2015. After obtaining written informed consent, the interviews were conducted by the investigator with the help of semi-structured questionnaire and responses were recorded for each study subject.

The health information and investigations during antenatal period was recorded from the available health records. All responses were entered by the investigator in Microsoft-Excel 2007 sheet. Data was analyzed by using Epi Info software version 7.1.4.0.[6] Statistical tools used in the study were Percentages and Chi-square test for difference in proportions and p value <0.05 was considered as statistically significant.

Results

Out of total 1100 live new born babies included in this study, 270 were low birth weight babies whereas 830 were normal weight babies. Thus the proportion of low birth weight babies was 24.54%. Mean birth weight of the babies was 2721± 448 grams.

Multiple logistic regression analysis was done to eliminate the confounders as well as for identifying the individual effect of various factors.

Maternal age, education, socioeconomic status and residence were found to be significant factors associated with the birth weight of the newborn. While considering age group 20-30 years as reference category, odds of having low birth weight baby is high in the age group below 20 years(OR 2.95;CI 2.09 – 4.17) and above 30years (OR 2.29; CI 1.57- 3.34) indicating teenage pregnancy to be a significant risk factor for LBW.

Table 1: Multiple Logistic regression analysis of socio-demographic factors associated with low birth weight

Parameters		Birth weight		OR (95%CI)	P Value
		LBW (n=270)			
Maternal age (Yrs)	<20	75	111	2.95 (2.09-4.17)	<0.0001
	20 – 29	141	616	1	
	30 – 39	54	103	2.29 (1.57-3.34)	
Maternal Education	Illiterate	49	34	4.51 (2.38-8.56)	<0.0001
	Primary & sec	109	381	1.10 (0.67-1.80)	
	Higher Sec.	88	323	1.04 (0.63-1.73)	
	Graduate & PG	24	92	1	
Socio economic status	Class I	12	52	1	<0.0001
	Class II	68	286	1.03 (0.52-2.04)	
	Class III	79	285	1.20 (0.61-2.36)	
	Class IV	90	201	1.94 (0.99-3.81)	
	Class V	21	6	15.17(5.03-45.71)	
Residence	Urban	136	507	1	<0.005
	Rural	134	323	1.55 (1.17-2.04)	

The mothers who were illiterate had 4.51 times higher odds of giving birth to low birth weight baby than one who had education above high school level. Mother from poorest socio-economic status (Class V) had 15.17 times higher odds of giving birth to low birth weight baby than one who belongs to upper socio-economic status (Class I) by modified Kuppuswamy's classification. Residence in rural area had 1.55 times higher odds of having low birth weight baby than mothers residing in urban area.

Table 2: Multiple Logistic regression analysis of maternal factors associated with low birth weight

Parameters		Birth weight		OR (95%CI)	P Value
		LBW (n=270)	**BW≥2.5K g (n=830)**		
Maternal height	<140	18	23	3.23 (1.68-6.18)	<0.0001
	140– 144	63	114	2.28 (1.57-3.29)	
	145– 149	76	227	1.38 (0.99-1.92)	
	≥150	113	466	1	
Age at 1st Pregnancy	⩽ Yrs	66	114	2.03 (1.44-2.86)	<0.0001
	>18 Yrs	204	716	1	
Antenatal Visits	0	36	37	3.15 (1.91-5.18)	<0.0005
	1 – 3	98	353	0.90 (0.67-1.21)	
	⩾	136	440	1	
Parity	1 & 2	194	668	1	<0.0005
	3 & 4	51	129	1.36 (0.95-1.95)	
	5 & 6	25	33	2.61 (1.51-4.49)	
Diet during pregnancy	Less than before	89	137	3.18 (2.2-4.58)	<0.0001
	Same as before	107	331	1.58 (1.13-2.2)	
	More than before	74	362	1	
Interpregnancy Interval	<18 months	60	116	1.95 (1.34-2.84)	<0.005
	18 – 24 months	97	288	1.27 (0.93-1.73)	
	⩾	113	426	1	
Any morbid condition	Present	154	301	2.33 (1.76-3.08)	<0.0001
	Absent	116	529	1	
Mishri use	Yes	21	13	5.3 (2.62-10.74)	<0.0001
	No	249	817	1	
Physical activity	Sedentary	207	746	1	<0.0001
	Moderate & Heavy	63	84	2.7 (1.88-3.88)	

As far as maternal factors were concerned, maternal height, parity, birth interval, and number of ANC checkups were significantly associated with low birth weight of the new born. Odds of exposure for mothers who had height <140 cm associated with giving birth to LBW baby was 3.23 times more as compared to mothers having height >150 cm .The proportion of low birth

weight was found 36.66% in mothers who had first pregnancy ⩽ 18 years of age. The proportion of LBW babies was lower in mothers who had their first pregnancy at ⩾ 18 years i.e. 22.17%. A statistically significant association was found between mother's age at first pregnancy and birth weight of baby. Among the mothers who delivered their baby at the age ⩽ 18 years had 2.03 higher odds of having low birth weight baby than who delivered their baby at later age.

As the parity of women increased from 3- 4 and 5-6, the risk of delivering low birth weight babies also increased by 1.36 times and 2.61 times respectively. Among the mothers with inter birth interval less than 18 months, the odds of low birth weight newborn was 1.96 times higher than those with birth interval of more than 24 months. The mothers who had co-morbidity during pregnancy had 2.33 times risk of LBW baby as compared to mothers who did not have any co-morbid condition during pregnancy. Moderate and heavy work during pregnancy increased risk of having LBW baby to 2.7 times as compared to mothers who had sedentary work during pregnancy.

The proportion of low birth weight was high 49.31% in mothers who had no visits as compared to 23.61% in mother who had ⩾ 4 visits during antenatal period. As the number of antenatal visits increased, the proportion of LBW babies decreased and it was found statistically significant. The proportion of low birth weight babies who had hemoglobin less than 9 gm% was 38.41% as compared to 19.03% in mothers having hemoglobin ⩾ 11 gram%. A significant association was found between hemoglobin percentage in gram% during pregnancy and birth weight.

Discussion

The cross-sectional study was carried out to find out the proportion of low birth weight and to explore the socio-demographic determinants. The proportion of low birth weight found was 24.54% comparable to other studies carried out by Deshmukh et al[7] in 1998 carried showing LBW prevalence 30.3%. Joshi et al[8] in year 2002 at Allahabad found the proportion of LBW was 32.59% in males and 36.37% in females.

The proportion of births with a low birth weight is lesser among children born to older women (age at birth >=20 years) which indicates prevention of teenage pregnancy necessary to avoid low birth weight. Prevalence of LBW was low among women with high socioeconomic status. The women with high socioeconomic status have better nutrition; have adequate care than women with poor socioeconomic status. It corresponds with the findings of Deshmukh et al[7], Joshi et al[9], Roy et al[10], Manna et al[11] who reported that maternal education, per capita income, birth interval, parity and maternal age were significantly associated with birth weight.

The studies carried out by Ghate et al[12], Mumbare et al[13] showed statistical association between maternal height and low birth weight and similar observations were found in the present study.

The present study showed that the proportion of births with a low birth weight is lesser among children born to older spacing period is more than 24 months and this difference was found statistically significant. The comparable results were observed in study by Kumar et al[14], Roy et al[9] and Agarwal et al[15]. The percentage of low birth weight was increased in mothers having anemia during pregnancy and significant association was found between hemoglobin percentage in gram% during pregnancy and birth weight. The observation in the present study was comparable with other studies by Yadav et al[16], Agarwal et al[15] and Narrain et al[17].The other factors which showed association with LBW were morbid conditions during pregnancy, mishri use and moderate to severe activity during pregnancy. Similar observations were found in another study by Thomre[18] et al who carried out multiple logistic regression analysis of maternal factors associated with low birth weight.

Conclusion

The present study revealed statistically significant association between maternal factors and Low Birth weight babies. The factors were maternal age, maternal height, maternal education, antenatal visits, anemia and diet during pregnancy, interpregnancy interval, associated co-morbid conditions during pregnancy, physical activity during pregnancy and socio-demographic factors like residence, socio-economic status.

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ORIGINAL ARTICLE

Comparison Between Amnisure Test And Conventional Clinical Assessment In Detection Of Premature Rupture Of Membranes (PROM)

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ABSTRACT

Objective : The objective was to determine efficacy of Amnisure ROM test using placental alpha-microglobulin-1 test for accurate diagnosis of true ROM in women with watery discharge after 26 weeks gestation and compare it with conventional clinical methods.

Methods & Materials : This was a prospective longitudinal study carried out in a tertiary referral centre in women between the gestational ages of 26-42 wks presenting with the complaints of PROM. Conventional clinical examination was conducted by one clinician and amnisure test by another one. Each clinician was blinded to the results of other examination. The sensitivity, specificity, positive predictive value and negative predictive value of each examination were then calculated.

Result : The sensitivity, specificity, PPV and NPV of Amnisure ROM test was found to be 90.4%, 73%, 75%and 82% which are quite high as compared to the conventional clinical method. Conclusion: The use of Amnisure as a diagnostic tool helps to establish the correct diagnosis and determine the treatment options.

Keywords : Amnisure ROM test, placental alpha microglobulin-1, rupture of membranes.

Introduction

Premature rupture of membranes (PROM) is defined as spontaneous rupture of the fetal membranes before the onset of uterine contraction and its incidence is about 10%, while preterm PROM is defined as PROM before 37 weeks of gestation.It is recorded in about 30% of women with PROM. The breakage of amniotic fluid is responsible for about 20-40% of preterm deliveries with its serious consequences such as cord prolapsed, infectious morbidity (chorioamnionitis, neonatal sepsis, neonatal pneumonia) , increased risk of neonatal death, pulmonary hypoplasia of the fetus, development of fetal deformities, postnatal endometritis and premature separation of placenta (abruption placenta) [1-2]. Early and accurate diagnosis of PROM allows gestational age-specific obstetric interventions aimed at optimizing perinatal outcome and reducing the risk of serious complications. However, a false positive diagnosis of PROM may lead to unnecessary interventions including hospitalization, antibiotics and corticosteroid use, stimulation of labor and the problem of prematurity[3]

The accuracy of "fern test" (crystallization of amniotic fluid on drying) may give false-positive results due to fingerprints or contamination with semen and cervical mucus as well as false-negative results due to technical error (dry swab) or contamination with blood [4.] Reported sensitivity and specificity for the fern test were51% and 70%, respectively, in patients without labor and 98% and 88%, respectively, in patients in labor [5.]

The Amnisure ROM test is a new method to diagnose rupture of the fetal membranes (ROM). The test detects placental alpha-microglobulin-1 (PAMG-1) in cervicovaginal fluid. The concentration of this protein in amniotic fluid is 1000–10,000 times higher than in the case of cervicovaginal fluid (2000–25,000 ng/ml versus 0.05–2.0 ng/ml) [7.] Therefore, the presence of high concentrations of PAMG-1 in cervico vaginal fluid is considered evidence of ROM, and the threshold of the test for the diagnosis of ROM has been set at 5.0 ng/ml. This study compared the efficacy of PAMG-1 and standard methods in the diagnosis of PROM with the final diagnosis of PROM at delivery.

Materials And Methods

This study , a prospective longitudinal study was conducted in the department of obstetrics and gynaecology at B. J. Government Medical College and

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Sassoon General Hospitals, Pune between March 2016 to June 2017. This study was approved by the institutional ethics committee. The study included women with pregnancies with gestational ages varying from 26wks -42wks who presented in the labour room or in the ANC O.P.D with the suspicion, signs or symptoms suggestive of PROM without gross rupture of membranes. The other exclusion criteria were placenta previa, vaginal bleeding, evidence of active labour, presence of signs of chorioamnionitis or gross meconium. After obtaining the informed consent of the subjects, detailed history was taken and physical examination was conducted. Initial evaluation including the standard clinical assessment (visualization of pooling in the posterior fornix and fern test) for rupture of membranes was performed. Clinical examination included a sterile speculum examination of the patient in lithotomy position to expose the posterior fornix and cervix under a good light source. A sterile cotton swab was used to collect same secretion which was smeared thinly on a glass slide and allowed to dry for 10 minutes, and ferning was confirmed under a microscope with lens magnification of 10 x. The woman was diagnosed to be having PROM if one of these two tests or both were found to be positive. The examination was conducted by the clinician blinded for the results of Amnisure test .The test for PAMG-1 using Amnisure (International LLC, Boston, USA) was performed for these women by a clinician other than the one who did their conventional evaluation. A sample of vaginal fluid to be tested (collected by vaginal swab) was placed into a vial with solvent with the patient identification details. The solvent extracted the sample from the swab for one minute, after which the swab was disposed. The AmniSure test strip, a lateral flow device, was then placed into the vial. The sample flowed from the pad region of the strip to the Test Region. If PAMG-1 was present in the patient sample it bound with antibodies in the test region producing a second line. The test result was indicated over the next 5-10 minutes. One line (Control) indicated no membranes are ruptured. Two lines indicated there is a rupture. After delivery, each patient's clinical record was reviewed for their clinical course from initial diagnosis of prelabour rupture of foetal membranes. The true positives and negatives were determined definitively upon review of the medical records after delivery. For this study, the final diagnosis was taken to be the demonstration of scanty or no amniotic fluid and the absence of foetal membranes on vaginal examination at delivery. The total number of women included in this study was one hundred and thirty. The sensitivity, specificity, negative and positive predictive values were calculated for the Amnisure and for the other clinical examination methods.

Results

The average age of women participating in the study was found to be 23.6yrs. The mean gestational age was found to be 35.3 wks.46% of the women had gestational age below 37 wks whereas 54% of the women had gestational age above 37 wks. Eighty-eight (69%) women had Amnisure positive at the first evaluation. Seventy-three (57%)women had positive findings at the first clinical evaluation. Three women were lost to follow-up. Ninety-five (75%) women were found to have definitive rupture of membrane after the review of their labour records. Thirty-two (25%) women had intact membranes and so no ROM. Three women were lost to follow-up.

TableI: Test results of patients tested with Amnisure and Clinical Evaluation Methods

	Clinical Evaluation Results		
		Positive	Negative
Amnisure Test Results	Positive	66	22
	Negative	7	32
	Total	73	54

Table II: Evaluation of both tests.

TEST TYPE		AMNISURE		
METRIC		VALUES	%	VALUES
Sensitivity	TP/(TP + FN)	66/73	90.4%	66/95
Specificity	TN/(TN + FP)	39/54	73%	32/54
Positive Predictive Value	TP/(TP + FP)	66/88	75%	66/73
Negative Predictive Value	TN/(TN + FN)	32/39	82%	25/54

TP: True Positives; FP: False Positives; T: True Negatives; FN: False Negatives.

Data were entered in Microsoft excel sheets after the analysis of the data sheets provided by the clinicians who were double blinded. The sensitivity, specificity, positive and negative predictive values for both Amnisure test and clinical examination were then calculated separately. The sensitivity of amnisure test was found to be 90.4% as against that of conventional clinical assessment methods which was only 69.4%. The specificity of Amnisure is also more with the value of 73%. The positive predictive value and negative predictive value of 75% and 82% respectively make a superior test as compared to conventional clinical assessment. The results are clinically significant.

Discussion

PROM is associated with significant maternal and perinatal mortality and morbidity. Unfortunately, there is absence of an accurate and simple diagnostic tool to establish the diagnosis as the traditional way to diagnose ROM is subjective. Several alternative tests – including alpha-fetoprotein , insulin-like growth factor binding protein-1 [8], fetal fibronectinand prolactin have been suggested for the diagnosis of ROM. However, tests based on these analyses have not produced a satisfactory diagnostic performance.

In a study by Abdelmane et al [9] the sensitivity, specificity, positive and negative predictive values of the Amnisure test were found to be 93.6%, 75.0%, 80.2%, 91.5%, while they were 65.5%, 89.2%, 94.9% and 45.8% for clinical examination alone. Their results were comparable to our results. The population studied was also non-Caucasian. Cousin et al. [10] reported a sensitivity of 98.0%, specificity of 100%, positive predictive value of 100% and a negative predictive value of 99.1% in a population with a ROM prevalence of 44.8%. These values were higher than our study. Lee et al. demonstrated that the Amnisure test has a better diagnostic accuracy than the nitrazine test, even when conventional clinical criteria were used (a combination of pooling, nitrazine and ferning) [11]. The PAMG-1 immunoassay provides a quality diagnostic tool that was rapid, accurate, and with higher sensitivity and specificity compared to the other methods used currently. First of all, Amnisure can be done without inserting a speculum with what is being practiced currently. It also serves as single test that is able to help determining and establishing the correct diagnosis, especially when the diagnosis of ROM is inconclusive.

Conclusion

The placental alpha microglobulin-1 immunoassay is noninvasive, rapid, and accurate in detecting ROM. Its performance appeared to be superior compared to conventional clinical evaluation (pooling and ferning). The use of AmniSure as a diagnostic tool helps to establish the correct diagnosis and determine the treatment options. Unfortunately, its usage is currently limited by its cost. In cases where the diagnosis is in doubt particularly in premature rupture of membranes, the placental alpha microglobulin-1 might act as a valuable tool. **The** gold standard test to diagnose rupture of membrane is injection of indigo carmine directly into the amniotic sac. However, it is too invasive to be used as routine practice or for research purposes. As a result, we could only rely on noninvasive clinical features such as absence of membranes and absent or scanty liquor as clinical guide for confirming leaking liquor.

Conflict of Interests

The authors declare that there is no conflict of interests.

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ORIGINAL ARTICLE

Can The Reitan Number Connection Test (NCT) Alone Be Used For Diagnosis & Grading Of Hepatic Encephalopathy?

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ABSTRACT

Background: Minimal hepatic encephalopathy (MHE) impairs quality of life and predicts overt hepatic encephalopathy (HE) in cirrhotic patients. Diagnosis of MHE can be aided by Reitan number connection test (NCT), however there is a need for normative data for NCT in terms of age and education in order to use this psychometric test for the diagnosis of hepatic encephalopathy.

Objectives: To highlight the role of NCT in diagnosis of HE and formulate the cutoff score and grading system for Indian population. Also to delineate the effect of age and level of education in implementing NCT.

Method: Fifty cirrhotics (cases) and fifty controls were evaluated for NCT score (time taken to complete NCT-A). Cases were graded using West - Haven criteria for HE. Controls were evaluated for age and level of education.

Results: The mean NCT scores for cases and controls were 149.68 and 75.94 seconds, respectively. Multiple linear regression for age and level of education showed significant differences in NCT score. The cutoff NCT score for diagnosing HE in this population was 100 seconds using ROC curve.

Conclusion: This study has been successful in establishing the significance of NCT-A in the diagnosis of hepatic encephalopathy but the grading system could not be deduced. The confounders of age & level of education were proved to be significant. Most of the candidates enrolled in this study were from the lower socio-economic stratum with primary education. A large scale study is required to get a normative criterion for the Indian population.

Key words

Hepatic encephalopathy, number connection test (NCT)

Introduction

Hepatic encephalopathy (HE) is a reversible neuropsychiatric state that complicates liver disease. Its diagnosis is essentially a clinical one[1]. While an overt hepatic encephalopathy does not usually cause any diagnostic difficulty, sub-clinical hepatic encephalopathy may be more problematic and need further evaluation.

Currently, there is no agreement on which test is the gold standard for diagnosis of Hepatic Encephalopathy. An ideal test should be easy to use, cheap, and possible to perform in a simple bedside manner and have a high specificity and sensitivity. None of the available tests have all of these features. Also there is no single method which can precisely and reproducibly quantify the severity of hepatic encephalopathy.

The most common technique is the assessment of mental state, which by itself has multiple aspects such as state of consciousness, orientation, personality and behaviour, intellectual function etc[2]. Each of these aspects is difficult to assess and quantify individually.

Electrophysiological assessment is useful for all kinds of hepatic encephalopathy. However it generally requires expensive and sophisticated equipment and skilled staff.

The Reitan number connection test appears to be a promising answer to this problem. This test tests the diffuse affection of brain as observed in patients of Hepatic Encephalopathy. It is also regarded as a sensitive psychometric measure for the assessment of subclinical hepatic encephalopathy (SHE) or Minimal Hepatic Encephalopathy (MHE).

The problem faced in the implementation of NCT is the inter-individual variability. Most groups define the limits of the normal range by studying small control groups. Others use scores given in the literature without ensuring the comparability of the test versions used[3, 4]. Thus, there is a need for normative data for the number connection test results in terms of age and education in

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order to use this psychometric test for the diagnosis of hepatic encephalopathy. Prevalence of MHE has been reported to vary between 22% and 74% in patients with cirrhosis of the liver, depending on both the examinable dimensions of the disease and fixed diagnostic cut-offs[5].

Patients with MHE had a significant impairment of daily functioning, for example, social interaction, alertness, emotional behaviour, sleep, work, home management, recreation and pastimes compared with cirrhotic patients who did not have MHE[6].

Aims & Objectives

Aim

To Establish the Significance of The Reitan number Connection Test in Diagnosis of Hepatic Encephalopathy.

Objectives

1) To delineate the reference NCT score in normal individuals & study the influence of age & education on NCT score

2) To formulate a grading system of HE by using NCT score.

Methodology

Study design: Prospective unicentric cross sectional study of two groups of individuals:

1)Population : normal healthy individuals of different demographic variants

Sample size: 50

Inclusion criteria: age>18years, with minimum primary school education

Exclusion criteria: presence of gross psychiatric or neurological disorders, chronic liver disease, chronic alcoholism or inebriation while the test was being undertaken.

2)Population: Indoor patients of a tertiary care Government hospital during the stipulated two month duration of the study

Sample size: 50

Inclusion criteria: age>18years, with minimum primary school education, liver cirrhosis diagnosed on USG(small shrunken liver, raised echogenicity, nodularity, dilated veins, splenomegaly), presence of normal vision, presence of gross & fine motor skills

Exclusion criteria: grade 4 of HE, acute viral hepatitis, stroke, renal disorders, COPD, HIV dementia, gross psychiatric or neurological disorder except HE.

Number Connection Test part A *(NCT-A)*

This test is a derivative from the Trail Making Test 32 and measures cognitive motor abilities, In the NCT - A patients have to connect numbers printed on paper consecutively from 1 to 25. A low score indicates a good performance.

Data Collection Procedure

All the individuals fulfilling the inclusion criteria were explained the details of the study being carried out & confidentiality was assured. A Written Informed Consent form was filled in to enroll the individual as a candidate for the study. Each candidate was asked the demographic details as stated in FORM-1(The Reitan number connection test) [5] especially the age & level of education. These were entered by the investigator.

NCT-A was carried out in all candidates.

The data of NCT scores for the first group (controls) was evaluated statistically & significance of influential factors like age & education was determined.

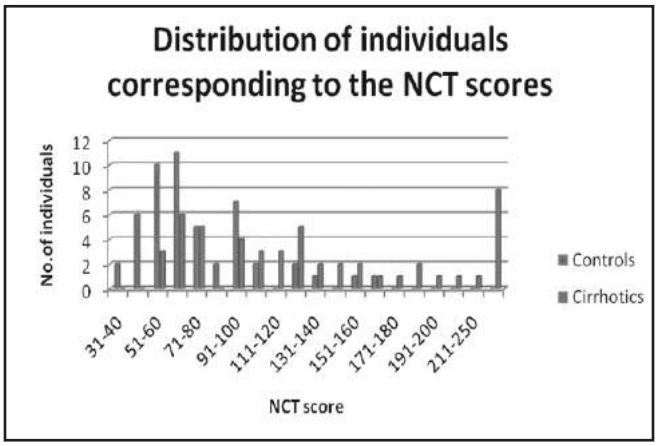
In the second group (patients), established diagnostic clinical features of HE as per the *West Haven Criteria* for semi quantitative grading of mental state were noted in FORM2 & grading of the patients was carried out irrespective of the NCT score.

A comparative statistical analysis was carried out of NCT scores of patients belonging to each grade of HE using statistical tools.

Observations & Results

In group A, the NCT score (time taken to complete the number connection test) showed a lot of variation with mean of 75.94 seconds ($CI_{95\%}$ 67.80 - 84.08).

In group B, crude data showed that, on the whole, cirrhotic patients performed the psychometric tests more slowly and with lower accuracy than Controls. The NCT scores in cirrhotics showed mean=149.68 seconds ($CI_{95\%}$ 124.16 to 175.20).



Graph 1: Showing the distribution of individuals corresponding to their NCT score

Analysis to determine Inter-individual variability

o Due to Age

Ncttime	Coef	Robust SE	t	P> t	Lowest	Highest
Age	1.211374	.2270363	5.34	0.000	.7548866	1.667861
_cons	23.09988	8.205346	2.82	0.007	6.601928	39.59784

Table I: Showing coefficient for inter individual variability in NCT score due to age

Regression analysis of this data was done using STATA software for statistical analysis, which showed that for 1 year increment in age there is 1.21 second increment in the NCT score(p=0.00) with minimum increment of 0.75 to maximum of 1.67seconds, which is significant.

o Due to Level of Education

Ncttime	Coef	Robust SE	T	P> t	Lowest	Highest
_Iedu_2	-35.75128	10.24511	-3.49	0.001	-56.36178	-15.14079
_Iedu_3	-42.81319	10.4753	-4.09	0.000	-63.88677	-21.7396
_cons	103.3846	9.538342	10.84	0.000	84.19595	122.5733

Table II: Showing coefficient for inter individual variability in NCT score due to level of education

Similarly the simple linear regression analysis done to assess the effect of education level on NCT score revealed that the time taken by a primary educated candidate was 35.75 sec more than that by secondary educated with p=0.01 & for higher secondary the difference was of 42.81 sec with p=0.00. This shows that the variation due to education level is significant.

o Multiple linear regression analysis was done to assess the combined effect of age & education. This proved that the variation due to age & education is significant.

Diagnosis & Grading of Hepatic Encephalopathy

To find out the cut-off NCT score for diagnosis of subclinical HE, the sensitivity(Sn) & specificity (Sp) were calculated for increasing cut-offs. The NCT score at which the sum of Sn & Sp is maximum will fetch us the cut-off level for each grade.

The maximum sum was found to lie at 100 seconds as the cut-off for non-diseased & diseased. The same score corresponded with maximum (Sn+Sp) for grade1 & 2 cut-offs.

Using this cut-off, out of the the thirteen patients with no clinical features of HE, 3 (23%) were found to be in subclinical hepatic encephalopathy, indicating they need treatment.

Discussion

The Reitan Number Connection Test (NCT-A) is an effective tool for diagnosis of Hepatic Encephalopathy as proved by the non-overlapping 95% confidence intervals of the scores of group A & group B. The utility of the test for grading & the inter-individual ariability was assessed further.

The inter-individual variability with respect to age & education level is significant.

In control subjects, psychometric assessment was found to be influenced by age and education, a well-known phenomenon, even if the importance of these confounders had not always been adequately considered in the assessment of cirrhotic patients in the past Weissenborn et al[3] had expressed NCT results on the basis of multivariate regression taking into account age and education in his study. Additionally, the parameters of the equation explaining NCT variability as a function of age and education that Weissenborn et al found in German controls, also those found in Italy are close to the parameters that we found in our study.

The cut-off value for diagnosis of MHE was found to be 100seconds. This is significantly greater than the cut-off suggested by the Western literature which was 40 seconds.

Limitations

We could not find out the age & education normative criteria for the Indian population due to the small sample size but could definitely highlight the need for the same.

Also the grading system for HE could not be deducted from our study.

The likely explanation for this is the small sample size (50) of patients taken into consideration.

The reference clinical grading of HE can further be assisted by use of serum ammonia value, which could not be done in our study.

Use of a highly sensitive tool like EEG for comparison can fetch a better perspective into the diagnostic utility of psychometric tests especially in the diagnosis of MHE.

Conclusion

This study has been successful in establishing the significance of the Reitan Number connection Test (NCT-A) in the diagnosis of hepatic encephalopathy but the grading system could not be deducted.

The confounders of age & level of education are significant as proved by this study. Most of the candidates enrolled in this study were from the lower socio-economic stratum mostly with primary education. A large scale study is required to get a normative riterion for the Indian population.

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ORIGINAL ARTICLE

Treatment Of Diabetic Foot Ulcers With Autologous Bone Marrow Cells, Platelets, Fibrin Glue And Collagen Matrix

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ABSTRACT

Objectives: To study the role of autologous bone marrow cells, platelets, fibrin glue, collagen matrix in treatment of diabetic foot ulcers

Methods: Autologous bone marrow was aspirated under Spinal Anaesthesia and bone marrow-total nucleated cells were separated and concentrated. 100 ml peripheral blood was taken and platelets, fibrin glue and collagen matrix were prepared according to standard procedures. The Bone Marrow-total nucleated cells were injected 1.5 cm deep into the wound and platelets and fibrin glue was locally applied over the wound and dressing was done. Patient was followed up for six weeks, with assessment of wound every week.

Results: 35 patients were studied out of which 3 patients had complete closure of the wound. One patient did not show significant improvement. Rest all the patients had significant reduction of wound size after 6 weeks.

Conclusion: Patients treated with Autologous bone marrow cells, platelets, fibrin glue and collagen matrix did show significant reduction in the wound size. Use of these components was safe and cost effective.

Key Words: Bone Marrow, Platelets, Fibrin Glue, Collagen Matrix

Introduction

Diabetic foot ulcers are defined as foot affected by ulceration that is associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with diabetes. [1] Foot problems complicating diabetes are a source of major patient suffering and societal costs. Only two-third of foot ulcer will eventually heal. Upto 28 % foot problem complicating diabetes may result in some form of lower extremity amputation. Every year more than 1 million people with diabetes lose at least a part of their leg as a consequence of complications of diabetes. This translates into the estimates that every 20 seconds a lower limb is lost due to diabetes somewhere in the world.

The management of diabetic foot ulcers is a major clinical challenge and needs multimodality approach. Different modalities like hyperbaric oxygen therapy, electric stimulation, negative pressure wound therapy, bioengineered skin, growth factors are used for treatment of diabetic foot ulcers, but any one type of treatment alone cannot bring complete closure of wound. [2,3] [4,5,6] Several studies have proposed the use of autologous bone marrow stem cells as a novel approach for treating diabetic foot ulcer.[2,3,6,7] The role of platelet derived growth factor, fibrin glue and collagen matrix and its clinical application in wound healing is well known. In the present study, we have tried a combined approach including autologous bone marrow stem cells, platelets, fibrin glue, collagen matrix for treatment of diabetic foot ulcers.

Material and Methods

The study protocol and informed-consent form was reviewed and approved by Ethical Committee. The study was carried out over a period of 2 years from May 2013 to October 2015, including diabetic foot patients, having Diabetes Mellitus for at least 3 months on treatment with Oral hypoglycemic or Insulin. The wound size less than 6 cm was included in this study.

The study was conducted on 35 patients out of which 24 were male and 11 female. Patients were in the age group of 18 to 60 years. Out of the 35 patients, 18 patients had ulcer over Right foot and 17 patients had ulcer over Left Foot. For all the diabetic foot patients HbA1c was done at admission. Out of 35 patients, 26 had HbA1C less than 8 and 9 patients had HbA1C more than 8. The patients having blood sugar levels more than 300 were treated with Insulin. The patients having blood sugar levels less than 300 were treated with oral hypoglycemics.

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Procedure

A) Platelet isolation: Before bone marrow aspiration, 100 ml peripheral blood was taken and platelets were isolated by Centrifugation. First centrifugation was done at 2000g for 2 min and second centrifugation was done at 4000 *g* for 8 min. The supernatant plasma was separated.

B) Fibrin : Fibrinogen concentrate was prepared from the separated plasma using cryoprecipitate method i.e. -70°C freeze and thaw, plasma was centrifuged at 6500 *g* for 5 min. 4 ml of supernatant plasma was mixed with platelets and stored at -30°C.

C) Collagen Matrix: 1 ml of BM-TNC was mixed with 9 ml of serum.

D) BM-TNC :

3 Bags were used for preparation of Bone Marrow-TNC.

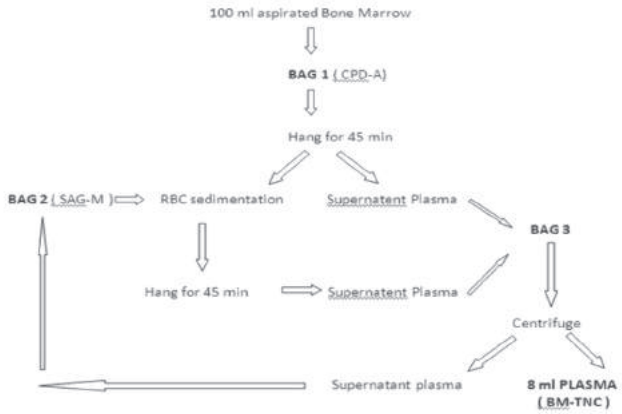
Bag 1 – Commercial 450ml Triple blood donation bag (63 ml CDP-A).

Bag 2 – 100ml Saline – Adenine- Glucose- Mannitol (SAG-M) plus 26 ml HES

Bag 3 – Empty bag.

Around 100 ml of bone marrow was aspirated under Spinal Anesthesia with bone marrow aspiration needle from the Ileum bone. Out of 35 patients , bone marrow was aspirated from Right ileum in 17 patients, Left ileum in 15 patients. Bilateral aspiration was required in 3 patients. Bone marrow was concentrated to 95% purity and to a final volume of about 8 ml. The 100 ml of aspirated bone marrow was transferred to Bag 1 and hung on stand for 45 min to allow RBC sedimentation. The supernatant was extracted using plasma extractor and transferred to Bag 3. To obtain remaining trapped BM-TNC from RBC sediment contents of Bag 2 were transferred to Bag 1. The Bag 1 was shaken gently and hung for 45 min and the supernatant was transferred to Bag 3. Bag 3 was centrifuged then at 400 *g* for 12 min. After completion of centrifugation, the supernatant was transferred to Bag 2 using Plasma extractor and cells were resuspended in about 8 ml of remaining plasma.

Surgical debridement of wound was done prior to the application of BM-TNC**.** This allowed the bone marrow cells to come into contact with viable wound tissue. Using a 23 gauge needle, 5 mL of BM-TNC was implanted in the wound by 1.5 cm deep injections at various sites and the margin of the wound. Following the injection, 2 mL BM-TNC were mixed with platelets and fibrin, applied to the wound and allowed to form a clot on the wound. Collagen matrix was then impregnated with 10 mL BM-TNC suspension (1 mL BM-TNC mixed with 9 mL serum) and placed on the fibrin clot. Finally, paraffin gauze pads were placed over the wound and a bolster of rolled gauze pads placed over the paraffin gauze and dressing done. After 3 days, on each day, the entire dressing was removed, the wound irrigated with Normal Saline and then covered with paraffin gauzes and dressing done. The wound was closely observed for 6 weeks the formation of granulation tissue and reduction in size. Bates-Jensen Wound Assessment Tool was used to assess the wound and accordingly scored at 3 weeks and 6 weeks.



Results

We have studied a total number of 35 cases. The Graph Pad Instant statistical package (Graph Pad Software Inc.) was used for statistical analysis. Wounds of 3 patients completely closed after 6 weeks - BWAT Score 13 ($p < 0.05$). Wounds of 31 patients significantly reduced in the size ($p<0.05$). One patient did not respond to the treatment ($p>0.05$).

Wound status after 6 weeks	No. of Patients(n=35)	p value
Complete closure	3	$p < 0.05$
Size reduction	31	$P < 0.05$
No change	1	$p > 0.05$

Study review after three weeks

The initial three weeks have shown rapid progress of healing, werein the average wound size has reduced from (The BWAT Score mean of the wound initially =34.82 to The BWAT Score mean of the wound at three weeks = 24.8). The total size of the wound has reduced to 28.9% at the end of three weeks.

Study review after six weeks

Once the momentum of the healing process has set in, the wound has progressed to closure. All the wounds have reduced to more than 50% of initial size (The BWAT Score mean of the wound at Six weeks = 16.97) at the end of the six weeks.

Table 1 : Study review after three weeks and six weeks

Assessment (After the debridement of the wound) score (mean)	F/U Week -3 Score (mean)	F/U Week -6 Score (mean)
34.82	24.8	16.97

The local treatment with BM-TNC on diabetic wounds improved granulation tissue in the wound bed and caused significant reduction in wound size .

The healing was rapid in first three weeks and once the momentum was gained the wound slowly progressed towards complete healing within 6 weeks.

HbA1c and Wound Healing

Study according to HbA1c : Of the 35 patients we studied, 26 Patients were with Hb A 1c < 8 and 9 Patients were with Hb A 1c > 8.

In the patients with Hb A1c Less than 8, the average reduction in the size has been 52.98%. In patients with Hb A1c more than 8, the average reduction in the size has been 47.22%.

Table 2 : Correlation HbA 1c and wound healing

	Assessment (After the debridement of the wound) (mean)	F/U Week -6 Score (mean)	% of reduction in size
The Patient With Hb A 1c < 8%	33.03	15.53	52.98%
The Patient With Hb A 1c > 8%	40	21.11	47.22%

Cost effectiveness

Patients under study were from middle and low socioeconomic class with average annual income of Rs.120,000/-. The expenses borne by the patients were about Rs.2,000/- on an average. Comparing this with other methods of treatment, it was found to be very cost effective.

Table 3 : Cost of the different treatment modalities in India

Sr.No	Methods of Treatment	Approximate Cost in Rs.
1	VAC Treatment	Rs 50,000-57,000
2	Fixator treatment costs	> Rs.100000
3	growth factors	Rs 12000
4	Our Procedure	Rs 2000

Table 4 : Master Chart

Sr No	Age (Years)	Sex	BSL (mg/dl)	Hb A 1 c %	Wound site	Assessment (post Debridement) BWAT Score	F/U Score Week-1	F/U Score Week-3	F/U Score Week-6
1	47	Male	223	7.1	Lt Foot	32	31	25	17
2	45	Male	312	7.6	Rt Foot	30	25	19	16
3	45	Male	415	7.5	Rt Foot	30	25	19	16
4	47	Female	355	6.8	Lt Foot	27	24	18	15
5	50	Male	522	9.2	Rt Foot	40	37	35	32
6	55	Female	322	7.4	Rt Foot	34	30	24	15
7	41	Male	234	6.8	Left foot	31	27	20	13
8	49	Male	342	7.1	Rt Foot	36	32	26	17
9	55	Male	546	8.6	Rt Foot	44	39	32	24
10	43	Male	320	6.7	Left foot	32	28	21	13
11	41	Female	280	6.6	Rt Foot	32	29	22	15
12	40	Female	268	6.8	Left foot	36	29	23	16
13	50	Male	356	8.2	Left foot	37	33	27	20
14	41	Female	422	8.2	Left foot	37	34	29	19
15	58	Male	228	6.8	Rt Foot	26	24	17	14
16	58	Male	432	8.4	Lt Foot	39	35	29	19
17	45	Male	388	7.4	Rt Foot	36	33	27	17
18	44	Female	424	8.2	Left foot	40	37	28	18
19	51	Female	486	9	Rt Foot	43	39	30	20
20	50	Female	356	7.1	Rt Foot	40	36	27	17
21	56	Male	438	7.6	Rt Foot	40	38	29	19
22	59	Male	332	7	Left foot	33	32	26	15
23	50	Female	288	6.9	Left foot	34	33	28	16
24	50	Female	544	8.8	Rt Foot	42	39	32	21
25	55	Male	390	7.4	Left foot	32	32	23	15
26	38	Male	280	6.4	Left foot	34	32	24	15
27	47	Male	348	7.2	Rt Foot	32	30	21	15
28	41	Male	240	6.4	Left foot	29	24	17	13
29	55	Male	486	7.1	Rt Foot	37	34	26	14
30	45	Male	372	7	Left foot	35	31	25	17
31	45	Male	290	7.2	Left foot	28	28	18	15
32	46	Male	328	6.8	Rt Foot	34	31	25	16
33	54	Male	312	7.8	Rt Foot	35	32	25	18
34	54	Male	456	8.2	Left foot	40	38	31	20
35	52	Male	424	7.4	Left foot	34	32	24	15

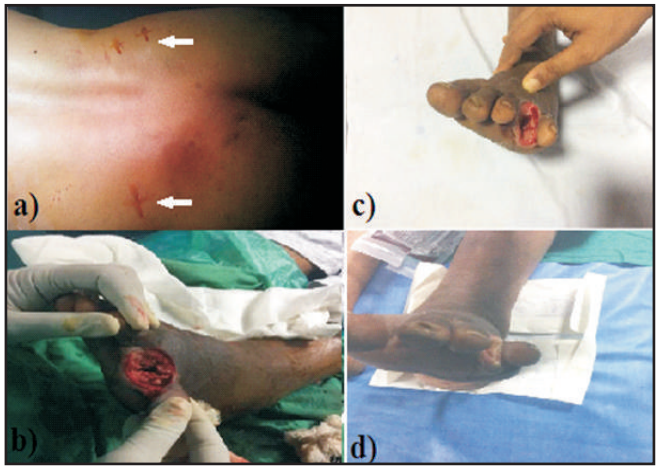


Fig. 1: a) Bone Marrow aspiration site(white arrow – Ileum bone) .

b) Wound on day 1 – after surgical debridement before injecting bone marrow.

c) Wound at 3 weeks.

d) Wound at 6 weeks.

Fig. 2: Bone Marrow aspiration needle

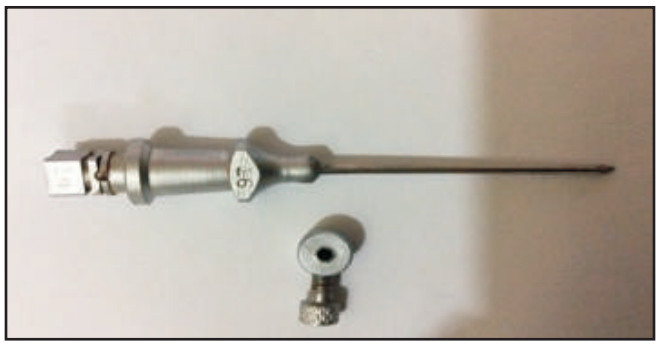
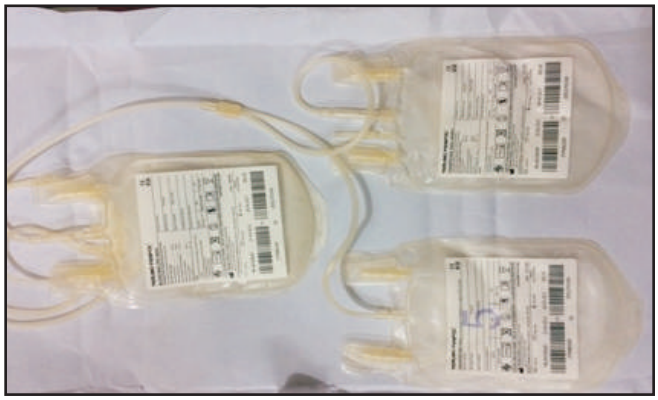


Fig. 3: Triple Bag



Discussion

Diabetic foot ulcers are neuropathic in the presence of peripheral diabetic neuropathy and absence of ischemia; ischemic if the patient presents with peripheral artery disease but no diabetic peripheral neuropathy; and neuroischemic if neuropathy and ischemia coexist [1].

The prevalence of diabetic foot ulceration in the diabetic population is 4–10%. The condition is more frequent in older patients. It is estimated that about 5% of all patients with diabetes present with a history of foot ulceration, while the lifetime risk of diabetic patients developing this complication is 15%. It was found that the recurrence of foot infection was common among Indian diabetic patients (52%).[8]

Foot ulcers are a significant complication of diabetes mellitus and often precede lower extremity amputation. The most frequent underlying etiologies are neuropathy, trauma, deformity, high plantar pressures, and peripheral arterial disease, improper footwear and standards of footcare.

Impaired local blood circulation as a result of micro and macrovascular disease and peripheral neuropathy causes foot ulceration in up to 25% of patients with diabetes mellitus. Foot ulceration is associated with increased morbidity and mortality, and has a negative impact on the quality of life of diabetic patients and poses a serious burden on the health care system and society . The cost of treating one diabetic foot ulcer has been estimated to be Rs. 30,000-40,000.[9]

Considering the pathophysiology of chronic nonhealing wounds, the more widely recognized causative factors are (a) Phenotypically altered and/or senescent mesenchymal cells that fill the dermis of the skin (b) Significantly decreased local concentration, stability and bioavailability of growth factors in the extracellular matrix, impair tissue repair and suppress cell proliferation and angiogenesis.[10]

Several novel approaches for diabetic foot ulceration treatment have been proposed recently which suggest the use of bone marrow stem cells, platelet-derived wound healing factors, fibrin glue or bone marrow-impregnated collagen matrix.[4,5,6,7]

Role of Bone Marrow, Platelets, Fibrin Glue, and Collagen Matrix :

- Bone Marrow regenerate components of blood, and non-hematopoietic stem cells
- Platelets used as a source for cytokines
- Collagen matrix acts as a scaffold for regeneration resulting in induction of angiogenesis and fibroplasia
- Fibrin glue provides an important temporary extracellular matrix for wound healing

Each of these approaches has been reported to increase the response time of healing in chronic wounds. But, as the wound environment is dynamic and requires the presence of all ' contributing components, it is unlikely that one type of treatment alone can bring a wound to complete closure.[2,3] The bone marrow is an important source of hematopoietic stem cells, including Mesenchymal cells which can be differentiated into several other cell types such as vascular endothelia, neurons, fibroblasts and skin keratinocytes. Considering the plasticity of bone marrow stem cells to produce new cells, it is conceivable that they may replenish lost cells during wound healing These cells are recognized as key players in tissue regeneration and rebuilding of tissue

compartments.[11] In the present study, we used autologous bone marrow-TNC, concentrated in a small volume and platelet, fibrin glue, collagen matrix. We have used local injections as well as application over the wound after surgical debridement followed by regular dressings. There is significant reduction in wound size and decrease in time required for complete wound closure. Several studies suggest that bone marrow-derived stem cells may contribute to wound repair and regeneration.[2,3,7] The combined approach of using autologous BM-TNC, platelets, fibrin glue and collagen matrix provides local factors required for wound healing.

The clinical benefits of systemic administration of MSCs were also observed in a study carried out by Lu et al performed on diabetic patients with critical lower limb ischemia. Patients were injected with autologous BM-MSCs or bone marrow mononuclear cells (BM-MNCs) in one of their legs. In the contralateral leg they were injected with saline serum as control. The results at 24 weeks after transplantation showed an improvement in pain and a significant increase of the healing rate of the ulcer.

In 2009, Dash et al published the results of a test carried out in 24 patients with ulcers in the lower extremities due to diabetes or vasculitis. These patients received autologous BM-MSCs intramuscularly at the edges of the wound. Twelve weeks after transplantation, in the group treated with MSCs, ulcer size decreased by 73%, whereas in the control group the reduction was of just 23%. The study highlights that autologous implantation of BM-MSCs in non-healing ulcers accelerates the healing process and improves clinical parameters significantly.

Falanga and colleagues applied up to three applications of autologous, culture-expanded, mesenchymal stem cells with a fibrin glue system to acute and chronic wounds. The acute wounds healed within eight weeks and the chronic wounds decreased or healed in 16 to 20 weeks

Hassan Raveri et al reported on the treatment of eight patients with aggressive, refractory diabetic wounds. The marrow-derived cells were injected/applied topically into the wound along with platelets, fibrin glue and bone marrow-impregnated collagen matrix. Four weeks after treatment, the wound was completely closed in three patients and significantly reduced in the remaining five patients. Their study suggest that the combination of the components mentioned can be used safely in order to synergize the effect of chronic wound healing.

Badivas et al mention that the direct application of autologous Bone Marrow- derived mesenchymal stem cells (BM-MSCs) in patients with chronic wounds can achieve the closure of the wound and tissue reconstruction. In this study, they observed that the direct injection of fresh whole BM into the edges of the wound followed by topical application of cultured MSCs managed to completely close chronic ulcers in 3 patients where traditional therapy had failed.

Sarasua et al performed a clinical trial on 22 patients with spinal cord injury having grade IV pressure ulcers where conventional treatments had failed. Autologous BM-MNCs were injected topically. In 19 patients (86.36%), the pressure ulcers treated with BM-MNCs were fully healed after a mean time of 21 days. During a mean follow-up of 19 months, none of the resolved ulcers recurred. Their data indicate that celltherapy using autologous BM-MNCs could be an option to treat type IV pressure ulcers in patients with spinal cord injury, avoiding major surgical intervention. All these results suggest that cell therapy with BM-MSCs or BMMNCs applied either topically or systemically yields clinical benefits for the treatment of chronic wounds. Furthermore, some remarkable results can be achieved in the treatment of chronic wounds by combining BM-MSCs with tissue engineering, i.e. application of cells on an adequate support/scaffold which ensures cells remain viable and may efficiently migrate in the wound bed.

This novel approach is a breakthrough for treating Diabetic Foot ulcers and its complications, helps in avoiding amputations. In the long run, a holistic approach like this is certain to be effective. It becomes apparent that in this economically productive age group if the patient loses his limb, then it is not just only economic loss to the nation but also a social burden.

Conclusion

Increased longeivity in our society has translated into a much higher incidence of chronic disorders and their sequele such as nonhealing wounds. Because of highly complex nature of wound that result from destruction or loss of function of specific native cells, traditional medical therapies have been only moderately effective. Diabetic foot ulcers were treated successfully with a combination of bone marrow- TNC, platelets, fibrin glue and collagen matrix. As the procedure is autologous, it is very effective in rapid wound healing, complete wound closure and improvement in quality of life as compared with other commercial and costly wound care modalities

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The novel work reviewed here is highly promising , cost effective with collective goal of identifying new therapeutic approaches to diabetic wound healing that are broadly applicable and can safely accelerate the transmission of basic research findings into clinical advances.

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CASE REPORT

A Rare Case Of Vulvovaginal Varices In Pregnancy And Review Of Literature

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ABSTRACT

Vulvovaginal varix during pregnancy is a rare condition. Only few cases of vaginal varicosity have been reported in literature. Present case was 22 year woman admitted with 38 weeks of gestation and intrauterine fetal demise with huge vulvovaginal varix. We observed reddish blue dilated mass in suburethral area of anterior vaginal wall protruding through vagina and obstructing vaginal lumen. Both lateral and anterior vaginal walls showed large dilated veins. There were also multiple strawberry sized soft non-tender masses on vulva. We performed caesarean section to prevent potential risk of profuse intrapartum hemorrhage. Whether intrauterine fetal demise was consequence of vulvovaginal varices or co-incidental is not known. These huge vulvovaginal varices were regressed on day seven of postoperative period. After reviewing current literature, we noted that present case is the eleventh case of vaginal varicosities.

Keywords - Vulvovaginal varices, intrapartum haemorrhage, intrauterine fetal demise.

Introduction

Vulvar varicosity tend to occur in second trimester of pregnancy, however it is rare in non-pregnant woman. Incidence of vulvar varices reported is 4%[1], and are found on labia majora and minora. However only few cases of vaginal varices are reported. The vulvovaginal varices are seen as multiple strawberry sized tortuous, soft swellings over vulva and vaginal walls. During pregnancy or labour, rupture of varices due to spontaneous laceration or from trauma can lead to torrential haemorrhage. We report a case of huge vulvovaginal varices in term pregnancy with intrauterine fetal demise.

Case Report

A 22 year G2A1 was referred to us for intrauterine fetal demise with huge vulvovaginal varicosity. She completed 38 6/7 weeks of gestation and complained of swelling over vulva since three months and mass coming out per vaginum causing discomfort and pain since ten days. There was also history of absent fetal movement since one day, hence ultrasound was done and intrauterine fetal demise with reduced liquor was diagnosed. None of the family members had history of varicosity of leg veins. Patient reported discomfort during sitting and walking and increasing pain at vulva.

On examination, patient was haemodynamically stable. Uterine fundal height was corresponding to 32 weeks gestation with fetus in cephalic presentation. Patient had mild uterine contractions. Fetal heart sounds were absent on auscultation. Genital examination revealed multiple strawberry sized masses on vulva. (Figure-1)

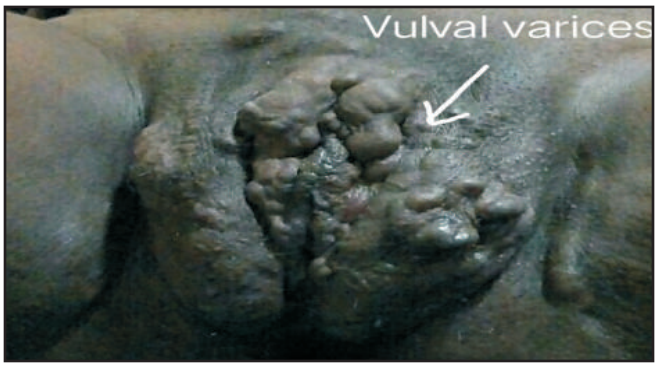

Figure 1: Vulval varices

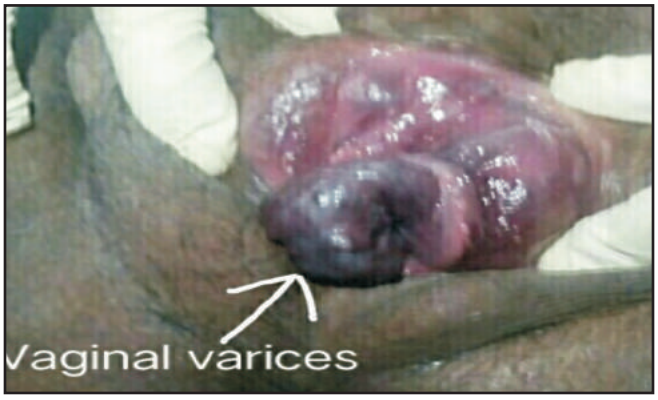

Figure 2: Vaginal varices

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There was tortuous, soft, tender, compressible swelling bilaterally over external surface of labia majora, minora and mons. Also there was reddish blue colored strawberry sized vascular lesion on suburethral vaginal wall protruding out and obstructing vaginal lumen. Vaginal varicosities were seen over anterior and both lateral vaginal walls on per speculum examination. (Figure-2, 3) Varicose vein were seen on groin area with no evidence of varicose veins of both legs. Caesarean section was performed immediately to avoid unpredictable intrapartum torrential haemorrhage due to tearing of vulvovaginal varices. Male baby of 2.9 kg was delivered. There was no evidence of dilated veins over uterus or in pelvis. On postoperative day four, vulvovaginal varicosity regressed in size and patients pain and discomfort was alleviated. (Figure-4)

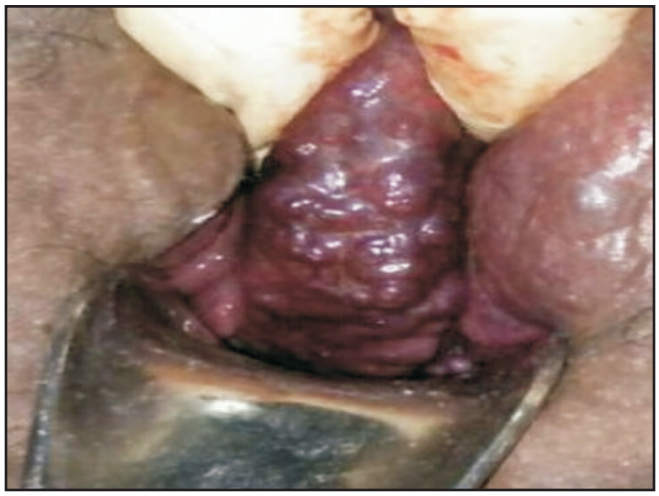

Figure 3: Vaginal Varices

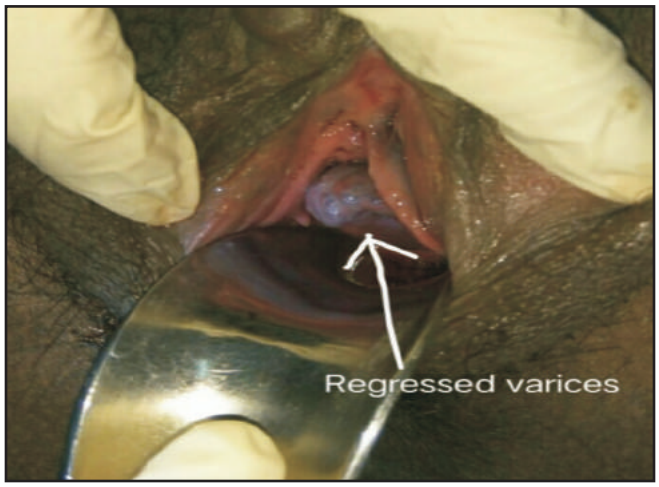

Figure 4: Regression of varices after delivery

Discussion and review of literature

Vaginal varix during pregnancy is a rare presentation compared to vulvar varices. By reviewing the current literature, we found that only ten cases of vaginal varicosities in pregnancy are reported between 1967 and 2017[6, 7, 8, 9, 10, 11, 12, 13]. As per our knowledge, present case is the 11th case of vaginal varicosity which also presented with massive vulvar varicosities.

Pathogenesis of vulvovaginal varicosities proposed are incompetent veins, increased estrogen and progesterone level targeting thin walled vulvar vein to dilate but exact etiology is unclear.[2] Huge varicosity of vulva and vagina is distressing for patient. It causes vulvar pain, pruritis, dyspareunia and discomfort. Isolated vulvar varicosities can be asymptomatic, but can cause feeling of fullness, swelling, discomfort and pain. Vulvar varices tend to appear during second trimester and regress after delivery[3]. Long period of standing, exercise and sex can aggravate condition. Varicosities tend to occur more frequently with increasing parity. In present case patient noticed vulvar swelling in sixth month of pregnancy and was second gravida with one abortion. Vulvovaginal varicosities are diagnosed clinically with soft, tortuous, dilated and engorged venous plexus which are seen bilaterally on labia majora, minora and vagina with bag of worms feel on palpation. Doppler ultrasound is preferred method for diagnosis. Vulvar varices can get thrombosed and present as tender and non-compressible swelling. In present case patient had intrauterine fetal demise at term, whether it was co-existing or vulvovaginal varices was also one of contributory factors is unknown.

Most cases of vulvovaginal varicosities occur secondary to pregnancy but in non-pregnant women, association with pelvic congestion syndrome or Klippel Trenaunay Weber (KTW) syndrome[1,2,14,15] is also observed. When vulvar varices are associated with pelvic congestion syndrome, main symptoms are dyspareunia, dysuria and dysmenorrhea. While KTW syndrome is a congenital disorder with a triad of extensive cutaneous hemangioma (port wine stain), hemi hypertrophy of the body below neck (leg and arm of one side) and venous varicosities.

Severe antepartum hemorrhage due to rupture of vaginal varices is reported by Purslow et al[4]. Few cases reported in literature presenting with vaginal bleeding from

vaginal varices as complication of portal hypertension[10]. These cases were successfully treated with liver transplant surgery. Few cases reported round ligament varicosities associated with uterine varicosities in pregnancy. Roger N et al reported intra-peritoneal haemorrhage from rupture of uterine varicose vein during pregnancy. Sergey Gavrilov evaluated hundred and one women with vulvar varicosities during 2000 to 2014[16]Among these, sixty one non-pregnant patients with varicose veins of pelvis and enlarged vulvar veins were in group one and forty pregnant women with vulvar varicosities in group two. Vulvar varices were observed between eleven and thirty eight weeks of pregnancy. In this study, only two pregnant patients had complications in the form of thrombophlebitis of vulva veins at twenty eight and thirty two weeks of pregnancy respectively. These two patients required prophylactic low molecular weight heparin to prevent deep venous thrombosis. Treatment of vulvar varicosities in pregnancy is mostly conservative. It was concluded in the study that significantly dilated vaginal varicosities can be considered an indirect indication for caesarean section. Visual detection of large one centimeter or more venous varices on vaginal wall confirmed by ultrasonography should alert the obstetrician while choosing mode of delivery. Isolated vulvar varicosities should not be a contraindication to vaginal delivery.

Since only few cases have been reported in literature, there are no standard recommendations regarding safest mode of delivery. There is limited evidence that favors cesarean birth over vaginal birth. Adverse fetal outcome in form of fetal death[4] and fetal brain damage[17]due to massive hemorrhage from rupture of vaginal varices were reported. Many reported cases of vaginal varicosities were delivered by caesarean section due to risk of rupture of varicosities. In contrast to this, Furuta et al[3] noted vulvovaginal varices are compressed by fetal head during second stage of labour and fetus can be delivered successfully vaginally. In present case, we informed patient about risk of bleeding from huge vulvovaginal varices during vaginal delivery and patient gave consent for cesarean section. Due to paucity of evidence regarding risk factors predicting rupture of varices during vaginal delivery and safe mode of delivery, decision should be individualized in each case.

Treatment of vulvovaginal varices is mostly conservative during pregnancy to get relief of symptoms. Applying cold compress to vulva to relieve vulvar pain and firm support with compression support garments are useful. Avoiding standing for long period of time and lifting heavy weight and leg elevation during rest which promote circulation can prevent worsening. Vulvovaginal varices regress spontaneously during postpartum period. In present case, we also observed the same. Persistent, large and symptomatic varices after delivery are effectively treated by sclerotherapy.

Conclusion

Vulvovaginal varicosities tend to occur most often during pregnancy in 2nd trimester. Vaginal varicosities is a rare presentation compared to vulval varicosities. Till today there is no consensus on optimal mode of delivery. Majority of cases noted in current literature favored cesarean delivery due to risk of profuse intrapartum haemorrhage. Due to paucity of evidence regarding risk factors predicting rupture of varices during vaginal delivery and safe mode of delivery, decision should be individualized in each case.

Conflict of interest : None

Funding source & sponsorship : None

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CASE REPORT

'Dani's Stitch'-A Conservative Introital Tightening Method For Uterovaginal Prolapse In Surgically High Risk Geriatric Women

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ABSTRACT

Prolapse of uterus with cysto-rectocele is one of the commonest problems seen in the menopausal women. Majority of these patients are elderly debilitated and require hysterectomy with repair[1]. We report two cases of third degree uterovaginal (UV) prolapse with **medical illness,** unfit for major surgery in lithotomy position for prolonged time. Due to medical problems in these patients, we used the introital tightening procedure - Dani's Stitch as an alternative treatment modality. This conservative operation was performed successfully in these patients with minimal post-operative morbidity.

Key words: UV Prolapse, Dani's stitch, local anaesthesia

Introduction

Most of the patients with uterovaginal (UV) prolapse are elderly requiring hysterectomy with perineal repair as definitive line of management. However, some of these patients are unfit for anaesthesia or for prolonged surgery in lithotomy position due to old age and related medical or surgical disorders like uncontrolled diabetes, hypertension and heart disease. Use of vaginal pessaries[2] and options like Le Fort's colpocleisis[3] are the common modalities of treatment in such cases with their own limitations and complications. Dani's Stich[4] is an alternative method of introital tightening for these high risk geriatric women who are unfit for prolonged lithotomy position or anesthesia.

CASE 1: A 62 year multiparous female, farmer by occupation was referred to our institute in view of third degree uterovaginal (UV) prolapse with cysto-rectocele with heart disease, hypertension, hyperthyroidism and anemia for further management as anaesthetic fitness was not given at the referring institute for vaginal hysterectomy.

On admission patient complained of a mass coming out of vagina since 3 years. Initially the mass was small, reaching up to the introitus. Gradually the mass increased in size and came completely out of vagina on standing, coughing and straining at stools. The mass was reducible in lying down position. She also had complaints of incomplete evacuation of urine. There were no bowel complaints. She had breathlessness on exertion since 2 years, for which her cardiac evaluation was done at a Civil Hospital, 140km away. Her 2D Echo was suggestive of moderate MR, mild AR, mild TR, mild pulmonary hypertension, with ejection fraction of 60%, probably rheumatic in origin. She was diagnosed as hyperthyroidism 2 years back and was taking Tab. Carbimazole 10 mg and Tab. Propranolol 20 mg for around six months and then stopped. She was also a case of hypertension.

In view of her poor cardiac status she was started on Tab. Digoxin 0.25mg, Tab. Losartan 50mg, Tab. Spironolactone 50mg, Torasemide 10mg and Tab. Acetyl salicylic acid 75 mg

Her hemoglobin was 5.5gm% and was transfused 3 units of packed cells for anemia correction. On examination, her vitals were stable. Pulse was 80/min, BP was 150/90 mm of Hg. On CVS examination pansystolic murmur was present. Her respiratory system examination and abdominal examination were normal. On local examination there was evidence of third degree uterovaginal prolapse with cysto-rectocele. On per vaginal examination uterus was of normal size. On per rectal examination rectocele was confirmed. Papanicolau (PAP) smear was taken which was normal.

The diagnosis was 62 year female P2L2A1

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tubectomised with third degree UV prolapse with cysto-rectocele with heart disease (moderate MR, mild AR, mild TR, mild pulmonary hypertension), with hypertension with hyperthyroidism with severe anemia not in cardiac failure.

After admission and necessary references, she was labeled as a very high risk case for anaesthesia for vaginal hysterectomy and pelvic floor repair in lithotomy position. So we offered her Dani's Introital Tightening Stitch as conservative line of management which could be done under local anaesthesia, considering her high risk status.

Patient and relatives were counseled, and written informed consent was taken. The palliative nature of the procedure was explained to the patient.

Figure 1 shows the introitus before surgery. The procedure was done under local anaesthesia in lithotomy position. Bladder was emptied and 1% lignocaine was injected all around the introitus. A small transverse incision was taken on anterior vaginal wall 1 cm below the external urethral meatus. A small vertical incision was taken on the posterior wall just inside the posterior fouchette at 6 o'clock position. Aneurysm needle of right side introduced submucosally (Figure 2) through the 6 o'clock incision and removed anteriorly through sub urethral incision. Polypropylene No. 1 doubled looped suture was threaded on the needle and withdrawn through 6 o' clock incision. Similar procedure repeated on other side and opposite end of suture was brought posteriorly through 6 o' clock position so that both loose ends of sutures were on posterior side. The introitus was tightened by pulling two loose ends so that 1 ½ finger PV was possible and then 5-6 knots were tied. The knot was buried in the posterior incision with absorbable chromic catgut suture No 1-0. The anterior sub-meatal incision was closed with the same suture material.

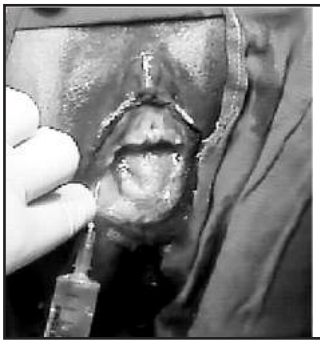

Figure 1: Introitus before surgery

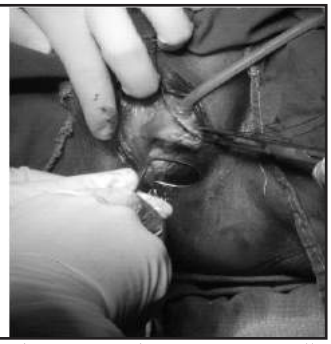

Figure 2: Passing aneurysm needle submucosally, from 6 o'clock to 12 o'clock position on the right side

Post operatively she received antibiotics and analgesics and was discharged after three days. Follow up was done after one month and the stitch was found to be well in situ and her urinary complaints had resolved.

CASE 2: 70 yrs old postmenopausal nulligravida with procedentia with decubitus ulcer and uncontrolled hypertension was admitted .She was a chronic tobacco chewer. On medical reference she was diagnosed as hypertensive heart disease with ECG showing global T wave inversion and sinus bradycardia. Chest X-Ray was suggestive of cardiomegaly with CP angle blunting. Her 2-D Echo was suggestive of LVEF 40% with pericardial effusion. Because of high risk for major surgery, the patient and relatives were counseled and she was subjected to Dani's introital tightening stitch under local anesthesia. The procedure was uneventful. There was no intra-operative and post-operative complication and patient was discharged on post operative day 3. After two months of follow up her stitch was in place and there were no signs of erosion.

Discussion

The Introital Tightening Stitch was discovered by Dr. Suhas Dani[5] (Ex Prof. and Head of the Dept. of Obst. And Gynaec, B. J. Govt. Medical College, Pune) to meet the need of the elderly patients with UV prolapse who are unfit for major surgery under anaesthesia due to old age, medical or surgical conditions. This is a very simple procedure with a small learning curve, using non absorbable suture material like nylon or Polypropylene no-1 or mersilene tape can also be used[5]. The procedure can be performed under local anaesthesia in about 10 to 15 minutes with no major complications. The patient can be discharged in a couple of days. The procedure though temporary, provides a good alternative as a conservative operation for geriatric women who are unfit for prolonged anaesthesia as compared to other conservative methods like vaginal pessaries and Le Fort's colpocleisis. Problems seen in follow up period are cutting

through of stitch and erosion of stitch [6]. However, proper patient selection, technique and counseling to patient give good result. Additionally, availability of the cervix for PAP smear screening and preservation of coital function are the major advantages over the Le Fort's colpocleisis surgery.

Both patients have followed up and the stitch was intact. We did not come across any erosion in our cases. Erosion of the suture is a major factor accounting towards the failure of the procedure. This is seen when the stitch is very tightly placed. To avoid this we pull the stitch in such a way so as to occupy 1 ½ finger in the vagina. Use of the double-looped non-absorbable polypropylene No-1 suture showed good results. Alternatively, nylon-polyamide suture No-1 can also be used.

Less operating time under local anaesthesia with early ambulation reduces the risk of prolonged immobilization like thromboembolism, DVT among others[7].

Injuries to the bladder and the rectum, which are complications seen in major surgery like vaginal hysterectomy, are extremely rare following this conservative approach. Also complications of urinary incontinence and retention seen with Le Fort's colpocleisis are not seen with this approach.

Thus, this case series shows that we can advocate a minimally invasive surgical procedure-Dani's introital tightening stitch for debilitated geriatric patients with prolapse who have chronic medical illnesses and are high risk for major gynecological surgery. This is indeed a boon for such patients who have a speedy post-operative recovery with minimal complications.

Conflict of interest: Nil

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CASE REPORT

A Rare Case Report Of Carcinoid Tumor In Meckel's Diverticulum

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ABSTRACT

A 60-year-old male presented with an abdominal lump, dull-aching pain and early satiety since 2 months. Ultrasonography showed a large solid heterogeneous hypo echoic mass showing internal vascularity and few anechoic areas of necrosis. CT scan showed a well-defined heterogeneously enhancing mass in the mesentery along with mild spiculated peripheral linear fat stranding. Exploratory laparotomy showed an incidental finding in the form of Meckel's diverticulum, and the mass appeared to be in contact with the mesentery, which was adjacent to the part of bowel having Meckel's diverticulum. The mass was resected with a segment of normal bowel using Endo-GIA stapler. Histo-pathology showed cells with round to oval nuclei, salt pepper chromatin and moderate amount of eosinophilic cytoplasm suggestive of Carcinoid tumor of Meckel's diverticulum. Meckel's diverticulum and carcinoid tumors are both rare clinical entities individually. The occurrence of carcinoid tumor in Meckel's diverticulum is very rare.

Keywords: Meckel's Diverticulum; Carcinoid Tumor; Endo-GIA Stapler; Enterochromaffin Cells

Introduction

Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract and is caused by incomplete obliteration of the vitelline duct during intrauterine life. It has prevalence of 2% in the general population. A majority of the cases remain asymptomatic but symptomatic cases occur most commonly in the earliest years of life. The average rate of symptomatic cases seen is only 2-4%.[1]

Carcinoid tumors account for one-fifth of all small intestinal neoplasms and are found most commonly in the terminal ileum. Carcinoid tumors in the gastrointestinal tract arise from amine precursor uptake and decarboxylation of cells with neuroendocrine origin.[2] Carcinoid tumors can occur throughout the respiratory or GI tracts, but most originate in one of three sites: bronchus, colon-rectum, and Jejuno-ileum. However, these tumors are infrequent in Meckel's diverticula and observed only in 0.5-3.2% of the cases. They are usually incidental findings at surgery or autopsy.[3]

Case Report

A 60-year-old male presented to a tertiary care center with an abdominal lump and dull-aching pain, early satiety since 2 months. On enquiry, there was no history of altered bowel movement, trauma, or any surgical illness in past. On examination, lump was felt in umbilical region, slightly on the left. The lump was 6×5 cm, non-tender and soft in consistency. Ultrasonography showed a large solid heterogeneous hypo echoic mass showing internal vascularity and few anechoic areas of necrosis. CT scan showed a well defined heterogeneously enhancing mass of size 4×5×6 cm in the mesentery at L3-L4 vertebral level. Puckering was seen involving the adjacent bowel loops along with mild spiculated peripheral linear fat stranding suggestive of desmoplastic reaction **(Figure 1)**. Decision was taken to perform an exploratory laparotomy. Upon exploration, the mass was noticed, around which the small bowel loops and mesentery was clumped. Incidentally, Meckel's diverticulum was noticed 60 cm proximal to the ileo-cecal junction and the mass appeared to be in contact with the mesentery which was adjacent to the part of bowel having Meckel's diverticulum. Decision was taken to resect segment of bowel, which was clumped along with margin of normal bowel. Endo-GIA Stapler was used for resection and anastomosis of the ileum. Post-anastomosis bowel patency was adequate **(Figure 2)**.

Histo-pathology showed malignant cells with round to oval nuclei, salt pepper chromatin and moderate amount of eosinophilic cytoplasm suggestive of Carcinoid tumor of Meckel's diverticulum **(Figure 3)**. Post-

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operative course was uneventful. Due to lack of definitive evidence and therapy related toxicity, chemotherapy was not given to the patient. At 12-month follow up patient does not have any recurrence of symptoms.

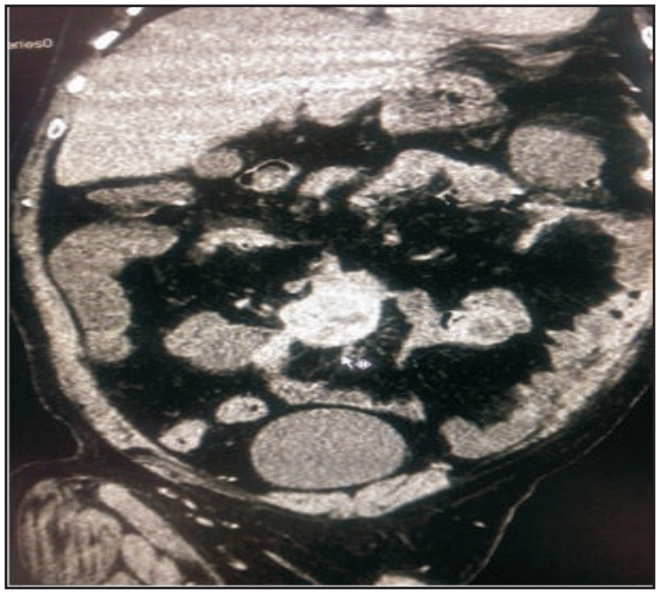

Figure 1 : Well defined heterogeneously enhancing mesenteric mass at L3-L4 level. Also note puckering involving adjacent bowel loops along with mild spiculated peripheral linear fat stranding (Desmoplastic Reaction)

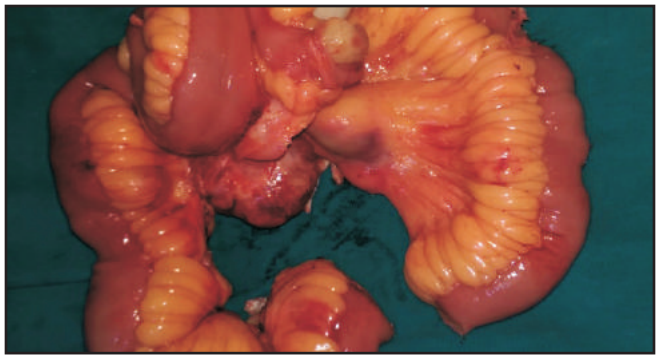

Figure 2 : Excised mass with adjacent bowel. Meckel's Diverticulum is also noted along the mass.

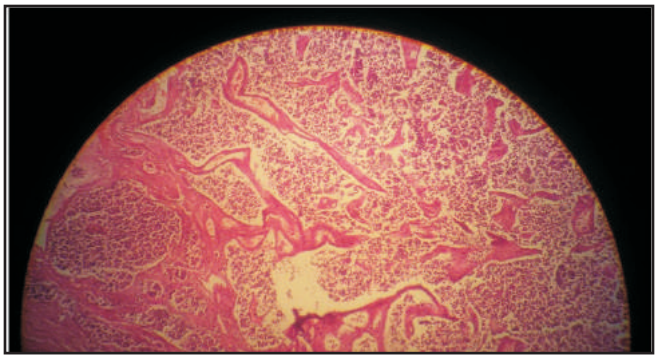

Figure 3 : Histopathology slide suggestive of carcinoid tumor

Discussion

Meckel's diverticulum is a slight bulge in the small intestine present at birth and a vestigial remnant of the omphalomesenteric duct (also called the vitelline duct). It is localized approximately 45 to 60 cm proximal to the ileocecal valve, on the projection of the terminal branch of the superior mesenteric artery, which represents the rotational axis of the fetal gut.

Malignancies of Meckel's diverticulum are found in only 0.5–3.2% of the cases. In a review of 600 cases of Meckel's diverticulum presenting with complications, less than 4% were found to have a tumor. Most of them are commonly benign tumors like leiomyomas, angiomas, and lipomas. Malignant neoplasms include adenocarcinoma, sarcoma, carcinoid tumor and GIST. After sarcomas, carcinoid tumors are the second commonest malignant tumor arising in Meckel's diverticulum.[4] Carcinoid tumors are neuroendocrine tumor, derived predominately from enterochromaffin or Kulchitsky's cells. Such tumors are usually small, a majority measuring 1 cm or less in diameter. Carcinoids can theoretically occur in any anatomical region, but are most commonly found in the appendix, with the ileum being the second most common site. They may have malignant behaviour but usually show a low aggressiveness, being asymptomatic in 70 to 80% of cases. Symptoms can be periodic abdominal pain, gastrointestinal bleeding and obstruction, or due to carcinoid syndrome (10 to 20%) with acute episodes of skin flushing, diarrhoea, asthma attacks, hepatomegaly and development of cardiac lesions.[5]

Meckel's diverticulum and carcinoid tumors are both rare clinical entities individually. Hence, occurrence of carcinoid tumour in Meckel's diverticulum is even rarer.

Modlin et al. reported 0.48 to 0.74% incidences of such cases.[6] The association between carcinoid tumors and Meckel's diverticulum is validated by a common embryological origin, arising from incorrect interactions between the neural crest and endoderm. The mean age at which carcinoid tumors in Meckel's diverticulum are found is 55 years. They are seen four times more commonly in men than women.[4]

Clinical presentation depends on the stage of disease and size of the lesion. Lesions smaller than 10 mm with intact muscle layers are asymptomatic, whereas those with more aggressive local characteristics are frequently associated with local and systemic signs and symptoms.

Metastases are more common in women than men, most likely because of hormonal factors. Liver is the most common site for metastatic lesions, with a 5-year survival of approximately 30% in patients with hepatic metastases. According to Moertel et al., carcinoid tumours smaller than 1 cm have an incidence of 2% of metastasis, whereaslesions with a size between 1 and 2 cm metastasize in 50% of cases, and those larger than 2 cm metastasize in 80% of cases.[7]

Once a carcinoid on Meckel's diverticulum is confirmed, treatment is done according to the disease stage and size of lesion. The excision of Meckel's diverticulum is required in symptomatic cases, regardless of age. Simple Meckel's diverticulum excision is considered adequate by most of the studies in the case of lesions of less than 10 mm in size. For larger lesions, resection of the ileum and corresponding mesentery is generally recommended. According to their ability to metastatize early, carcinoid tumors of Meckel's diverticulum should be considered as relatively aggressive. Therefore, resection of the adjacent ileal segment and corresponding mesentery is recommended for tumors larger than 5 mm. The presence of secondary lymphatic or hepatic dissemination is not considered as a contraindication to surgery. For asymptomatic cases, the most appropriate treatment to adopt is however controversial. Cullen et al supported prophylactic transverse diverticulectomy before the age of 80 years. The operative mortality and morbidity rate for diverticulectomy is only 1 - 2% and 2%, respectively.[8] Laparoscopy is preferred as it is quick and simple to perform. Rate of post-operative complications is 2% and 0% mortality rate following diverticulectomy. However, as no direct examination and palpation of the diverticulum is possible, the risk of incomplete resection of the lesion is a drawback. Five year survival ranges around 75% post-surgery, while for patients with metastasis, it decreases to 20-50%.

In conclusion, a patient with Meckel's diverticulum should be looked for possible complications and intervention should be done accordingly. The history of vague abdominal pain with lump, age of the patient, and the imaging features make carcinoid tumor with a mesenteric spread a strong primary diagnostic consideration even if it is a rare entity.

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CASE REPORT

Bowen's Disease On Photoprotected Site : A Diagnostic Challenge

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ABSTRACT

Bowen's disease is an intra-epidermal squamous cell carcinoma i.e. carcinoma *in situ*. It usually affects the fair skinned individuals with a peak incidence in sixth to eighth decade of life. Most common sites are the head and neck followed by the extremities. The etiological causes known are chronic ultraviolet radiation exposure, human papillomavirus infection, arsenic exposure, previous radiation, immunosuppression, trauma and genetic factors. The risk of development of invasive carcinoma is 3-5% in extra-genital lesions and 10% in genital lesions. We present a case involving an atypical site which responded to topical 5-fluorouracil 1% cream.

Key words - Bowen's disease, 5 fluoro-uracil

Introduction

Bowen's disease is an intraepithelial carcinoma or squamous cell carcinoma *in-situ* of the epidermis. It can be found on both sun exposed and unexposed areas; head and neck and lower limbs being the common sites.[1] Exact incidence in india is not reported. Although several treatment modalities are available for Bowen's disease, no single therapy has been proven to be superior to others.[2] 5 fluorouracil is a topical chemotherapeutic agent which has been widely used by dermatologists successfully in treating Bowen's disease, actinic keratosis, superficial basal cell carcinoma and even invasive squamous cell carcinomas.[1,3-5] We describe an unusual case of Bowen's disease presenting as a single plaque on thigh which responded to topical 5 fluorouracil (1%) cream.

Case

A sixty seven-year-old elderly female presented with a single erythematous plaque on anterior aspect of right thigh since eighteen months. The lesion initially started as a tiny asymptomatic erythematous papule. The lesion gradually enlarged to form a plaque associated with moderate pruritus and occasional clear ooze. Before presenting to us, she had been treated with topical steroid antibiotic combinations for few weeks and systemic antibiotics without any improvement. Dermatological examination showed a single irregular shaped erythematus plaques of size 9 × 4 cm on the anterior aspect of the right thigh which was covered with thick semi adherent yellowish crust. Removal of overlying crust showed a non-indurated erythematous mildly oozy base without frank bleeding (Figure 1). There was no local lymphadenopathy or skin lesions elsewhere. Keeping the provisional possibilities of fixed cutaneous sporotrichosis, tuberculosis verrucosa cutis and chromoblastomycosis, a skin biopsy was performed using a 4 mm punch from the plaque which showed epidermal hyperkeratosis, irregular acanthosis with many dyskeratotic cells, mitotic figures keratinocyte dysplasia and atypia. Dermis showed perivascular lympho-histiocytic infiltrate in upper part without any invasion. These histological features were consistent with squamous cell carcinoma *in situ* Bowen's disease (Figures 2A, 2B).

Therefore, a diagnosis of Bowen's disease was made and the patient was started on topical 5 flurouracil 1% cream 6 days a week. The patient took therapy regularly for thirteen weeks showing few persistent papules and development of erosions (Figure 3), beyond which she stopped it on her own due to complete subsidence of the lesion. There is no recurrence observed till 6 months follow up.

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Discussion

Bowen's disease is an intraepithelial squamous cell carcinoma first described by John Bowen in 1912. It usually occurs as a solitary plaque which is often asymptomatic but multiple lesions can occur in 10- 20% of the cases.[2] Bowen's disease generally presents as an erythematous, irregular, scaly plaque. The well established clinical variants include pigmented, subungual/periungual, palmar, genital, perianal and verrucous Bowen's disease,[2] and it has also been reported to mimic malignant melanoma.[6] Our case was unusual in form of its atypical location over the anterior aspect of thigh which is photo-protected site. The common sites for Bowen's disease include the chronically photo-exposed sites like head and neck and dorsae of hands and lower legs. [1, 2] There have been few studies with large cohorts, [8-10] analyzing the site distribution of Bowen's disease. Thestrup- Pedersen *et al*. described six hundred seventeen cases of Bowen's disease out of which 73.5% cases occurred over photo-exposed sites (head and neck, and hands).[8] Kossard *et al.* analyzed data of one thousand one histologically proven cases of Bowen's disease and found head and neck region to be the commonest site (44%) followed by lower limb (29.8%), upper limb(19.8%) and torso (6.5%).[9] On the other hand, in the series of one hundred eight cases discribed by Cox lower limbs were the commonest sites (75%), followed by face and scalp (13%) and hands and wrists (11%).[10] But none of these studies give any details about photo-covered areas. Although anecdotal reports of Bowen's disease occurring over thigh have been described, it still remains a rare site.[7,11-13]

Treatment options for Bowen's disease include cryotherapy, curettage with cautery, excision, topical 5-fluorouracil (5-FU), topical imiquimod, radiotherapy, CO2 laser, photodynamic therapy (PDT) and topical diclofenac.[14] The current British Academy of Dermatologists (BAD) guidelines, mention that for Bowen's disease, excision may be a better option than all other modalities and that micrographic surgery may be considered for tissue sparing or for poorly defined or recurrent lesions. It also adds that cryotherapy, radiotherapy, PDT, laser and topical 5-FU are all fair options. All therapeutic options have failures and recurrence rates at least in the order of 5–10%, and no treatment modality appears to be superior for all clinical situations. Hence, a follow-up for possible recurrence at 6-12 months is recommended, although few authors recommend that gold standard for cure rate in skin cancers (as for other cancers) should be 5 year-point after treatment.[15] A more practical approach is to follow such patients for at least 1 year post-treatment to detect a recurrence.

Figure 1- A single irregular shaped erythematus plaques of size 9 × 4 cm on the anterior aspect of the right thigh which was covered with thick semi adherent yellowish crust.

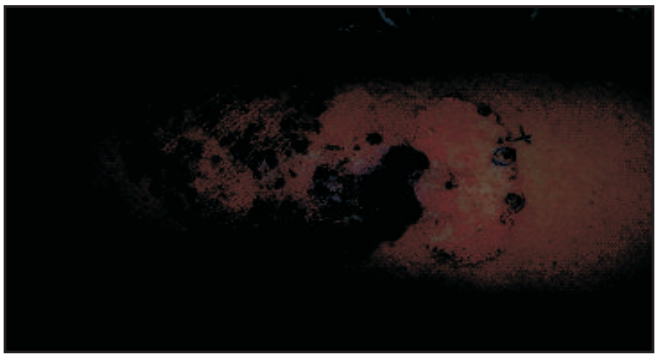

Figure 2A

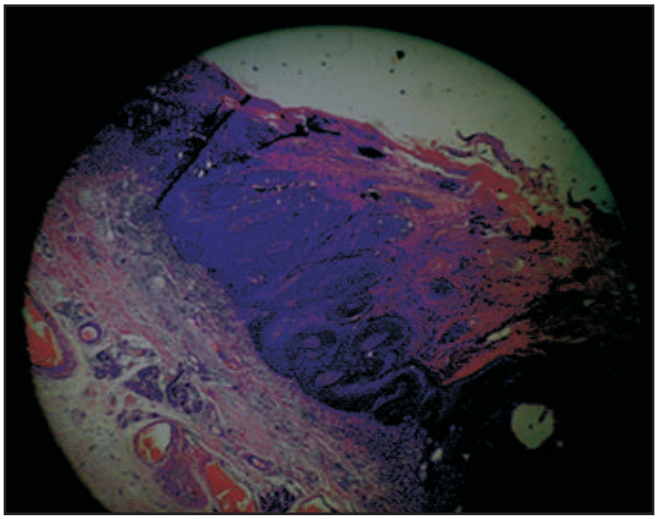

Figure 2B

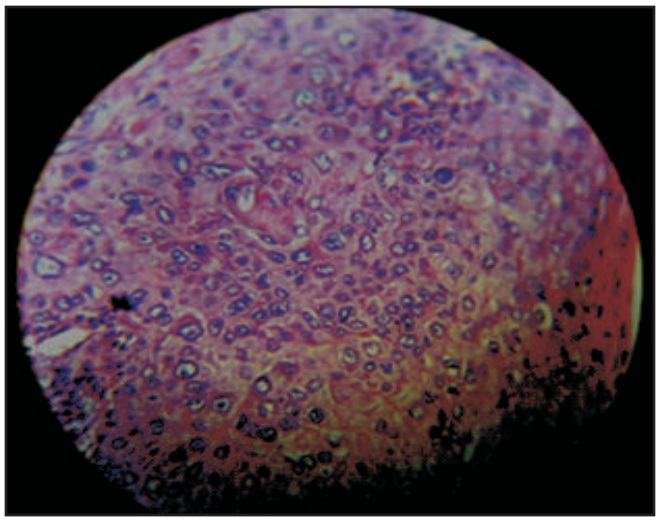

Figure 2A & 2B - Epidermal hyperkeratosis, irregular acanthosis with many dyskeratotic cells, mitotic figures and keratinocyte dysplasia and atypia. Dermis showed perivascular lympho-histiocytic infiltrate in upper part without any invasion.

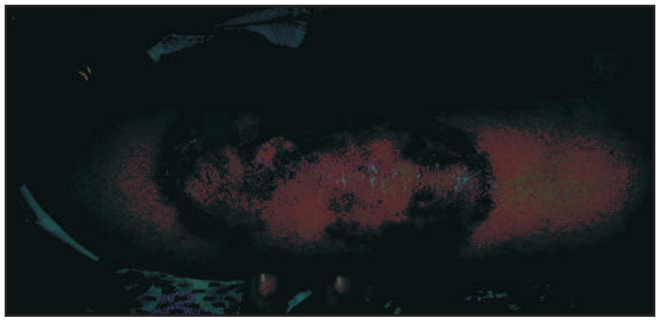

Figure 3- Few persistent papules and development of erosions

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Conflict of Interest – None

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CASE REPORT

Uncommon Association With A Common Syndrome : TSC

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ABSTRACT

Introduction: Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome of variable phenotype with development of multiple hamartomas. The classical triad being seizures, low intelligence and angiofibromas. Case: 21 year old male presented with facial angiofibromas since birth along with ash leaf macules, shagreen patches, Koenen tumors and fibrous plaque on the left cheek confirmed histologically. He had suprasternal angiofibromas , an uncommon site for their occurrence. He also had a hyperpigmented velvety plaque in right groin since birth which microscopically was consistent with linear epidermal nevus. Systemic findings included renal angiomyolipomas, simple renal cysts, history of seizures and mental retardation. A definite diagnosis of TSC was made according to criteria proposed by the US National Tuberous Sclerosis Alliance. Conclusion: In this case, apart from usual manifestations, the patient also had adenoma sebaceum at unusual site – suprasternal & biopsy proven verrucous epidermal nevus in groin. Till date such associations have not been widely reported in literature.

Keywords : Tuberous sclerosis complex, verrucous epidermal nevus, angiofibroma

Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome characterized by a widely variable phenotype and multiple hamartomas, especially in the brain, skin, retina, kidney, heart, and lung. Commonly mutated genes are TSC1 at 9q34 and TSC2 at 16p13.3. Also, 50% to 84% cases are sporadic as new mutations. The classic triad of TSC is seizures, mental retardation, and angiofibromas, which occurs in only 29% of patients.[1] Skin involvement is cardinal for suspecting the diagnosis.

Case

Twenty one year old male farmer presented to our OPD with complains of asymptomatic reddish lesions on face, skin colored lesions on trunk since birth, both of which slowly increased in size with age. He had developed single raised lesion on left side of his cheek at the age of 12 years which had been asymptomatic till date. There was history of epilepsy (records not available) but the patient had no convulsions even after discontinuation of medications since last five years. The patient was a drop out of mid-school owing to poor scholastic performance however, being capable of self-care, and carrying out basic activities of daily life. There was no history of visual disturbance, palpitations, syncope, chest pain, flank pain, hematuria. Neither the parents nor other siblings had any of the above complains or lesions.

General physical examination was within normal limits. Dermatological examination revealed multiple firm, discrete red brown papules extending from the nasolabial folds to malar areas, cheeks and also on the nose suggestive of facial angiofibromas.(Figure1&2) Similar lesions were present over the suprasternal area.(Figure 4) There was an irregular shaped plaque approximately 6x5 centimeters on left cheek slightly erythematous with nodular surface and firm consistency. This was considered to be fibrous plaque.[6][Figure3] There were irregularly thickened, slightly elevated skin coloured plaques on left shoulder, lumbosacral area and right flank suggestive of shagreen patches. (Figure 5) Few ovoid hypopigmented macules on the back, chest and abdomen suggestive of ash leaf macules.[Figure6] The finger and toe nails showed firm excrescenes emerging from the nail folds, more conspicuous in the left toenails-the Koenens tumors.(Figure 7&8) Other

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skin findings included multiple flat grayish black papules on the right inguinal area; of which some were follicular oriented. They appeared to have coalesced into a linear hyperpigmented plaque with rugosities and velvety thickening in groin and as they were present since birth, linear epidermal nevus was a plausible diagnosis.(Figure 9)

Thus the likely diagnosis of Tuberous sclerosis complex was made. This prompted for further investigations to look for systemic involvement. Ophthalmological examination revealed depigmented patches in the right retina suggestive of retinal phakomas and deficiency of limbal stem cells. Abdominal ultrasound showed multiple cysts of varying size in bilateral renal parenchyma indicating polycystic kidneys. There were ventricular premature beats on ECG but the echocardiography was normal. Chest X-ray was normal. CT (contrast) imaging of the thorax and abdomen revealed simple cysts as well as angiomyolipomas in the renal parenchyma.[5]

Plain and contrast MR imaging of the brain showed extensive ill defined hyperintensities in the cortical and subcortical areas. Ill defined nodular heterogenous signal intensities in bilateral subependymal regions of lateral ventricles. To sum up, MRI findings were suggestive of tuberous sclerosis in addition, there was bilateral temporal lobe hypoplasia and cerebellar atrophy.[7] Patient's scores on Binnet Kamath test and Solution Focused brief therapy were 44 and 49 respectively, indicating moderate mental retardation.

Local ultrasound of facial plaque reported multiple iso to hypoechoic nodules in dermis over left zygomatic area. Few nodules had cystic areas with internal echos but no vascularity. Dental evaluation was within normal limit.

Punch biopsies were sent from different skin lesions for histopathological examination. H&E stained slide from facial plaque had an unremarkable epidermis with dermis showing abundant collagenous stroma around mature pilosebaceous units; thus concluding it to be a fibrous plaque. (Figure 11&12) Microscopy of the groin plaque had a compact orthokeratosis in the stratum corneum, papillomatosis, irregular but marked acanthosis and mild perivascular inflammatory infiltrate in the superficial dermis consistent with linear verrucous epidermal nevus. (Figure 13 &14)

Based on the diagnostic criteria proposed by the US National Tuberous Sclerosis Alliance, the patient fulfilled more than two major features, thus definite diagnosis of tuberous sclerosis complex was reached.

Discussion

A definite diagnosis of TSC requires 2 major features or 1 major and 2 minor features.[2]

Major features:

1. Facial angiofibromas or forehead plaque
2. Nontraumatic ungual or periungual fibroma
3. Hypomelanotic macule (3 or more)
4. Shagreen patch (connective tissue nevus)
5. Multiple retinal nodular hamartomas
6. Cortical tuber
7. Subependymal nodule
8. Subependymal giant cell astrocytoma
9. Cardiac rhabdomyoma, single or multiple
10. Lymphangiomyomatosis
11. Renal angiomyolipoma

Minor features:

1. Multiple randomly distributed pits in dental enamel
2. Hamartomatous rectal polyps
3. Bone cysts
4. Cerebral white matter migration lines
5. Gingival fibromas
6. Nonrenal hamartoma
7. Retinal achromic patch'
8. Confetti' skin lesions
9. Multiple renal cysts.

Careful skin examination of patients is the easiest and most accessible method to establish a diagnosis. The most common skin lesions are ash-leaf spots occurring in more than 90% of patients.[2,3] Other cutaneous features include forehead plaques, shagreen patch and facial angiofibromas. Koenen fibromas develop in upto 50% of cases, with onset around puberty. Feet are more commonly involved than the hands.[4] The presence of periungual fibromas, as in facial angiofibromas, it is

nearly always pathognomonic for TSC. Neurologic manifestations are the leading cause of morbidity and mortality in TSC. Brain hamartomas often cause intractable seizures most commonly seen as infantile spasms.[1] Many patients suffer from mental retardation and autism. Angiomyolipoma is the most common renal lesion (up to 80%). Cardiovascular features are often the earliest systemic diagnostic finding. Retinal hamartomas causing no visual disturbance occur in 40% to 50% of patients.[1] Other findings include dental enamel pitting and radiographic abnormalities. The bones of the hand and feet may show cyst like areas. With the variable expression of TSC, it is often difficult to diagnose this entity. As in the case presented, all the pieces of the puzzle may not come together until later in life.[3] Follow-up testing after the diagnosis puts focus on treatment or prevention of problems.

Figure 1: Angiofibromas: discrete firm red-brown papules; centrofacial distribution

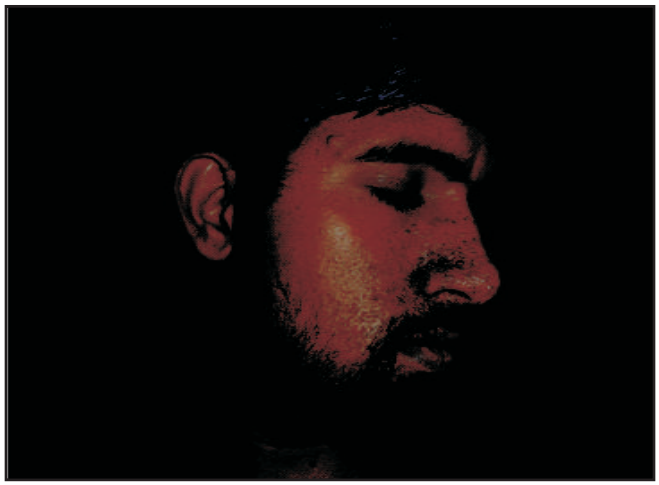

Figure 2: Angiofibromas

Figure 3: Fibrous plaque – left cheek

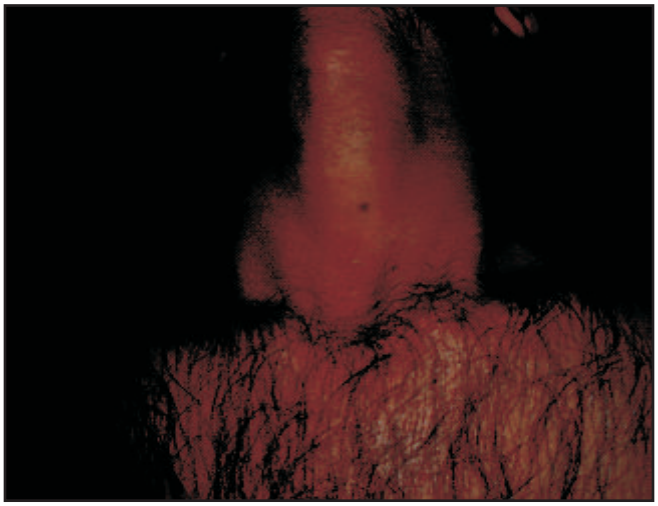

Figure 4: Angiofibromas – suprasternal location

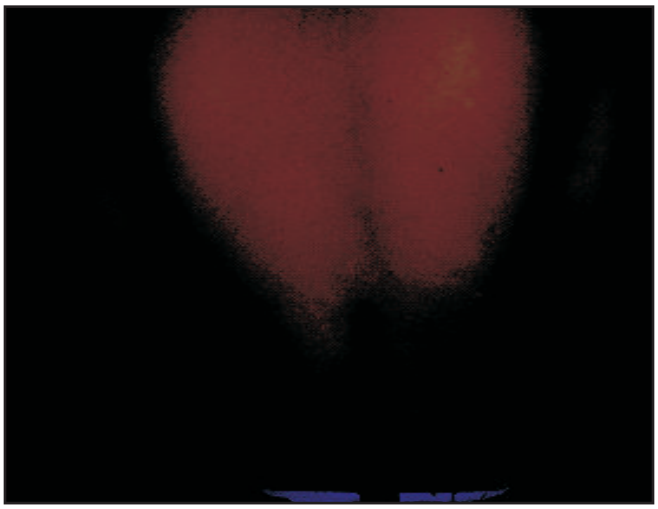

Figure 5: Shagreen patch – irregularly thickened slightly elevated skin colored plaques on sacral area

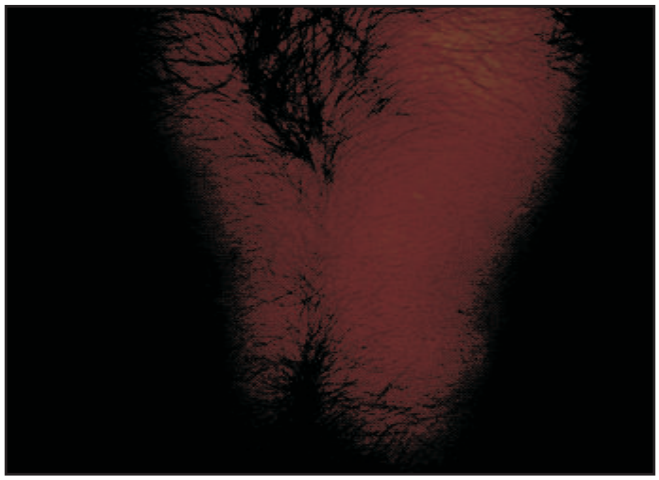

Figure 6: Ash leaf macules – hypopigmented macules on chest

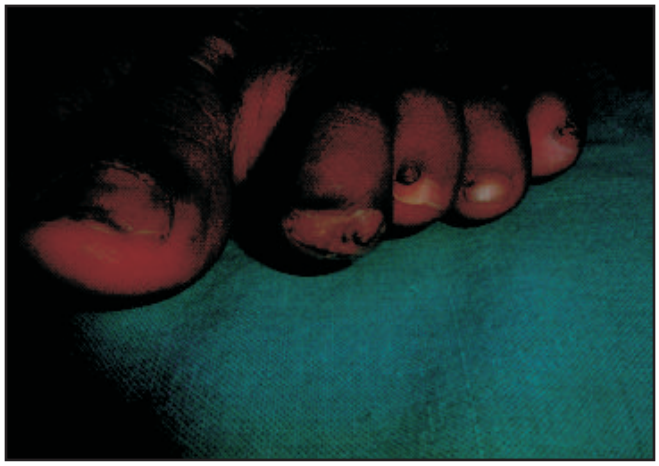

Figure 7: Koenen tumor over toe nails

Figure 8: Koenen tumor over finger nails

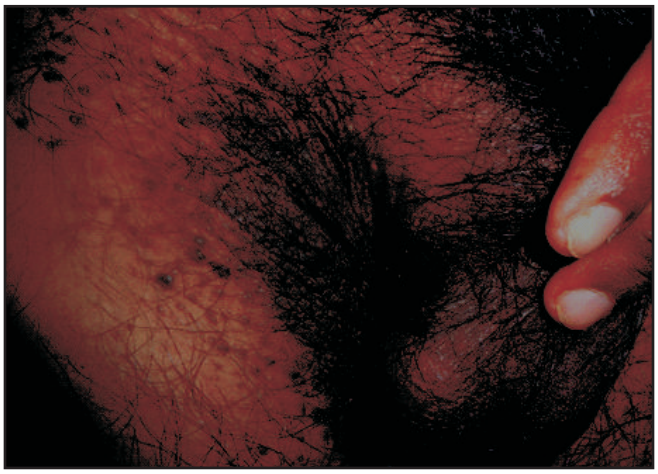

Figure 9: Linear verrucous epidermal nevus - linear hyperpigmented plaque in right inguinal region

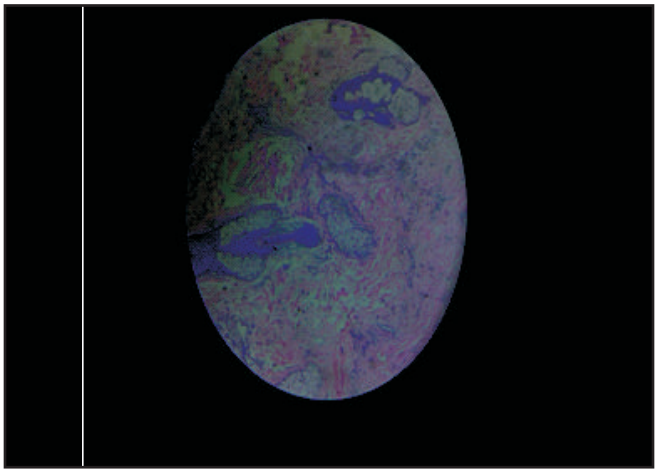

Figure 10 Fibrous plaque: abundant collagenous stroma around mature pilosebaceous unit (10X)

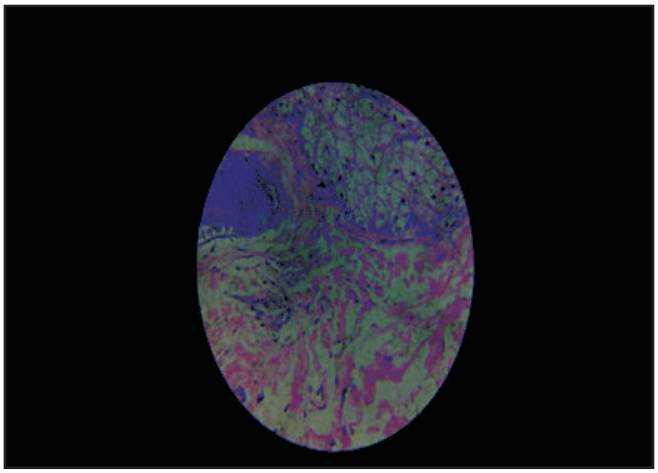

Figure 11 Fibrous plaque (40X)

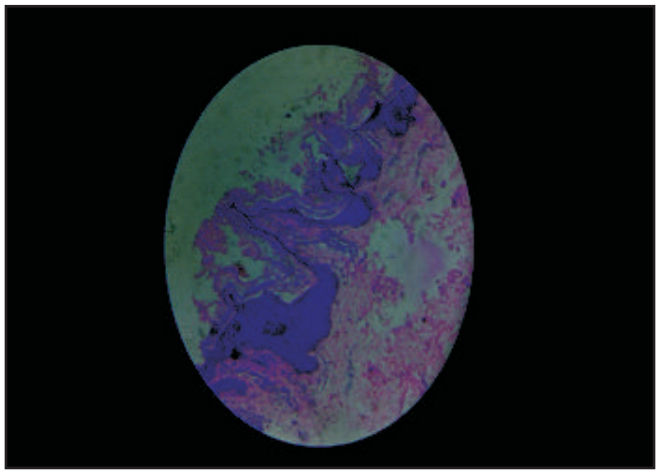

Figure 12: Verrucous epidermal nevus: orthokeratotic stratum corneum, irregular but marked acanthosis. Mild perivascular lymphocytic infiltrate. (10X)

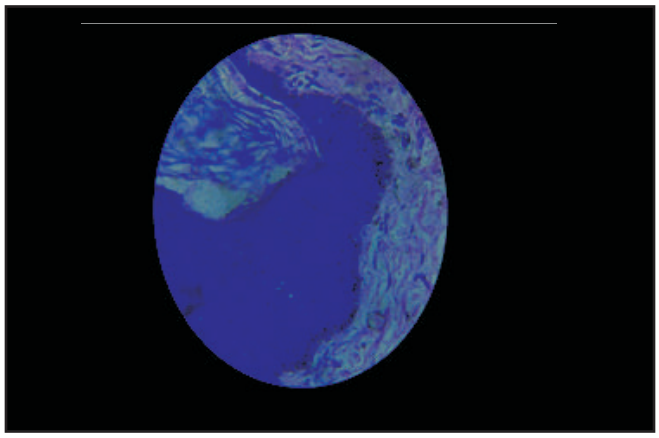

Figure 13 Verrucous epidermal nevus (40X)

Legends

Figure 1 & 2: Angiofibromas: discrete firm red-brown papules; centrofacial distribution

Figure 3: Fibrous plaque – left cheek

Figure 4: Angiofibromas – suprasternal location

Figure 5: Shagreen patch – irregularly thickened slightly elevated skin colored plaques on sacral area

Figure 6: Ash leaf macules – hypopigmented macules on chest

Figure 7 & 8: Koenen tumor over toe and finger nails

Figure 9: linear verrucous epidermal nevus - linear hyperpigmented plaque in right inguinal region

Figure 10 & 11: 10x & 40x magnification. Fibrous plaque: abundant collagenous stroma around mature pilosebaceous unit

Figure 12 & 13: 10x & 40x magnification. Verrucous epidermal nevus: orthokeratotic stratum corneum, irregular but marked acanthosis. Mild perivascular lymphocytic infiltrate.

Conclusion

TSC is a multisystem disorder with variable clinical manifestations. To decrease the morbidity from seizures, an early diagnosis of TSC is essential. As in our case, it can be associated with fibrous plaques and angiofibromas at atypical sites with uncommon association of linear epidermal nevus. Till date such associations have not been widely reported in literature.

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Conflict of interest: None declared

Acknowledgement: Department of Pathology, BJGMC, Pune.

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CASE REPORT

Spectrum Of Abscesses In Medical Ward

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ABSTRACT

Introduction: Abscess is a confined collection of pus in body pockets. It can be a surgical emergency as it may lead to frank septicemia and complicate the patient's condition warranting urgent attention and drainage. In medical wards, amoebic abscesses usually are common in diabetic or immunosuppressed patients. Concurrent management of localized infection is very important aspect in such cases admitted to medical wards.

Discussion : We present a collective illustration of seven cases with atypical presentation of the abscesses. All the cases were admitted in medicine ward with different systemic involvement and with different causative organisms. The cases belonged to an age group of 25 -50 years, with M: F ratio being 1:1. There were two cases of liver abscesses, one fungal and one bacterial. Two cases of recurrent cerebral abscesses were admitted. Both of which presented with severe headache, one was diagnosed to have bacterial abscess on drainage, while the other, who was a known case of Cyanotic heart disease turned out to be a recurrence of CNS Tuberculoma. Another case of breast lump diagnosed as neoplastic breast mass on USG which revealed caseation on excision biopsy. A diabetic male admitted with fixed flexion deformity of the hip joint with femoral entrapment neuropathy had a large psoas abscess that was treated with AKT with resultant neurological improvement. A rare presentation of splenic abscess was documented in presence of coexisting urosepsis. All the cases were managed with appropriate antimicrobial therapy and source reduction either surgically or with percutaneous catheter drainage. Out of the seven only one patient was immunocompromised and one had recurrence with different system involvement.

Conclusion : This case series highlights the importance of clinical judgement in cases with atypical presentation. In such cases, early microbiological diagnosis with resultant source driven antimicrobial therapy and eradication of the focus; great outcomes can be achieved with lesser systemic complications.

Case Series

We present a case series of 7 abscesses that were admitted to the medicine wards in a span of 15 months. The cases had multiple risk factors which were different in each case. All the cases were different from one another in their causative organisms as well as their clinical presentations. The cases had an average hospital stay of 30 days with mortality rate of 11%. All the patients required drainage of the collected pus and antimicrobial therapy.

Case 1:

50-year-old male, security guard by occupation known case of ICS (latest CD4 -23) for 10 years not on regular anti-retroviral therapy was admitted with abdominal pain and 4-5 episodes of bloody vomiting with fever of a week duration. He also had a history of chronic alcohol intake with frequent history of hospitalization for decompensated alcoholic liver disease and portal hypertension.

He was averagely built with gross distension of abdomen. He was admitted in shock with systolic BP of 70mmHg and pulse rate was 110bpm. Significant pallor and icterus was present. Clubbing of grade III was noted. Was Afebrile on admission. Oral candidiasis was also

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present. Per abdomen examination revealed a grossly distended abdomen with superficial dilated veins and prominent umbilical hernia. No hepatosplenomegaly was appreciable.He was hemodynamically stabilized with multiple transfusions and pressor support. Upper GI scopy was done for hematemesis which revealed extensive esophageal candidiasis with grade III varices for which banding was done.

Lab parameters showed anemia and leukocytosis (WBC – 24,000/cmm) indicative of active sepsis with hyperbilirubinemia. Blood culture and fungal culture of blood did not grow any organism. Ultrasonography revealed Multiple hypoechoic lesions spread throughout liver with largest in the VIth segment of the right lobe; which were initially thought to be of neoplastic etiology. He also was found to have newly diagnosed chronic hepatitis B and HBV Viral Load was >450000 with negative HbeAg. Serum alpha-fetoprotein was elevated up to 400 IU/ml.

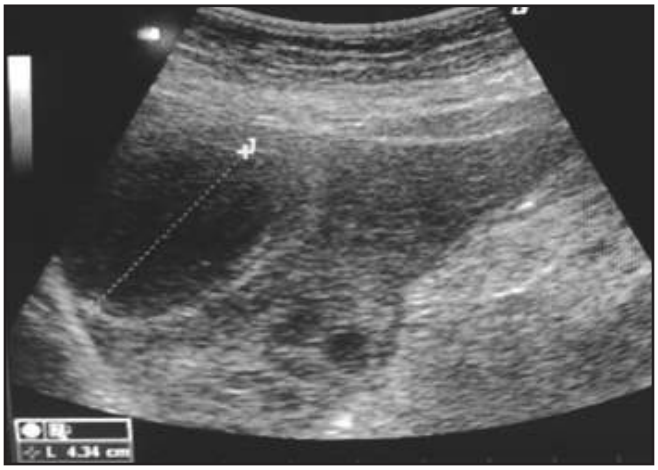
CT scan of the abdomen was performed which showed multiple heterogenous abscesses. Abscess was drained, around 700ml of turbid pus was collected which showed hyphae on KOH mount and grew Candida Albicans on SDA. Patient was treated with IV Amphotericin B and ART according to creatinine clearance, with improvement in liver enzymes and general condition. However, we lost him to a massive hematemesis secondary to portal hypertension.

Multiple liver abscesses in the settings of immunocompromised states point to tubercular or fungal etiology. However, candidal liver abscess in absence of invasive candidiasis is quite rare.

Case 2:

A 52-year-old diabetic female and with no other morbid medical history admitted with fever, anorexia and jaundice for 1 week, with edema on bilateral lower limbs and with recent onset behavioral changes. On admission she was febrile and anasarca was present with marked icterus. She was hemodynamically stable. On admission she was disoriented with increased sleepiness. She also had history of heavy alcohol intake in the past. Blood investigations showed severe hypoproteinemia (Alb-1.8) and hyperbilirubinemia with AKI. WBC count was 22,000 on admission. She was started on supportive therapy with IV fluids and antibiotics. She also had recurrent hypoglycemia in the initial few days of admission, indicating severe liver dysfunction. Ultrasonography of the abdomen showed multiple hypoechoic lesions in the liver with thick walled content which were non-tapable initially. After 2 weeks of antibiotic therapy and IV Albumin replacement, she underwent USG guided drainage of the localized collection with pigtail insertion. The aspirated contents grew E. coli on aerobic culture media, after culture directed IV antibiotic therapy, she showed significant improvement clinically as well as in lab parameters. She was also given IV Albumin, and was discharged after 4 weeks of hospitalization. This was a rare presentation of multiple pyogenic liver abscesses with severe hypoproteinemia, which was successfully treated with source reduction and Albumin replacement.

Fig 1.1 (Ultrasound of liver abscess)

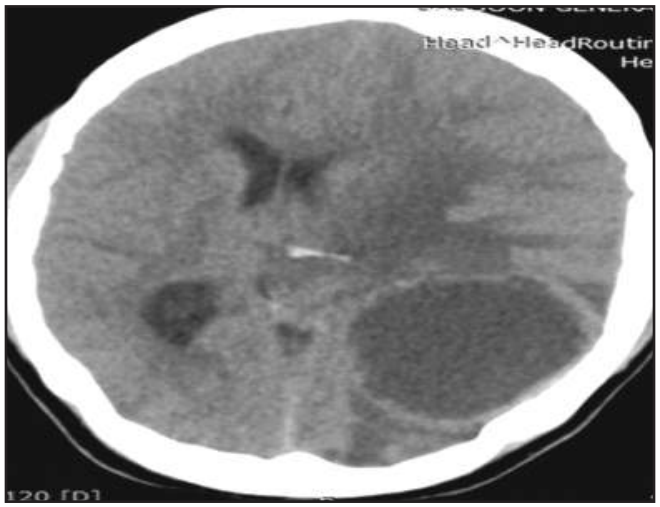


Case 3:

A 28-year-old married female with no prior morbid medical illness admitted to ED with severe headache and vomiting for one week. On admission she was vitally stable with slight gait impairment and complained of intense headache. She was grossly oriented without any cranial nerve involved. There was no focal neurological deficit. There were no other systemic findings. Findus examination revealed mild blurring of disc margins. She had history of being treated with anti-tubercular therapy for multiple tubercular breast abscesses 3 years back. CT brain with contrast showed a large abscess with thick walled cavity.. She underwent drainage of the brain abscess with burr hole technique. Microbiological studies of the drained pus grew Staphylococcus Aureus. She was started on appropriate culture directed antibiotic therapy. She started showing signs of

improvement with uneventful post-operative recovery. She was discharged without any residual neuro-deficit after a hospital stay of 40 days

Fig 1.2 (CT Brain showing a thick walled cavity with pus)



Case 4:

A 24-year-old female known case of congenital cyanotic heart disease, was admitted with complaints of severe throbbing headache that was persistent throughout the day without any positional variation for the past 4 months with increasing severity and with altered sensorium and multiple episodes of vomiting for the past 4 to 5 days. On admission she was hemodynamically stable although complained of severe throbbing headache and required support while walking. She had history of being treated with anti-tubercular therapy under DOTS for CNS tuberculoma in six years back. Fundus examination revealed mild disc margin blurring. CT scan of the brain was performed with IV contrast which showed a large intracerebral brain abscess with many other small ring enhancing lesions.She underwent surgical drainage of the abscess with burr hole technique. 100 ml of fluid was drained. Microbiological and Gene Xpert testing of the sample was performed and Mycobacterium Tuberculosis was detected. She was started on category II AKT for relapse of her CNS Tuberculosis. Sensorium improved markedly after only one week of anti-tubercular drugs and she was discharged after an uneventful stay of 15 days. There was no residual neuro-deficit documented at the time of the discharge.

Case 5:

52 year old male known case of Diabetes Mellitus and Hypertension on irregular treatment was admitted with complaints of pain in the right hip with inability to stand or squat since 15 days. It was progressively increasing requiring him support while walking. He also complained of numbness over the anterolateral area of right thigh. On examination, power was decreased (3/5) with decreased sensation on right thigh USG. Knee Reflex was depressed and ankle reflex present. Nerve Conduction Velocity study was performed, suggestive of acute axonal sensorimotor femoral neuropathy. Ultrasonography was performed to screen possible causes of nerve entrapment. There was bulky right psoas with heterogenous echogenicity compressing the neurovascular bundle and inguinal ligament near the femoral triangle.The abscess was drained (700ml) with percutaneous pigtail drainage. Gram staining and AFB did not show any micro-organisms; although anti-tubercular therapy was started with the clinical suspicion of extra pulmonary Tuberculosis. He improved dramatically after AKT and regained power.

Case 6:

30 year old female known case of chronic kidney disease since three years, secondary to post-partum cortical necrosis, was admitted for initiation of renal replacement therapy with uremia. There was no other major medical or surgical history. She incidentally noted a painless, mobile and solitary lump in the left breast around 1 week back. There was no history of breast mass or tuberculosis in other family members. USG of the left breast revealed a poorly defined mass lesion with septations suggestive of possible neoplastic etiology. Fine needle aspiration cytology of the lesion showed epithelial cells with fibrous stroma without any confirmatory evidence of neoplasia or infectivity. Hence excision biopsy was planned. It revealed caseation, Langhans giant cells with epithelioid cells and inflammatory stroma. There was no other tubercular focus in the body. She was started on anti-tubercular therapy according to eGFR and was discharged on maintenance hemodialysis after RNTCP registration. This case supports the importance of tissue diagnosis in such atypical cases of tubercular mastitis.

Case 7:

A 20-year-old young female without any prior morbid

medical history was admitted with high grade fever with chills of 7-8 days duration. She also complained of burning micturition. She was febrile on admission with tachycardia of 110 bpm. On examination she had tender abdomen with marked guarding in left hypochondrium. She had a WBC count of 18700/cmm with multiple pus cells in the urine. USG abdomen revealed a large spleen with splenic abscess. Blood culture taken immediately on the day of admission before IV antibiotics grew Salmonella Typhi. Whereas urine culture grew E. coli. She was started with class III cephalosporins and supportive therapy with control of temperature spikes, she showed gradual improvement in her clinical condition. This was a very rare case of Salmonella splenic abscess that was successfully managed with IV antibiotics.

Discussion

All the seven cases were admitted over a period of one year 2016-17 with different clinical presentations. Microbiological diagnosis was established in 6 out of the seven cases which prompted targeted antimicrobial therapy. This case series underlines the undebated importance of tissue diagnosis in medical microbiology which helps us to plan targeted antimicrobial therapy.

Multiple abscesses usually denote fungal or pyogenic etiology. Most common cause of liver abscess in immunocompromised patients is usually a fungal or tubercular. Candida liver abscess is a very rare disease and most of the reported cases have been diagnosed in patients with hematologic malignancies during periods of neutropenia resolution.[1] In a review by Thaler et al, only 8 of 73 patients with candida liver abscess had an underlying disease other than a malignancy. There have been mentioned various approaches for management of fungal liver abscess, Amphotericin in its either form is the drug of choice.[2] Low CD4 count, Portal pyemia, Alcoholic liver disease, hypoalbuminemia and multiple lesions pose hazard for patient outcome. Occurrence of pyogenic liver abscesses have been documented in association with severe hypoproteinemia,[3] especially in alcoholic and diabetic patients.[4]

In a retrospective analysis of 72 patients with pyogenic liver abscesses by Chen SC et al,[3] the overall mortality rate was 26.4%, majority involved right lobe of the liver and were solitary. The most common concomitant diseases were diabetes mellitus and underlying malignancy. Multivariate analysis revealed that underlying malignancy ($p = 0.034$), profound hypoalbuminemia (<2.5 g/dl) ($p = 0.008$), and multiple abscesses ($p = 0.004$) were the most significantly prognostic factors for mortality. Local source reduction with surgical drainage and Protein supplement in the form of fresh frozen plasma or IV Albumin supplement is absolutely indicated.

In a study of 125 patients with pyogenic brain abscesses, the incidence of multi-loculated brain abscess was 20%. In these 25 patients, hematogenous spread from a remote infectious focus was the most common cause of infection. Headache and hemiparesis were the most common symptoms in patients with multiloculated abscess. Viridans streptococci were the most commonly isolated pathogens.[5] Tubercular mastitis is rarely reported worldwide.[6] Tuberculous mastitis usually affects women from the Indian sub-continent and Africa. It often mimics breast carcinoma and pyogenic breast abscess clinically and radiologically; may both co-exist. Routine laboratory investigations are not helpful in its diagnosis. In all the reported cases, the diagnosis of tubercular involvement was made on excision biopsy. Fine needle aspiration usually fails to demonstrate the extensive caseation or acid fast bacilli situated deeper in the lesion. Hence, spectrum of abscesses in medical ward deserves special mention in view of its complications and how easily they can be managed with timely microbiological diagnosis and good clinical judgement.

Acknowledgments

1. Department of Microbiology, Pathology and Radio-Diagnosis, B.J. Govt Medical College and Sassoon General Hospitals, Pune.

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The Research Society

B. J. Medical College And Sassoon General Hospitals, Pune - 411 001

ANNUAL REPORT

(April 2016 To March 2017)

Dear Life Members,

I. GOVERNING COUNCIL:

The office-bearers of the current Governing Council (2016-2017) were :

President	Dr. Dilip Pande
Vice-President	Dr. S.A.Sangle
Hon. Secretary	Dr. P.M. Bhalerao
Hon. Joint secretary	Dr. P.V. Ranbale
Hon. Treasurer	Dr. Sarfaraj Pathan

Ex-officio members

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Dr. Medha Khandekar

Dr. Amol Shinde

Dr. Vasudha Belaonkar

Dr. Savita Kamble

Dr. Sangeeta Gawali

Medical Journal Of Western India:

Vol :- 45, No 2, August 2017

Editorial :- Plagiarism: Time for introspection ; By Dr Neela Aundhakar

Review articles :- 2

Original articles :- 6

Case reports :- 9

Annual Conference :

1) The 43rd Annual Conference of Research Society BJMC and SGH, Pune was held on 21st ,22nd,23rd Feb 2016. It was organized by Department of Surgery under able guidance of Dr Sudhir B. Dube. It was attended by delegates,staff and students. The event was inaugurated by Dr Hardikar, Orthopedic Surgeon and Director of Hardikar Hospital and Mr Prakashji Chhabriya , Finolex Co. Pvt Ltd.

2) The annual conference was attended by 1504 delegates, who where thrilled by the academic feast, entertainment programmes and gala dinner

3) Total number of oral paper were 70 ; 49 posters and 38 interesting cases were presented

4) Dr B.B.Dixit Oration was by Dr Adarsh Chaudhari, on : 25 years in Surgery- what I learnt and what I want to learn.

5) Oral paper and poster presentation was done on day 1 of conference

Day 2 :- Dr B.B. Dixit Oration was followed by guest lecturers by Dr Shivani Gour, Dr S B Patankar,Dr Solav , Dr Vhora, Dr Parasnis, Dr C Santosh & Dr Alurkar

Day 3 :- Dr M.J.Joshi Guest Lecturer was delivered by Dr G.V. Rao , on Impact of science fiction on GI Surgery and Endoscopy Symposium on medical education challenges and frontiers were conducted by Dr A V Jamkar, Dr Ajay Kumar, Dr Sharad Jaitly.

Shri Anna Hazare, Dr Vishwanath Karad, Dr Arun Gadre shared their views in Symposium on Moral education and social responsibilities of doctor

The guest lectures were delivered by Dr Harish Shetty, Dr Ajaykumar, Dr akshay Kumarswamy.

Conference concluded after Valedictory function.

5. Prizes won :

1) Suchitan trophy :- Best paper of conference.

Winner :- Dr Deepali Kate.

2) Sphurti Trophy :- Best paper in Anaesthesia

Winner :- Dr Pallavi Sharma

3) Harshvardhan Prize :- Best paper in UG &PG Category

Winner :- Dr Ajit Avhad

4) Dr A. R. Bhadkamkar Award:- Best Paper in Anatomy

Winner :- Dr Deepali Kate

5) Dr Mrs V. A. Bhadkamkar Award :-Best paper in Pharmacology

Winner :- Dr Smita Wankhede

6) Dr Jejurikar Award :- Best Paper in Surgery

Winner :- Dr Astha Sarda.

7) Dr S. J. Kinnikar Award :- Best paper in medicine by PG student

Winner :- Dr Ajit Avhad

8) Dr Ajit Gokhale Prize :- Best Poster of Conference

Winner :- Dr Seema Kumari

9) Dr D. J. Patil Award :- Best Oral Paper in Interesting Cases.

Winner :- Dr Sahil Moriwala

10) Dr M. B. Gharpure Award :- Best oral paper in Dermatology

Winner :- Dr Shweta Threwal

11) Dr K.P.Niphadkar prize.:- best paper in immunology, pathology Microbiology by PG

Winner :- Dr Nicolas Dcunha

12) Dr Roentgen Teacher Trophy :- Best paper in Radiology

Winner :- Dr Monica Patil

13)Best oral paper in PG Category:- 1st prize

Winner :- Dr Ajit Avhad

14) Best oral paper in PG category :- 2nd prize

Winner :- Dr Pranav Satav

15) Best oral paper in PG category :- 3rd prize

Winner :- Dr Nicholas Dcunha

16) Best oral paper Lecturer Category (<5yrs) 1st prize

Winner :- Dr Ahmed Mariyam

17) Best oral paper Lecturer Category(>5 yrs) 2nd prize

Winner :- Dr Smita Panse

18) Best oral paper in AP Category :-

Winner :- Dr Deepali Kate

19) Best Poster in AP Category :-

Winner :- Hasina A. Sayyed

20) Interesting Case Presentation :- 1St prize

Winner :- Dr Sahil Moriwal

21) Interesting Case Presentation:- 2nd Prize

Winner :- Dr Ankur Karanjkar

22) Interesting Case Presentation :- 3rd prize

Winner:- Dr Rahul Dawre

23) BestPosterPostgraduate category:- 1st Prize

Winner :- Dr Seema Kumari

24) BestPosterPostgraduate category:- 2nd Prize

Winner :- Dr Rupali Bandagi

25)Best PosterPostgraduate Category :- 3rd Prize

Winner :- Dr Vaishali Gokhale

26) 1970 batch UG oral Paper 1st prize

Winner :- Shamali Nehete

27) 1970 batch UG oral paper 2nd prize

Winner :- Shaunak Lohite

28) Best Oral Paper Outside Institute

Winner :- Dr Smita Dhane

29) Best Poster Outside Institute

Winner :- Dr Prashant Sakhavalkar

30) Best Oral paper UG

Winner :- Shamali Nehete

Life Members :- 70 new members were added

6. Auditors

Deekay and Company Pune was continued as auditor for this period.

ACKNOWLEDGMENTS

The honorary secretary is thankful to the members of the governing council, past office bearers, Editor-in-chief, and the members of the organising comittee of the annual conference for their valuable help in fullfilling the objectives of the trust.

Hon. Secretary

Research Society

B.J.M.C. & S.G.Hs, Pune 411 001.

Correction in sequence of authors due to printing mistake in August 2017 issue of MJWI.
An Extremely Rare Case Of Aneurysmal Bone Cyst of Skull Base
Syed Moinullah, Syed Azharuddin, Bikash Parida, Divya Bhattacharjya

Medical Journal of Western India

Instructions To The Contributors

Medical Journal of Western India is a peer reviewed indexed with Index copernicus. It is published biannually. It accepts original articles, review articles related to the different disciplines, case reports and short communications in the field of clinical practice and medical education. Case reports of only unique and rare character are accepted. Papers are published in English. Submitted papers are accepted after peer review. To achieve wider dissemination of knowledge and information, the published articles can be accessed online at www.bjmcpune.org/medicine.htm.

Submission of manuscript : Authors should submit electronic version (Microsoft word doc) of the manuscript to the editor via e-mail on medicaljournalofbjmc@gmail.com. Manuscripts should be in Times New Roman with font size of 12 points along with two hard copies. These articles should contain a covering letter, title page and abstract with key words. They should be written under appropriate sub-headings.

1. Undertaking : The manuscript must be submitted with a statement, signed by all the authors, regarding the originality and authorship. For original article a copy of ethics committee approval should be submitted.

2. Covering Letter : It should include name, address, contact details including e-mails and mobile number of the corresponding author.

3. Title page : It should include the title and the names of authors. Surname of authors are to be followed by initials and affiliations. **Title** should be informative, specific and short. The number of authors should not exceed 2 for review article 4 for case report and 6 for original article.

4. Main article : The main article should be drafted as a single microsoft word document elaborating following headings.

a) Abstract and key words : Abstract should not exceed 250 words for original articles and 150 words for case report.

For original article, the abstract must be in a structured form (Objectives, Methods, Results and Conclusion) and explain briefly what was intended, done, observed and concluded. Case report should have sections as: Abstract, Introduction, Case Presentation and Discussion.

b) Key words : Should not exceed 5- 6 words.

c) Manuscript : Manuscript should be typewritten, with wide margin on an A-4 size paper. It should be of 3000-4000 words for review article, 1500 to 2000 for original article and 750 to 1000 for case report.

d) Tables/Figures / Graphs.

i) The tables should appear in the text itself and should be numbered in Roman numbers (Table. I, II etc.)

ii) Should be limited to the essential (preferably not exceeding four).

iii) For figures: should be referred to as figures and numbered in Arabic numerals (E.g. Figure 1, 2)

e) Photographs:

i) The photographs should be of high definition type with legends. Maximum 4 photographs for original article,2 for case report.

ii) Coloured photographs will be charged extra as per the applicable rates (To be paid by D.D or Cheque to the Treasurer, Research Society, BJMC Pune).

f) Acknowledgment : Acknowledge only those who have contributed to the scientific content or provided technical support. Sources of financial support if any, should be reported. Conflict of interest should be mentioned.

g) References:

i) The list of references should be in the Vancouver style.

ii) References should be cited in the text in Arabic numbers. E.g Our observations are similar to those of Dowling et al.1.

iii) Maximum number of references: for review articles-40, original articles-20, case reports-06, short communications- 10

Note : 1.Accuracy of the references cited is the sole responsibility of the author/authors.

2. Views expressed by the authors do not necessarily reflect those of the Research society.