Rs.10

JIMA

Volume 64 (RNI) ◆ Number 11 ◆ NOVEMBER 2020 ◆ KOLKATA

JOURNAL *Of the* INDIAN MEDICAL ASSOCIATION

Official Publication of the Indian Medical Association

Indexed in INDEX COPERNICUS INTERNATIONAL Index Medicus

Volume 118 (JIMA) ♦ Number 11 ♦ November 2020 ♦ KOLKATA

Dr ©

Largest Circulated Medical Journal in India

ISSN 0019-5847

91 ST YEAR OF PUBLICATION

Visit us at https: // onlinejima.com

IMA National President Dr. Rajan Sharma being honoured by Commissioner Delhi Police Shri S N Shrivastava for Smoothly and Successfully running CORONA Helpline for Delhi Police

Dr Rajan Sharma
National President,
IMA

Dr R V Asokan
Honorary Secretary
General, IMA

Prof (Dr) Jyotirmoy Pal
Honorary Editor,
JIMA

Dr Sanjoy Banerjee
Honorary Secretary,
JIMA

JOURNAL of the INDIAN MEDICAL ASSOCIATION

Volume 118 (JIMA) ■ Number 11 ■ November 2020 ■ KOLKATA ■ ISSN 0019-5847

Contents

JOURNAL OF THE INDIAN MEDICAL ASSOCIATION

Editorial

Medical Research in India – Past, Present & Future

Prof. (Dr.) Jyotirmoy Pal
MD, FRCP, FRCP, FICP, FACP, WHO Fellow, Hony. Editor, JIMA

Great Poet Sukumar Roy in his poetry "Vigyansikhsa" specially written for children depicted invention of instrument to understand normal human physiology and pathology. Four inevitable incidences in life cycle – Janma-Mrtyu- Jara-Vyadhi. Our ancestors tried to find out way how to get rid of these clutches. Philosophers got pathway through Meditation, sacrifice , Where Science by analyzing natural consequences and inventing methods to overcome the clutches. So from the birth of Adam and Eve there was need and inquisitive human mind tried to get a solution. So necessity was mother of invention.

"Our Need will be the Real Creator"
— Plato's Republic 375 BC

PREHISTORIC MEDICINE :

Illness or disease were integral part of life even in Prehistoric period. In the absence of an obvious explanation, illness was thought a result of anger of God, the invasion of the body by evil spirits or the influence of stars and planets. Medicine practised by appeasing God through prayers and rituals and sacrifices, driving out evil spirits from the human body.

It is thus obvious that medicine in the prehistoric era (5000BC) was intermingled with superstition, religion, magic and witchcraft.

ANCIENT INDIAN MEDICINE :

India, with its rich cultural heritage, had been in the forefront in contributing the medical science of World. Practice and research in Indian Medicine can be traced back to Vedic age (5000 BC). Medical Practice was placed so high, Practitioner were placed in same height as God. Ashwinikumars, Dhanvantari were given a divine status.

One of the first Indian text dealing with medical practice was Atharva Veda which described Ayurveda. Indian medicine was synonymous with Ayurveda means "The Science of Life"(ayur, which means life, and veda, knowledge). Ayurveda was based on knowledge on role of different herbs and metals in healing process. Atreya Samhita is the oldest medical book in the World. Atreya was the son of Rishi Atri. Atri was the son of god Brahma. Rishi Atri was Acharya (Teacher) of Ayurveda.

It is believed that the Vaidyas received their training of Ayurveda during meditation which were later transcribed into book form.

Maharshi Atreya is acknowledged as the first great Indian Physician and Teacher. Atreya revolutionized the medical system of Ayurveda into the system we have today.

He held formal teachings with his students and established Code of Medical Ethics in India (150 years before Hippocratic oath). Two great physicians in ancient India were Susruta and Charaka.

Susruta (600 BC) in his book Susrutasanghita stressed more on curative medicine specially on surgery. Sushruta, was one of the first physician to study human anatomy, described in details about various anatomical structures in his compendium. Also Shashtrakarma, the art of surgery, was recognized as an important part of therapy in this compendium. Susruta was the first surgeon to perform rhinoplasty and ear lobe construction.

Susruta Samhita was re-edited by Chakrapani in the 11th Century.

Charaka written Charaka Samhita in the second century (200AD).- Charaka Samhita described Anatomy and Physiology and pathology. So focus shifted from natural forces as causation of diseases to external agents as diet, seasons, lifestyle etc. Charaka described more on preventive aspects than curative aspects. Charaka (200AD), the most popular name in Ayurveda medicine was the Court Physician to the Buddhist king Kaniska during Buddhist time.

The Golden Age of Indian Medicine was between 800BC to 600AD.Charaka and Susruta Samhita were translated in Arabic by the order of Haran al-Rashid (786-806 AD) the Khalif of Bagdad. In Arthasastra of Kautilya there was a mention of Postmortem. Learned men from different countries such as China, Tibet, Afganisthan, the Greeks, Romans, Egyptians, Persians came to the Indian Ayurvedic Schools to learn about this World Medicine.This Indian Ayurvedic System became popular in Europe and helped to form the foundation of the European tradition of medicine. Ayurveda grew tremendously during Buddhist Kings like King Ashoka (226 BC), who patronized Ayurveda as State Medicine and established Schools of Medicine and Hospitals. Fa-HIEN (399-414 AD) Chinees Buddhist traveller in his book described rich heritage of Ayurveda in Patliputra during Gupta Dynasty.

The Indian materia medica was extensive and consisted mainly of vegetable drugs, all of which were from indigenous plants. Charaka knew 500 medicinal plants, and Sushruta knew 760. But animal remedies (such as the milk of various animals, bones, gallstones) and minerals (sulfur, arsenic, lead, copper sulfate, gold) were also employed. The physicians collected and prepared their own drugs. Among those that eventually appeared in Western pharmacopoeias were cardamom and cinnamon.

But in Hindu Dynasty due to the doctrine of "Ahinsa" (non-violence) Indian Surgery suffered a setback.

Astasthanapariksa :

In South India there appeared an amalgamation of the tradtions – the Brahmin tradition of Ayurveda, rasa tradition (said to be revealed by Siva and described in Rasarnava) and the third Siddha tradition revealed by Agastya. "The examination of the eight places" appears to be the result of this confluence. Pancalaksanani-dana (diagnosis based on five manifestations) gradually gave place to astasthanaparkisa. Marcopolo Italian Traveller described rich heritage of practice of medicine and herbal treatment in Souther states particularly in Kerela.

Medieval Period :

With the advent of Muslims in India, Hindu Medicine eroded due to the lack of State help and support by the rulers. Firoz shah Tughluq (1388) patronized Unani system of medicine in India. In this system of medicine, any external factor if introduced in body encountered by internal forces within body which is responsible to maintain health, the failing of which may lead to derangement of the normal equilibrium that is disease. This concept brought the idea of immune system of body. But science failed to delink itself from religion and mysticism during mediavel period . Real darkness prevailed in India in terms of scientific advancement.

Advent of Europeans :

In the 16th century, it was the Portuguese who first introduced Western medicine into India. It got momentum with arrival of British merchants. East India company gradually established its grip over India both politically and in Trade. They had little faith on Traditional Indian Medicine. In 1775, hospital boards which comprised the Surgeon General and Physician General were formed. These were essentially constituted by staff of the Commander-in-Chief of the British Indian Army in each presidency. British people was struck by different tropical diseases. As compulsion they established first medical school in 1822 ,followed by First Medical College in Calcutta – Calcutta Medical College in 1835 by Lord William Bentink. Next year Madras Medical College was established. Gradually more Medical Colleges established in different part of Country like Dhaka, Lahore etc. Attempts at planned medical research may however, be said to date back to 1894 when the 'Indian Medical Congress' submitted resolutions to the Government urging the establishment and endowment of research institute. End of nineteenth century was notable for repeated epidemics in different parts of

country. Facing repeated occurrence of certain epidemics in the country, British Govt established central laboratories to investigate epidemics. In 1884, the foundation stone of India's first medical laboratory was laid down in Kasauli near Shimla and followed by Plague Research Laboratory (Bombay Bacteriological Laboratory)Pasteur Institutes. In 1900 for rabies. Indian Research Fund Association was established in 1911 to further prosecution of research and propagation of knowledge and experimental measures generally in connection with the causation, mode of spread and prevention of communicable diseases and to fund and support research activities in other areas as well. IRFA done commandable work on Malaria, Kalaazar, Plague, nutritional diseases. Two more institutes was given armament in combating infectious diseases. In 1914 School of Tropical Medicine for research in Tropical Diseases and in 1932 All India Institute of Hygiene and Public Health with help of Rockefeller Foundation for training and research in Public health. But unfortunately all these institutes were dominated by imperial people. To ensure self sufficiency (Swaraj) group of Proud Indians like Dr Radha Govinda Kar, Dr B C Roy etc established first nongovernment college R G Kar Medical College in Kolkata in 1916 for medical education and research in Colonial era.

RESEARCH IN COLONIAL INDIA :

In British period Medical research was chiefly confined to Tropical diseases. Few notable advents were work on Plague, Malaria, Cholera.

Plague :

There are reports of various plague outbreaks in India - 1812 outbreak in Kutch that spread to Gujarat and Sind, and lasted for approximately 10 years. 1828 and 1929 in Hissar district of Punjab, In 1836, in the Marwar state of Rajputana.

Being on the international trading route, there was immense pressure on the British Imperial government of India to control this emergency. The Plague Commission was constituted in 1896 under the chairmanship of Prof. T.R. Frasor, Professor of Materia Medica at the University of Edinburgh. The report of the Plague Commission in 1904 concluded that the disease was highly contagious and considered human transit as an important source of spreading the disease as they carried the germs with them. The Plague Research Committee was formed, various types of research was conducted in 1897.

Cholera :

People of British East India Company were not familiar with cholera. Before 1817, cholera was confined to Bengal but the 1817–1821 cholera epidemics in India shocked the Company. By 1830s, Cholera was known to be a life-threatening disease to the Western World. In India, it gained the focus of medical services due to its serious impact on the troops and officers of the Company; otherwise, it was a disease of poor people. After the 1868 Cholera epidemic in India, the Cholera Committee was set up to investigate the causes of the disease. The origin and generation of Cholera, the epidemicity and endemicity of the disease in India, transmissibility and propagation of Cholera, and measures necessary for its prevention were studied. The committee concluded that Cholera was frequent especially at religious festivals and fairs. Epidemics were attributable to the importation of disease by pilgrims, travelers, and troops.

Malaria and Sir Ronal Ross (1857-1932) :

Fever was one of the leading causes of deaths in India. The situation worsened in the early 19th century. One of the contributing factors was the establishment of the railways and irrigation network by the British government of India without keeping in view the efficient drainage systems for floods and rainwaters. This created many fresh water reservoirs for the propagation of mosquitoes. Due to the heavy death toll, economic loss, and risk to the lives of British officers serving in vulnerable areas like Punjab, a lot of research was done for malaria control.

Surgeon Major Sir Ronald Ross joined the Indian Medical Services in 1881. He started to study malaria in 1882. In August 1897, he demonstrated the life cycle of the malarial parasite stating that anopheles mosquitoes carried the protozoan parasites called "plasmodia". He was awarded Nobel Prize in Medicine in 1902. This discovery opened new horizons in malaria research and shaped the malaria control programs toward a new direction mainly focusing on the eradication of mosquitoes.

Upendranath Brahmachari (1873-1946) :

He started work in the Campbell Hospital (presently NRS Medical College) to discover a new drug to cure Kalaazar. After 5 years of toiling, Urea Stibamine was discovered, which quickly became essential for the treatment of Kalaazar.

Yellapragada Subbarow (1895-1948) :

Subbarow can best be described as an unfortunate scientist who did not get his due recognition.

His research led to the discovery of Polymyxin, an agent used even today. Aureomycin, the first of

tetracycline, was also discovered by him. He also developed a cancer treatment called methotrexate that has been used to treat numerous types of cancer and discovered diethylcarbamazine, the only known treatment for filariasis or elephant foot.

Ramnath Chopra (1882-1973) :

He worked as first professor of pharmacology in the newly established Calcutta School of Tropical Medicine in 1921. In his tenure, he conducted various studies on general pharmacology and pharmaco-therapy, along with surveys on drug addiction. His work encouraged research on Indian medicinal plants.

Medical Publications in Colonial India :

The establishment of the Asiatic Society of Bengal by Sir William Jones in 1784 was an outcome of the interest created at that time in scientific research. The society played a prominent part in the development of scientific activities and publication in that time India. The society also brought out Asiatic Researches which was the first Indian periodical started in 1788 and was later changed to Journal of the Asiatic Society of Bengal in 1832. The Medical and Physical Society of Calcutta was formed in 1823 and its Transactions were the first professional medical periodical published in India. During the nineteenth century a number of organizations were set up for encouraging scientific publications notably Indian Medical Gazette in 1866 , Indian Journal of Medical research in 1913, Journal of Indian Medical association in 1930.

It is worthy to mention achievements of Indians in Medical Science in Colonial era was without much contribution from Imperial Government. In terms of funding or patronization basically were self or help from few rich and novel Indians. So also in Public health. Hardly 10% population was under cover of medical care. Large population were neglected. Whatever they done only to save their population and to prevent spread from this part of the country to Europe .

In autobiography of Sir Prafulla Chandra Roy, 'Life and Experiences of a Bengali Chemist' in 1932, great Indian Scientist written with broken heart - **'While a student at Edinburgh I found to my regret that every civilized country includingJapan was adding to the world's stock of knowledge but unhappy that India was lagging behind. I dreamt a dream that, God willing, a time would come when she too would contribute her quota. Half-a-century has since then rolled by. My dream I have now the gratification of finding fairly materialized. A new era has evidently dawned upon India. Her sons have taken kindly to the zealous pursuit of different branches of Science. May the torch thus kindled burn with greater brilliance from generation to generation**!'

This sorry state of science and scientific research in colonial India was supposed to get a momentum after installation of democratic Govt after 1947. But major hindrance was poor state of public health, limited medical graduates , limited medical Colleges, research infrastructure and moreover no structured health policy to push forward medical education and research Policies. In editorial of JIMA in 1946 poor health structure was narrated by that time hon editor.

"**In this unfortunate country we have never had public health services in the sense in which they are understood in the West. We have a few hospitals and dispensaries , hardly one for a taluka , considering the vastness of the population. We have no facilities for the curative and preventive side of disease. ..... No country in the world is medically so badly served as India because the Government never considered the health of the people as its first and foremost concern and its national wealth, as much as it considers law and order and the police and the military to be**."

— JIMA Editorial, April, 1946

Significant breakthrough was eshtablishment of Bhore Committee in 1943 (sir Joseph Bhore) which in recommendation first time laid down what should be the future health structure in India. Though this committee recommended on public health, given future direction on medical education and research also. Medical education is intimately related to medical research. Bhore Committee laid down that " from the first, medical education must be carried out against a back ground of original investigation and research". But committee given more stress on bedside research or clinical research rather than laboratory based research.

1947- INDIA GOT INDEPENDENCE :

Bhore committee recommendation was largely accepted by newly formed Govt of Independent India. But as condition of public health was in bad shape , GOI taken more initiative for elimination of disease, eshtablishment of health Units, Medical Colleges for education and training of More Medical Graduates.

Research in Science and technology was in core of heart of Pandit Nehru first Prime Minister of India, He was the first person to initiate schemes to promote science and technology in India. For Nehru, scientific temper is something to be inculcated in society at large.

"**Science was not merely an individual's search for truth; It was something infinitely more than that if it worked for the community**".

— ***Pandit Nehru***

Indian Research Fund Association was renamed in 1949 as Indian Council of Medical Research (ICMR). Principal activity were laid down by Govt were to investigate on Communicable diseases – tuberculosis, leprosy,formulate guideline on different Tropical diseases – Malaria, Kalaazar, Hepatitis, filariasis etc. Also to be involved in capacity building and foundation of Apex laboratories in India.

Research Institute in Immediate Post Independence era :

Cholera Research Centre, Kolkata was created to study various aspect of cholera problem. Govt of India converted Malaria Institute of India to National Institute of Communicable Diseases to deal with communicable diseases.. GOI also established 2 other institutes for Tuberculosis in Banaglore and the Leprosy Research Institute in Madras. In 1951, when the first Five year Plan was to begin, institute for virus research in Poona i.e. Virus Research Centre eshtablished. Nutrition Research Laboratory which originally started as Deficiency Disease Enquiry was shifted from Coonoor to Hyderabad with enhancement in the scope of its activities.

ICMR (Indian Council Of Medical Research) :

ICMR has made outstanding contribution as a knowledge generating agency and contributed in understanding various diseases of national importance such as malaria, Japanese encephalitis, tuberculosis, AIDS, Kala-azar, Filariasis, Leprosy and Poliomyelitis, Additionally, ICMR has made extensive contributions in the areas of nutrition, reproduction and maternal and child health, occupational and environmental health and research complimenting health systems. Training and capacity building of young investigators, medical and allied health professionals and providing funding support for research projects to investigators all over the country are other very unique and significant contributions of ICMR.

Few Significant Contributions :

• **TB Diagnostic Initiative —** TruNAT Rif, an indigenous, cost effective, rapid molecular diagnostic kit for TB/MDR-TB has been developed, validated and has been recommended for roll out under RNTCP at Primary Health Centres (DMCs) in a phased manner. WHO also recognized this project.

•**Vector Borne Diseases Science** — to identify and prioritize gap areas in the control of various vector-borne diseases in the country such as dengue, chikungunya, Malaria, Filariasis, Kalaazar etc. PCR-based diagnosis procedure for visceral leishmaniasis from Urine samples- (Non- invasive method) was developed. Novel non-invasive method for diagnosis of visceral leishmaniasis by rK39 testing of sputum samples has also been developed.

• **Sentinel surveillance for Congenital Rubella Syndrome (CRS) in India** — Aim is assess the impact of Measles Rubella vaccination in India.

• **The JE diagnostic kits (MAC-ELISA)** — manufactured by ICMR-NIV is used by the National Vector Borne Disease Control Programme (NVBDCP) as one of the most sensitive serological test for JE.

• **ICMR-INDIAB** — an epidemiological study on diabetes: The study is a landmark study providing epidemiological data on diabetes, prediabetes, hypertension, dyslipidemia and obesity from the various States of India

• **Hypertension initiative** — Roll out of India Hypertension Management Initiative has been done for better control of hypertensive patients in the Public health system.

• **Reproductive Biology, Maternal & Child Health Development of Male Contraceptive RISUG**: An intravasal, non hormonal once injectable male contraceptive called Reversible Inhibition of Sperm Under Guidance (RISUG) has been developed and evaluated and was found to be safe, effective and acceptable by male of all religions.

Development of Female Contraceptive:

(1) A subdermal contraceptive implant - ImplanonR was evaluated as a spacing method and was found to be safe, efficacious and acceptable in Indian women.

(2) Development of Recombinant CG-LTB vaccine for prevention of pregnancy: A recombinant CG-LTB vaccine against Human Chorionic Gonadotropin (hCG) with high immunogenicity has been developed and found safe under pre-clinical toxicity studies.

Role of probiotics : in prevention of suspected sepsis in LBW infants was studied and found that Daily supplementation of LBW infants with probiotics for 30 days led to a non-significant 21% reduction in risk of neonatal sepsis

• **Anti-Microbial Resistance** — Antimicrobial Resistance Surveillance Research Network (AMRSN) is a comprehensive portal for collecting, validating and analyzing antimicrobial resistance data from

collaborating Centres in Hospitals across India.

• **Nutrition** — ICMR has taken up a project involving Nutrition Interventions in adolescent girls. ICMR also brought out the Indian Food Composition comprising of data of 526 varieties of Indian foods and their nutritive values.

• **Outbreak/epidemics/pandemics/ Disease Burden**

Preparedness of ICMR to handle Zika virus outbreak — NIV, Pune has strengthen its capacity to test the samples for Zikavirus received during the acute phase of the disease by RT-PCR.

National Hospital Based Rotavirus Surveillance Network : The study has been carried out at 4 Major referral labs, 7 ICMR Regional labs and 23 hospital sites to observe the trend in burden of rotavirus diarrhoea as well as impact of Rotavirus vaccine under Universal Immunization Program (UIP).

Working successfully to combat COVID-19 pandemic — by development of Diagnostic kits, testing laboratory , preparing guideline, COVID registry , clinical trials , vaccine research and capacity building. As a ambitious project National Institute of Virology in collaboration with Bharat Biotech is developing Inactivated vaccine against COVID19 – **Covaxin.**

RESEARCH IN DRUG DEVELOPMENT :

Since the initiation of drug discovery by Dr. Reddy's Laboratories in 1994, Indian companies have disclosed a total of 214 proprietary preclinical and clinical stage development compounds, of which 168 originated from large pharma companies, and 46 from contract research and biotech companies. Of these, 83 compounds were progressing in the pipeline despite this significant number of compounds, Zydus Cadila's saroglitazar, launched in 2013, remains so far the only compound that was entirely discovered and developed by an Indian company. In COVID era also Zydus cadila invested in vaccine development - a plasmid DNA vaccine targeting the viral entry membrane protein.

Before Globalization India had policy of process patent. This reduced need of clinical research and invention of new drug and its patent. But Globalization and GATT agreement in 1995 pushed India giving more attention on drug discovery . 2005 was watershed year in drug trial. Indian drug research policy undergone paradigm shift in 2005. Phase lag which was a major barrier was removed . There were bloomimg of Clinical research Organizations in India. There were several criticism on drug trial -lack of transparency, proper compensation etc. In 2013 Supreme court of India in a judgement Swastha Adhikar Mancha vs Union Of India directed to make a transparent and ethical policy in Clinical trial. In 2019 new policy on Clinical Trial laid down by DCGI and ICMR both for Clinical research and epidemiological study.

CONTRIBUTION OF INDIAN SCIENTIST AFTER INDEPENDENCE :

H N Chatterjee

Oral rehydration therapy (ORT), that is, drinking water with controlled amounts of salt and sugar, considered as "potentially the most important medical advance of the 20th century",was first discovered by H. N. Chatterjee, a medical practitioner working on cholera patients in Calcutta. Despite being published 1953 in The Lancet, it was unfortunately ignored, only to be rediscovered in 1968 by Western scientists.

Subhas Mukhopadhyay

A physician from Calcutta, Dr. Mukhopadhyay was the first one to create India's first test tube baby in 1978, but never got due recognition of the same. Unfortunately, all the bureaucratic interventions and false accusations were too much for this eminent researcher. Being frustrated, he decided to leave this world in 1981.

Hari Gobind Khorana

A genius before his time, Khorana was one of the pioneers in genetics and biotechnology. His work with Marshall W. Nirenberg and Robert W. Holley on the order of nucleotides in nucleic acids, carrying the genetic code, earned him the Nobel Prize for Physiology or Medicine, in 1968. He also made another breakthrough in the field, becoming the first to synthesize an artificial gene into a living cell..

Asima Chatterjee

Worked on periwinkle-derived alkaloids that have anti-cancer properties. She also contributed to the development of powerful anti-malarial and anti-epileptic drugs.

Dr J B Chatterjee

His researches and contributions have played a significant role in understanding the hematological aspects of tropical diseases. His work on nutritional and iron deficiency anemia and biophysical, biochemical, genetics of Hemoglobin E in Bengali people established him as a stalwart and an international figure in hematology.

Other Medical Breakthroughs From India :

(a) Cardiac Stents :

Former President of India Dr A P J Abdul Kalam

had significant contributions to medical science which are less discussed in Indian media and literature. He advocated, the role of biotechnology in medical science research, emphasized the use of science and technology for the benefit of common man. India's first indigenous low cost cardiac stent was developed by him in collaboration with Dr. Somaraju Bhupathiraju known as Kalam-Raju stent during 1994 – 1996. It reduced the cost of stents by 1/4th compared to prevailing market rate. In 2012, they developed a tablet computer for purpose of rural health care service, which was named the 'Kalam-Raju tablet'.

(b) Neurosurgery Techniques:

Dr. Atul Goel of Mumbai's KEM Hospital has been instrumental in neurosurgery creating an innovative technique that he calls atlantoaxial facetal distraction and craniovertebral realignment. The technique used to treat basilar invagination is fast being adopted across the world as a better alternative to the conventional procedure of surgery via the mouth.

(c) Potential Cancer Cure:

Indian scientists Partha Dasgupta and Sujit Basu made a breakthrough recently, that dopamine could also help kill tumors. If the human trials are successful, treatment for cancer could get a whole lot cheaper.

(d) New Vaccine For Hepatitis B:

A large part of the global burden of hepatitis rests with India, making an effective vaccine for the deadly hepatitis B virus a holy grail of sorts for India's medical researchers. Researchers at the All India Institute of Medical Sciences (AIIMS) may have found the solution with their creation of nano-particles that can be used in oral vaccination. Human trials on the vaccine are still underway and if successful could be approved for use by 2021.

ARE THESE ENOUGH TO MATCH WORLD COMMUNITY ?

India having immense potentiality of innovation contributed very less in modern medicine in terms of discovery. Post Independence Govt of India put stress more on elimination of diseases through different health programmes rather than innovation. 1st and 2nd Planning commission put more stress on Agriculture and Industrial development and preventive health. In last few decades of twentieth century there were significant advancement in research in nuclear science, defence technology, space and satellite technology, but not in medical science. But fortunately Union Govt gradually realized importance of medical innovation. India having dream of being superpower both politically and economically can not achieve without having patent of different drugs and vaccines. This require lot of investments from both Public and corporate side and encouragement from Govt side. Making regulations transparent and easier(without hampering safety of people out of research), lucrative opportunity for researchers , incentives for pharmaceuticals who are involved in research on drug development can bring new light in future India. So many Indians are working successfully in abroad in different research Institute. Why we can not attract them to work in India.

There are sporadic publications /research/award from Indian researchers, but lacking structured and patent research products which can give benefit both commercially and politically (what India done in ISRO).

RESEARCH POLICY IN 21st CENTURY IN INDIA :

The National Health Policy 2002 defined the goal for Health Research as follows: "**Over the years, health research activity in the country has been very limited. In the Government sector, such research has been confined to the research institutions under the Indian Council of Medical Research, and other institutions funded by the Central/ State Governments. Research in the private sector has assumed some significance only in the last decade. In our country, where the aggregate annual health expenditure is of the order of Rs. 80,000 crores, the expenditure in 1998 99 on research, both public and private sectors, was only of the order of Rs. 1150 crores. It would be reasonable to infer that with such low research expenditure, it is virtually impossible to make any dramatic break through within the country, by way of new molecules and vaccines; also, without a minimal back up of applied and operational research, it would be difficult to assess whether the health expenditure in the country is being incurred through optimal applications and appropriate public health strategies. Medical Research in the country needs to be focused on therapeutic drugs/vaccines for tropical diseases, which are normally neglected by international pharmaceutical companies on account of their limited profitability potential. The thrust will need to be in the newly emerging frontier areas of research based on genetics, genome based drugs and therapies, vaccine development and molecular biology etc.**"

Medical Research in the country needs to be focused on creating our own therapeutic drugs/ vaccines and other interventions especially for tropical

diseases for which there have been only few inventions in the last century. However, the development of new health products (diagnostics, drugs and vaccines) is a long and complex process and we need to have systems in place to encourage innovation and appropriate ethical and regulatory frame work for pre clinical work and clinical trials for bringing our health products to market.

"In Europe, Industry and Scientific Pursuits have gone hand in hand ... one helping the other.... The gigantic progress in Industry achieved in Europe and America is a history of the triumph of researches in the laboratories."

— Acharya Prafulla Chandra Roy

Happy to feel GOI in 2010 put his "Pharma Vision 2020", to have "one out of five to ten new drugs discovered in the world originating from India by 2020", which would have represented an average of at least three to six new medical entities (NMEs) per year, to a more realistic, but still highly ambitious target of "one NME per year and 10–12 incremental innovation launches per year by 2030".

It is absolutely essential to enhance the number of researchers and supportive workforce in the ICMR. ICMR will continue to be the fulcrum of future Health Research. To address this challenging task and to give a greater thrust and focus to Health Research, a new Department of Health Research (DHR) under the Ministry of Health & Family Welfare was created on 2007.

The Department has a vision "To bring modern health technology to the people through innovations related to diagnostic, treatment methods and vaccines for prevention".

MRU (Multidisciplinary Research Unit) :

Government of India approved the scheme for 'Establishment of Multi -Disciplinary Research Units (MRUs) under ICMR in the Government Medical Colleges/Research Institutions' as a path- breaking initiative to develop/strengthen the health research infrastructure in the country in 2013 under 12th plan. Aim was to strengthen research environment and infrastructure in Medical colleges, increase awareness and aptitude among young medical graduates. MRUs are established to enhance research in Noncommunicable diseases and issues based on local needs .

FUTURISTIC VISION :

We have glorious past , have resources , now have dream. But to fulfil have to walk a long. Foreign invasions, loots, colonial regimens put research motivation at a lowest level. We Indians accept research of western world without giving much thought even in sector of Public health and communicable diseases. It is well known that genetic, environmental, sociocultural, and dietary factors greatly influence manifestations and management of diseases; hence, health research done locally would have the greatest impact on the health of local populations. Multidrug-resistant tuberculosis, HIV/AIDS, malaria, and noncommunicable diseases (NCD) such as diabetes, heart diseases, chronic pulmonary obstructive diseases, and cancers are the biggest health-related challenges facing India today. Our research effort in these areas is not commensurate with our needs. Through research in Indian context we should prepare our own guideline to combat these diseases.

The reasons for such a sorry state of affairs are many. The often cited ones are lack of sophisticated research infrastructure, paucity of funds, and physicians "overburdened" with patient care. These certainly are there, but at a more basic level, the reasons may be hidden in our education system that promotes rote learning over a spirit of scientific inquiry and lateral thinking.

"**The True laboratory is the mind, where behind illusion we can uncover the laws of truth**".

— Acharya Jagadish Chandra Bose

India was ruled by foreign invaders centuries after centuries, society submerged with superstitions, divided on the basis of caste and religion, scientific thought taken a back stage in mind of Indian people. Medieval cloud obscured rational thinking of Indian youth.

In words of Acharya Prafulla Chandra Roy"***I have been teaching for half a century; in this period I have told thousands of students that solar and lunar eclipses are not caused by the demons Rahu and Ketu devouring the sun and the moon . . . They listened and agreed. But during the eclipses, the moment conch shells are blown in the houses, the moment prayer processions come out in the streets, these educated people also join the processions and throw away their food."***

So first and foremost duty is to create a scientific environment , environment of rational thinking.

"Where the mind is without fear and the head is held high
Where knowledge is free .....
Where the clear stream of reason has not lost its way
Into the dreary desert sand of dead habit .....
Into that heaven of freedom, my Father, let my country awake."

— Rabindranath Thakur
(Collected from Gitanjali)

Our Population starting from Politicians, Bureaucrats , media, including educated middle class tend to view any form of medical research as "using Indian patients as guinea pigs," or done "for the benefit of pharmaceutical industry." Every even honest attempt judged against political loss or gain. Or our parents thought opting of Medical researcher as carrier is sacrifice of a bright carrier.

More importantly, our medical education and institutions lack training curriculum in conducting systematic research; neither is there any emphasis on recording and documenting observations systematically in medical practice. In Indian psychology Medical graduates opt more clinical branches as future carrier having more lucrative packages. While medical research as carrier or opting basic medical sciences not priority to medical graduates.

If we want more medical research to happen in India, we need to address these shortcomings systematically. We need to encourage scientific inquiry and rational thinking in our young population; our medical education needs overhaul to include training programs in systematic research methodologies, and our medical institutions must nurture and mentor budding scientists treating them on par with clinical specialists. We should invest in building proper research infrastructure, and make resources available for supporting medical research at the institutional level. In addition, perceptions of the stakeholders including the general public need to be addressed to create a more open environment for medical research.

Equally, we must remember that research need not happen only in advanced institutions under sophisticated settings, it can be done at patient bedside in clinical practice. An astute, observant, and reasoning clinician can seek answers to many clinical questions through simple yet well-designed clinical experiments in his day-to-day practice, as beautifully illustrated through many well-known examples by Nanivadekar in his thoughtful essay. To this effect, we must inculcate in our medical students and clinicians an attitude of scientific curiosity and reasoning, and a habit of systematically recording and documenting their observations.

We must firmly believe that while clinicians are the patient interface working to perfect the existing practice of medicine, medical scientists are needed to generate new knowledge and test new theories and therapies to bring about betterment and innovations in healthcare. Contributions by both are equally essential to medical science and patient care.. We need both clinicians and medical scientists to make this world a better place.

Conclusion :

India has a rich cultural heritage, a strong social base and an impressive history. Her ontributions to medical science over ages cannot be underestimated. But today,we seem tohave lost our zeal to contribute.

অতীতকাল যত বড়ো কালই হোক
নিজের সম্বন্ধে বর্তমান কালের একটা স্পর্ধা থাকা উচিত।"
"মনে থাকা উচিত, তার মধ্যে জয় করিবার শক্তি আছে"

Probably in arena of Medical research we forget our power. Very few medical students are going for a full-fledged research, and very few contributions are made to the medical science. Prime minister Narendra Modi said Indian doctors have made a name for themselves world over but the country was far behind other countries in the field of research.Let us try to rectify it, and try to contribute something for the sick. Only then can claim to be real ancestor of Charaka and Susruta.

"It would be our worst enemy who would wish us to live only on the glories of the past and die off from the face of the earth in sheer passivity. By continuous achievement alone we can justify our great ancestry".

— Acharya Jagadish Chandra Bose

Like Prime Minister of India I am hopeful

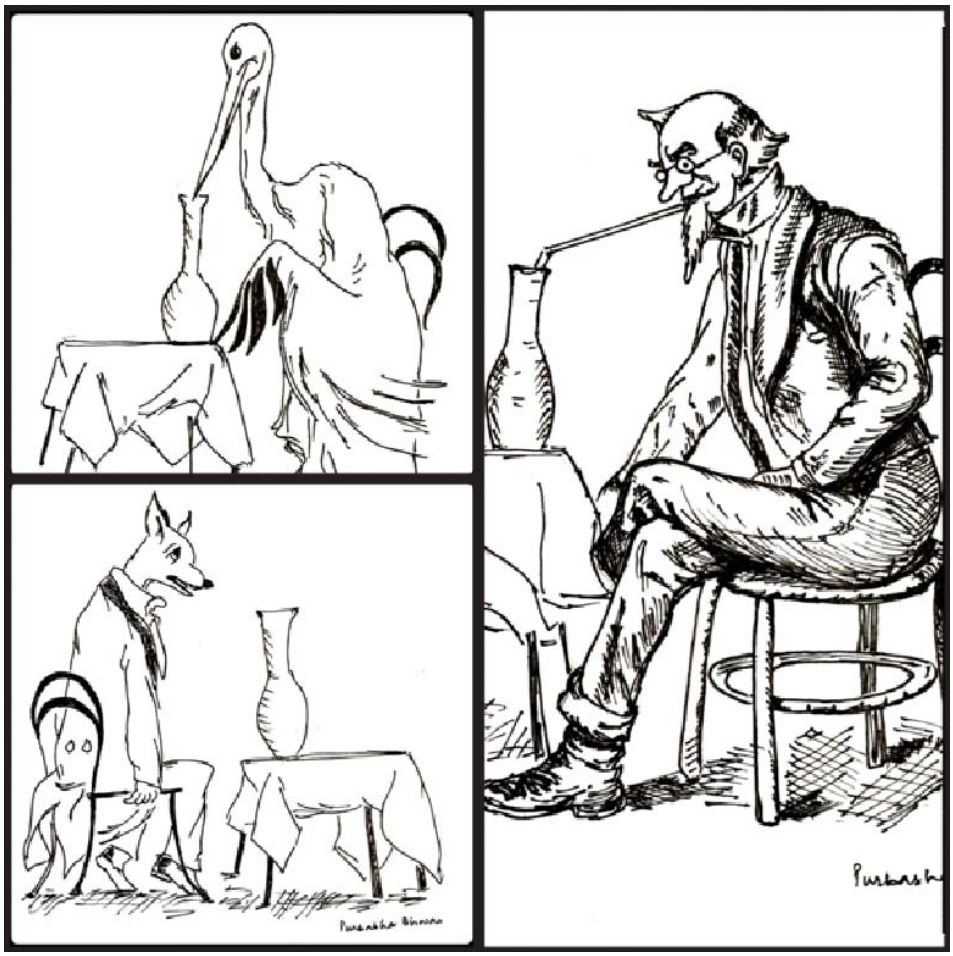
"India to be at Centre of Global Healthcare Effort With Its Experience, Research Talent"

JAIHIND JAIBHARAT BANDEMATARAM

রবীন্দ্রনাথের প্রকৃতি ও শিক্ষার সমন্বয়-

রবীন্দ্রনাথের শিক্ষাচিন্তায় প্রকৃতি, মানুষ ও শিক্ষার সমন্বয় ঘটেছিল। তিনি শান্তিনিকেতনে বিশ্বভারতী প্রতিষ্ঠা করে প্রকৃতি মানুষ ও শিক্ষা বিষয়ে হাতে কলমে পরীক্ষা-নিরীক্ষা করেছেন। রবীন্দ্রনাথের মনে করতেন যে শিক্ষা হবে মুক্ত প্রকৃতির কোলে মুক্ত আকাশের নিচে। চার দেওয়ালের মধ্যে আবদ্ধ শিক্ষা প্রতিষ্ঠানকে তিনিও **খোপওয়ালা বড় বাক্স** বলে অভিহিত করেছেন।

The aim of education or research according to Rabindranath, is the harmony of the students with the environment. The student should know his environment and create harmony with it. To quote Rabindranath, "***True education consists in knowing the use of any useful material that has been collected to know its real nature and to build along with life a real shelter for life".***



Review Article

ABC of the Peripheral Smear

Manisha Jain[1], Tuphan Kanti Dolai[2]

Peripheral blood smear examination is an inexpensive and powerful diagnostic tool to diagnose both hematological and non-hematological disorders. With the advancing newer technology, it is becoming like a "lost art". The peripheral smear often called as a window into the functional status of the bone marrow as it can provides rapid, reliable information about a variety of hematologic disorders. Systematically and thorough review of the smear is an important adjunct to other clinical data and in some cases, often sufficient to establish a diagnosis like hemoparasite infestation. Newly developed automated cell counters are increasingly providing sophisticated data however, only an experienced reviewer can weigh the relative significance of the findings and assess their importance within the context of other clinical data. Even with the availability of cumbersome data by automatic cell counters, there are a number of settings in which interpretation of the peripheral smear is especially important to guide for further management. This concise review provides a systematic approach while evaluating a peripheral blood smear, the findings and its clinical significance in diagnosing variety of the hematological disorders.

[*J Indian Med Assoc* 2020; **118(11):** 19-23]

Key words **: Peripheral blood smear, Preparation, Examination, Interpretation, Blood cells morphology, Reporting.**

A complete blood count (CBC) is the most common and foremost investigation used by physicians in the day to day health care practice for detection of disease and its monitoring. Recent advances in the technology of the automated hematological analyzers had significantly improved the quality by improving accuracy, precision and time per analysis. Although manual intervention has been reduced significantly nowadays, evaluation of the results by qualified clinical laboratory professionals is still essential.[1] The examination of a well prepared and stained peripheral smear is like a "*lost art*" in the modern era. Much valuable information can be gained from examining the blood smear than from any single haematologic procedure.

Preparation of a peripheral smear[2]: A well spread peripheral smear can be made using the wedge technique either manually or automated technique. A small drop of non-clotted blood (10µl- capillary or EDTA blood sample) is put on a clean glass slide (dust, dirt, grease, and fingerprint-free) approximately 1.5 cm from one edge. By using another glass slide edge as spreader at an angle of 30-45°, the blood should be dispersed along the length of the slide with the aim to prepare monolayer to disperse cells uniformly. An ideal smear should cover 2/3rd to 3/4th length of slide with free lateral margins, free from holes, streaks, or irregularities and preferably tongue-shaped with feathered edge.

Staining of a peripheral smear[2]: A well spread peripheral smearis air-dried and then fixed in methanol to later stained using prototypical stain, Romanowsky stains such as Wright's, Leishman or Giemsa stain as per standard technique. After staining well prepared well-stained slide monolayer is viewed under a microscope at different magnification for a complete

Editor's Comment :

- **The peripheral smear is a window into the functional status of the bone marrow**
- **A well prepared and well-stained smear examination under light microscope is particularly important in the evaluation of cytopenia or flagging in abnormalities in automatic hematological analyzer**
- **The peripheral smear should be evaluated in an optimal area to look for number, size, shape, and presence of any inclusions in red cells, white cells, and additional features including the presence of any abnormal cells including blasts or abnormal granulation or hemoparasite**
- **A well-framed format of the peripheral smear report contains the complete patient details, all the relevant information regarding the morphologic characteristic of each series of blood cells and authorized signature.**

Department of Haematology, Nil Ratan Sircar Medical College and Hospital, Kolkata 700014
[1]MBBS, MD (Pathology), DM Trainee
[2]MBBS, MD, DNB, DM, FICP, Professor and Head and Corresponding author
Received on : 03/09/2020
Accepted on : 30/09/2020

analysis of individual blood cell morphologic characteristics.

Evaluation of a peripheral smear : Firstly, an optimal area for the examination of peripheral smear is selected using 4X magnification of the microscope. The optimal area in peripheral smear for evaluation is at the junction of the body and tail of the smear where RBCs just touch each other without significant overlapping. At the next low magnification (10X), RBCs agglutination or rouleaux formation or platelet aggregation and parasites like microfilaria can be detected. At high magnification (40X) total, differential leukocyte count and platelet count can be roughly estimated and also can be correlated with the results of automatic hematological analyzers, if available. A detailed evaluation of blood cell morphology including size, shape, nuclear, cytoplasm or granules characteristics or parasite like malaria parasite detection can be done under oil immersion (100X).

Role of examination of a peripheral smear: Peripheral smear evaluation can provide valuable information regarding the diagnosis of various diseases or monitoring of the response of therapy. Special consideration on examination of blood smear by well-trained laboratory professionals should be taken in case of flagging of abnormalities on the automatic hematological analyzer. Systematic evaluation with special attention on the morphology of RBCs can diagnose the cause of anemia while the number and morphology of platelets are essential while evaluating thrombocytopenia. The presence of abnormal cells including nucleated RBCs, blasts or parasites including species identification (in case of malarial parasite) requires evaluation of a peripheral smear. Additional information like variation in shape, size or inclusions in RBCs with special attention to abnormal shaped RBC like sickle cell or spherocytes or schistocytes can guide for the requirement of further procedure/investigation. Abnormal nuclear lobulation or granularity like Auer rods in leucocytes might help in the diagnosis of various syndromes or sepsis or malignancy like Promyelocytic Leukemia or Clonal Hematopoiesis including Myelodysplastic Syndrome. The presence of abnormal cells including myeloblast/ lymphoblast or abnormal lymphoid cells (hairy cell/ Sezary cell) indicates the underlying malignant hematologic disorder (Fig 1).[1-4]

Interpretation and clinical significance of peripheral smear findings : Accurate interference of morphologic findings requires the selection of an optimal area by scanning the entire slide. Below mentioned are various morphologic findings of blood cells including red blood cell, white blood cell, and platelets which have clinical significance and need thorough evaluation, even further investigations or procedures like bone marrow evaluation to reach the diagnosis.

(1) Abnormal cell distribution :

(a) Rouleaux Formation : The appearance of red cells arranged as a stack of coins in an otherwise optimal area, a phenomenon called rouleaux formation, most commonly seen in conditions with increased total proteins like multiple myeloma.[5]

(b) Irregular clumps of red cells : May signify the presence of certain infections like Hepatitis C or cold agglutinins disease.[5]

(c) Broken cells or smudge cells : Presence of smudge cells signify artifact while preparing the smear or presence of fragile cells like lymphocytes in the case of CLL or even immature lymphoid cells like lymphoblasts.[4]

(d) Abnormal clumps of platelets : Signify normal or increased platelet number. Highly valuable to rule out pseudo-thrombocytopenia.[6]

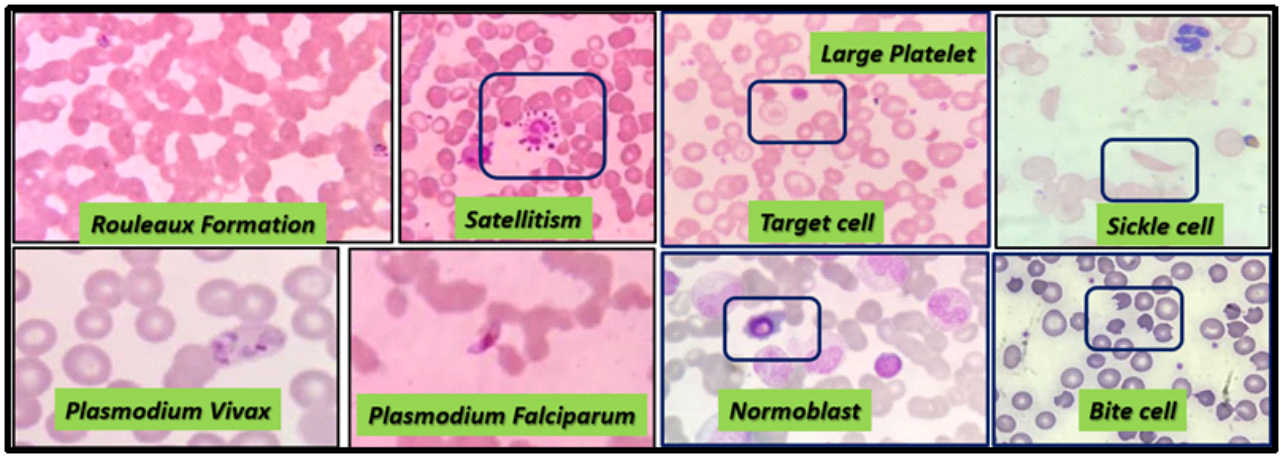


Fig 1 — Morphologic characteristic of RBCs and Platelets

(**2) Red blood cells:** A mature red cell is anucleate with the size of approximate of the nucleus of small mature lymphocyte (7-8µm), biconcave shaped with nearly 1/3rd central pallor and lacks any intracytoplasmic inclusions. Abnormal variations in shape, size or presence of cytoplasmic inclusion bodies signify associated clinical abnormalities.[2] Anisocytosis refers to variation in size and poikilocytosis refers to variation in shape of red cells. Various pathological conditions are associated with the presence of aniso-poikilocytosis of red cells and permutation combinations of other associated morphological findings can be helpful in diagnosing the cause of anemia.[7]

(a) Anisocytosis : Mean corpuscular volume provided by an automatic hematologic analyzer confirms the actual size of red cells (normal MCV- 81-99fl). However, MCV can be misleading in case of variations of size of red cells as in case of dimorphic anemia. A high red cell distribution width (RDW) is suggestive of presence of red cells with different sizes but a definitive appreciation of variation in size requires peripheral smear assessment. Microcytosis (<80fl) and macrocytosis (>100fl) are associated with various hematological and non-hematological conditions as depicted in Table 1.[2]

(b) Poikilocytosis : Various hematological and some non-hematological disorders are associated with the presence of distinctive red cells shape. Table 2 gives a brief review of various shapes and their clinical significance.[2]

The poikilocytes including acanthocytes, codocytes, echinocytes, stomatocytes, drepanocytes, and degmacytes are caused by membrane abnormalities while dacrocytes, spherocytes, schistocytes are caused by trauma to red cells in the vasculature.[6]

(c) Intracytoplasmic inclusion bodies: Inclusion bodies are aggregates of the stainable material. A normal red cell contains no inclusion bodies in the cytoplasm. Table 3 provides various cytoplasmic inclusions found in red cells and their significance.[2,6]

Table1 — *RBCs anisocytosis and associated clinical conditions*

RBCs Size	Clinical Significance
Normocytic	Acute haemorrhage, malignancy associated anemia, Enzyme deficiency
Microcytes	Iron deficiency, Thalassemia, Anemia of chronic disease, Lead poisoning, Sideroblastic anemia
Macrocytes	Megaloblastic anemia, Liver disease, Drug-induced, Alcohol, Myelodysplastic syndrome, Aplastic anemia
Both Microcytes and Macrocytes	Dimorphic anemia

Table 2 — *RBCs poikilocytosis and associated clinical conditions*

RBCs Shape	Clinical Significance
Schistocytes (Fragmented RBCs)	Microangiopathic hemolytic anemia including TTP, DIC, MAHA
Drepanocytes (Sickle cells)	Sickle cell anemia
Codocytes (Target cells)	Hemoglobinopathies, Thalassemia, Iron deficiency, Liver disease, Postsplenectomy
Spherocytes	Hereditary spherocytosis, Autoimmune hemolytic anemia, ABO incompatibility
Acanthocytes (Spur cells)	Neuroacanthocytosis, Abetalipoproteinemia, Liver disease, Post splenectomy
Echinocytes (Burr cells)	Artefacts, Uremia, Pyruvate kinase deficiency
Stomatocytes (Mouth Cells)	Artifacts, Hereditary Stomatocytosis, Alcoholism, Myelodysplastic syndrome
Degmacytes (Bite cells)	G6 PD deficiency
Dacrocytes (Teardrop cells)	Myelofibrosis, Marrow infiltration, Osteopetrosis

Table 3 — *RBCs inclusions and associated clinical conditions*

RBCs Inclusion	Inclusion	Clinical Significance
Howell Jolly bodies	DNA	Asplenism, Severe hemolytic anemia
Heinz bodies	Denatured hemoglobin	Unstable hemoglobin, G6PD deficiency, Oxidant-Drug injury
Pappenheimer bodies	Iron deposits	Thalassemia, Sideroblastic anemia, Post splenectomy
Hb H inclusion	Globin chains	Hemoglobin H disease
Basophilic stippling	Ribosomes	Lead poisoning, Thalassemia, Megaloblastic anemia, Myelodysplastic syndrome
Cabot rings	Microtubules remnants	Megaloblastic anemia, Myelodysplastic syndrome
Hemoglobin crystals	Hemoglobin	Hb C disease or Hb SC disease
Parasite	Hemoparasite	Malaria and Babesiosis
Red cell Ghosts	Devoid of hemoglobin	Intravascular hemolysis like fulminant falciparum or Clostridium perfringens infection

(d) Polychromatophils : Young red cells released from marrow called reticulocytes contain ribosomes and hence give bluish tin to cytoplasm which when stained with Romanowsky's stain appears as bluish-red cytoplasm and hence referred to as Polychromatophils. An increased polychromatophils in smear signify the response of marrow to hemolysis or hematinics.

(e) Nucleated red blood cells : Normal red cells are anucleated. Normoblasts (nucleated red blood

cells) are normally not found in the peripheral smear. However, severe hemolysis, profound stress erythropoiesis, hypoxemia or infiltration of marrow with granuloma, metastatic deposits, myelophthisic conditions like myelofibrosis are associated with the presence of nucleated red cells in the peripheral blood. The presence of nuclear or cytoplasmic irregularity suggests dyserythropoietic associated with conditions like myelodysplastic syndrome, and the presence of the binucleate normoblasts in the peripheral smear of a child suggests congenital dyserythropoietic anemia.[8]

(3) White blood cells : Mature leucocytes including granulocytes, monocytes, and lymphocytes are nucleated cells present in peripheral blood, having characteristic morphology. Granulocytes undergo sequential maturation in the bone marrow and only mature forms are released in the peripheral blood. The presence of immature granulocytes in the peripheral blood or any variation in the morphology is associated with various disorders (Fig 2).[8]

The change in the number of leucocytes (decrease in count- Leucopenia and increase in count- Leucocytosis) or change in lobulation or granularity is associated with various systemic disorders including nutritional disorders to hematological malignancies. Table 4 gives a summarize form of various disorders associated with it.[9]

(4) Platelets : The cytoplasmic fragments of megakaryocytes are released directly in the peripheral bloodas platelets (anucleated granular), are best visualized under oil immersion. Both the variations in number and size of platelets are associated with different hematological disorders. The evaluation of peripheral smear is most valuable to rule out pseudothrombocytopenia in case of low platelet count on automatic hematological analyzer.[1] The presence of platelet clumps due to technical error while taking a blood sample or sticking of platelets over neutrophils cell membrane, phenomena called satellitism are the most common causes of pseudothrombocytopenia. Table 5 provides the main variation in size and granularity of platelets and their associated clinical significance.[2]

Table 4 — *WBC characteristics and associated clinical significance*

Characteristic	Clinical Significance
Neutropenia	Viral infection, Drug-induced, Chronic idiopathic neutropenia, Cyclical neutropenia, Nutritional deficiencies including folate or Vit B12, Hematological malignancy
Neutrophilia	Bacterial infections, stress, Drugs, Myeloproliferative neoplasm
Eosinophilia	Helminth infections, Asthma, allergic reactions, Hypereosinophilic syndrome, Chronic eosinophilic leukemia
Monocytosis	Tuberculosis, Malaria, Viral infections, CMML
Basophilia	Chronic myeloid leukemia and other myeloproliferative neoplasm
Lymphocytosis	Viral infections, Autoimmune disease, Drug hypersensitivity, Lymphoproliferative disorder
Lymphopenia	HIV, Chemotherapy, Malnutrition, Alcoholism, Autoimmune disorders, Hematological malignancy
Hypolobation	Pelger-Huet anomaly, Pseudo-pelger-Huet anomaly seen in dysgranulopoiesis
Hyperlobation	Megaloblastic anemia, Uremia, Myelodysplastic syndrome, Drugs induced
Hypogranularity	Myelodysplastic syndrome
Hypergranularity	Alder Reilly anomaly, Chediak Higashi syndrome, Toxic granules in sepsis
Inclusions (Dohle bodies)	Bacterial infection, Sepsis, G-CSF induced, Pregnancy

(5) Other cells :

(a) Blasts : The presence of blasts (myeloblasts or lymphoblasts) in the peripheral smear signify the requirement of further evaluation of such patients including bone marrow examination to rule out underlying hematological malignancies. Myeloblasts are medium to large size with opened up chromatin and 1-2 prominent nucleoli and moderate basophilic cytoplasm with fine granules and Auer rods while lymphoblasts ae small to medium size immature cells with condensed chromatin, inconspicuous nucleoli, and scanty basophilic agranular cytoplasm; presence of either

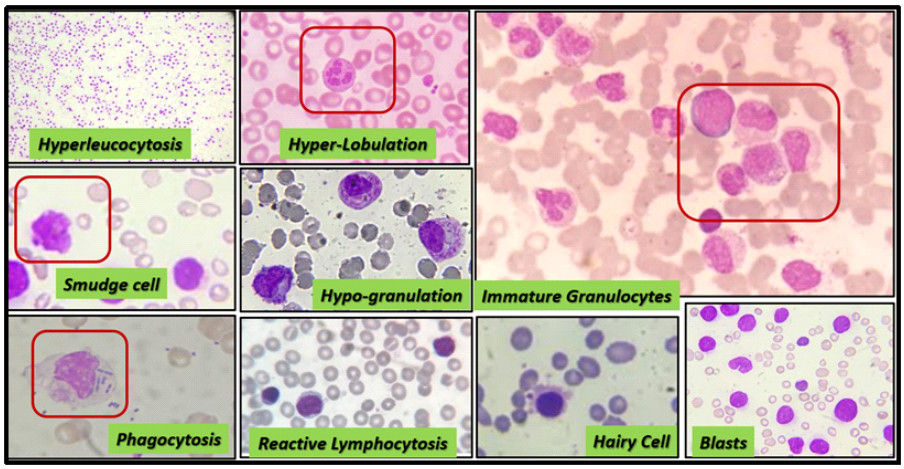


Fig 2 — Morphologic characteristic of WBCs

signifies underlying hematological malignancy including acute leukemia.[8,9]

(b) Atypical lymphoid cells: Apart from the presence of an increased number of small mature lymphocytes (Monoclonal lymphocytosis), presence of other atypical lymphoid cells with characteristic morphology in the peripheral smear warrants the further evaluation of such patient to rule out underlying leukemia or lymphoma. Reactive lymphocytosis is the most common diagnostic challenge in such patients and many times require ancillary techniques to rule out leukemia or lymphoma involvement.Table 6 summarizes the morphology and clinical significance of various atypical lymphoid cells.[1,3]

(c) Leukoerythroblastic picture : The combined presence of early precursors of granulocytes including myelocytes and metamyelocytes, normoblasts (intermediate and late erythroid precursors) and teardrop cells in the peripheral smear suggests marrow infiltration or fibrosis leading to outpouring of immature cells in the peripheral blood.[1,2]

Table 6 — *Atypical lymphoid cell morphologic characteristics and associated clinical significance*

Lymphoid cell	Morphology	Clinical significance
Turk's cell	Medium size, round nucleus, prominent nucleoli with abundant basophilic cytoplasm	Infectious mononucleosis, Viral infections
Large granular lymphocytes	Large cells with condensed chromatin and abundant fine granular cytoplasm	Viral infections, Large granular lymphocytic leukemia
Hairy cell	Medium size cell with oval nuclei, condensed chromatin, abundant cytoplasm, and regular cytoplasmic projections	Hairy cell leukemia
Villous lymphocytes	Small mature lymphocytes with bipolar villous projections	Splenic marginal zone lymphoma
Buttock lymphocytes	Small lymphoid cells with cleaved nuclei	Follicular lymphoma
Cloverleaf cell	Medium size lymphoid cells with hyperlobulated (cloverleaf or flower-shaped) nuclei	Adult T cell leukemia/ Lymphoma
Sezary cell	Lymphoid cell with cerebriform nuclei	Cutaneous T cell lymphoma
Plasma cells	Mature or immature plasma cell	Plasma cell Leukemia

Reporting the peripheral smear : The typical format of peripheral smear reporting including patient's detail including name, age, gender, registration number with date and time of sample collection and reporting. The main part of the report includes the detailed description of count and morphologic characteristics of each cell line including red cell, white cell, and platelets with special emphasis on the presence of any abnormal cells or hemoparasite. The end part of the report includes diagnosis or differentials in different hematological disorders and further advice regarding recommended laboratory evaluations for definitive diagnosis. The report will be incomplete without authorized signature of concerned hemato-morphologist. The interpretation of blood smear should be reconciled with the clinical features and other hematological or investigation findings.[2,3,9]

Table 5 — *Platelets characteristics and associated clinical significance*

Platelet Characteristics	Clinical Significance
Pseudo Thrombocytopenia	Clumping of platelets, Satellitism, Severe microcytic anemia
True Thrombocytopenia	Defect in production (due to marrow failure, infiltration or hematological malignancy) or excessive destruction (Immune-mediated, drug-induced, Heparin-induced, Thrombotic thrombocytopenic states, DIC) or Sequestration (Hypersplenism)
Thrombocytosis	Post hemorrhage/surgery, Postsplenectomy, Iron deficiency anemia, Drug-induced, Myeloproliferative neoplasm
Small Platelets	Familial thrombocytopenia like Wiskott Aldrich syndrome or X-linked thrombocytopenia
Large platelets	Bernard Soulier syndrome, Marrow recovery, ITP, MYH9 related anomalies, Myeloproliferative neoplasm, Alport syndrome
Giant platelets	Myelodysplastic syndrome, Myeloprolifeartive neoplasm

References

1 Lokwani DP, Agarwal MB — The ABC of CBC.1st ed. Jaypee Brothers Medical Publishers; 2013.

2 Lewis SM, Bain BJ, Bates I (Eds) — Dacie and Lewis Practical Haematology. 12th ed. London: Churchill Livingstone. 2017

3 Kawthalkar SM — Essentials of haematology.2nd ed. Jaypee Brothers Medical Publishers; 2013.

4 Sherri D Flax — Why Do We Still Need to Evaluate Peripheral Blood Smears? Ask the experts. The American Association for Clinical Chemistry. Jun 2017.

5 Amati F, Canellini G, Beris P — Polyclonal hypergamma-globulinaemia with hyperviscosity syndrome. *Br J Haematol* 2002; **116:** 2.

6 Singh T — Atlas and Text of Haematology. 3rd ed. Avinchal Publishing company; 2017

7 Adewoyin AS, Nwogoh B — Peripheral blood film - a review. *Ann Ib Postgrad Med* 2014; **12(2):** 71-9.

8 Bain BJ — Diagnosis from the peripheral smear. *N Engl J Med* 2005; 353-498.

9 Wintrobe, Maxwell M, John P Greer — Wintrobe's Clinical Hematology. 14th ed. Philadelphia: Wolters Kluwer Health/ Lippincott Williams & Wilkins; 2018.

Voice of the Expert

Medical Education — Vision 2030

Dr. Gurpreet S Wander
DM, FACC, FAMS
Professor & Head of Cardiology, Hero DMC Heart Institute, Dayanand Medical College & Hospital, Ludhiana
Past President Association of Physicians of India
Past President Hypertension Society of India

1. How medical education evolved after independence in India ?

Post-independence initially government medical colleges were more. We had 23 medical schools in 1947. Today we have the largest number of medical colleges in the world. There are 529 colleges with 70,970 MBBS seats across the country. Since 1988s the private medical colleges have increased and some of them provide high quality education with excellent facilities. The government medical colleges in public sector have done a great service however decision making has to be rapid with the changing pace. The hostels need improvement and modern technologies of education need to be incorporated. The private sector medical colleges contribute significantly although the admission process in some of them needs to be regulated more and made transparent. Medical graduates from India have the best reputation world over, this is since the level of education is good in our country. In future the public and private sector need to work in unison and cooperation with greater respect and faith in each other.

2. Do you think approach &attitude of doctorshave changed in last 70 years?

Definitely. The society has changed so much that it was bound to bring this change in us. The young doctors realise that they are working in a more demanding, transparent, and audited times. The consumer protection act with started 1987 has made them more cautious. They realise that proper documentation is important. Also, the corporate sector has come into the system and they must adapt accordingly. With some new rulings the 'Single person clinics' which are an excellent model of cost-effective medical care delivery at the doorstep will become more difficult to maintain. Hence, they are adapting to these new challenges and are now changing to collective and group practice which is the way to go now. If we learn from the west specially USA, the doctors have group practice there. There is sharing of responsibilities and resources and so there are less pressures. I would say with the changing time and challenges they are modifying their practices accordingly.

While the USA system has its advantages, we have to think in the Indian context also. USA is a country which allows free enterprise and promotes commerce in any form. But in India, starting a business venture is never easy due to a lot of socio-political, economic and other factors. Hence, a few doctors forming a business group will not be easy.

3. Do you think the reform of medical education is necessary in India?

Change is the only constant in the world. A lot of reforms have been made in the curriculum in the last 15-20 years. Most of them have been for the good. The occurrence of NEET which brings uniformity across the country for admission is the best thing. The national exit test (NEXT) which will start from next year is equally good. The final year exit exam will now be used as the basis for postgraduate admission. This will allow students to learn clinical skills during the internship. The initial induction course is also an excellent change from the past. The new MCI/NMC curriculum is competency based and recommends shift from didactic lectures to small group discussions, problems-based learning, role play, skill assessment, integrated teaching, demonstration, and emphasis on bedside clinics. We should lay more emphasis on clinicals in the third, fourth and fifth years. The skill labs have now been made mandatory by the NMC and will help in this direction.

4. What are the other lacunae present in the curriculum?

I do not feel there are many lacunae in the curriculum. I personally feel we have made many changes for the good, in it. The new proposed

competency based medical education (CBME) is more learner centric. There is a shift from the earlier pedagogy pattern to the more participation andragogy pattern. It will use the Miller's pyramid from cognition to performance stage of "knows, knows-how, shows how and does". It will be having more learner participation. The examination system still continuous to be the same for every professional yearly examination. We should not change from long answers to MCQs since many skills can not be tested by the MCQs. The aptitude of the medical graduates needs to be given greater value. We will have to depend on the judgement of the teachers and should provide them with some discretion to pick up students who may not scoring in the MCQs but have the desire and the aptitude for a particular speciality.

We think that the guidelines for recruiting medical teachers should be eased in India. For example, in all major western universities, which are ranked within the top 100 institutions of the world, there are visiting lecturers, who are essentially independent experts who are attached to the university part-time. But in India, such a concept is not there till now in the medical education. As the curriculum changes, there is need of more teachers. So, such recruitment procedures should be changed.

5. Do you feel present curriculum in Medical Education is adequate to combat future epidemic orpandemic?

The present pandemic has come after 100 years of the previous equally large 'Spanish flu' in 1918, towards the end of the second world war. The medical curriculums all over the world obviously were not emphasising on the special requirement on the medical care delivery chain during a pandemic. We started imagining that these epidemics are a feature of China or African countries. We now realised that with globalization and excessive travelling the world has become one and diseases will spread rapidly across man made borders. I am sure every country and so also ours will now have a special area of curriculum for the pandemic situations.

6. Technological advancement vs Clinical Skill – where should be the pivot?

This is an interesting question specially for the young graduates. Benjamin Franklin said, "Education is not the learning of facts but training the mind to think". We must train them to preserve the clinical skills and imbibe new technologies. The two are complimentary to each other. There is no reason to pick one over the other since someone who can use technology and has the clinical skills will be the best. Good history taking and physical examination will never ever the replaced, even with advanced artificial intelligence. On the other hand, the wearables and other gadgets that provide continuous information about the patient are providing useful information about disease progression. A smart doctor will be one, who maintains the clinical skills and learns how to use technology for the benefit of the patient and for better outcomes. Since, the ultimate purpose and aim of anything that we do is better patient care and outcome.

7. Where should we give stress in education : On communicable or non-communicable diseases ?

India is presently going through a double whammy. In the phases of epidemiological transition, we have a unique problem that non communicable diseases (NCDs) are increasing. More than 50% deaths in our country are due to the NCDs. Cardiovascular diseases cause 25% of the deaths in our country. With increasing longevity of life these NCDs have become more important. The present longevity for an Indian male is 67 years and for female 70 years. At the time of independence, the median longevity was around 45 years. The non-communicable diseases like dengue and other tropical diseases are still very common in our country. The COVID-19 pandemic has brought viral infections into the centre stage. Looking at all this, I feel we should continue to lay stress or both NCDs and communicable diseases.

8. How we can bring change in attitude of the doctorswhich is compatible with the future needs ?

The national medical commission (NMC) has started an induction course for fresh entrants into MBBS. This course emphasis on soft skills and there is ample time for discussing with young future doctors about these. The AETCOM (Attitude, Ethics & communication) module is being incorporated in the medical curriculum now by the NMC. This will be across all years of the MBBS course and medical ethics will be taught uniformly. We need to make them

realise that this is the most noble profession, and they have a great responsibility to carry this legacy. The change will come if we as teachers and practicing doctors become role models for the youngsters. Each one of us should realise that the future generation will follow what they see us doing. The future for them has great potential but there are significant challenges as well.

9. Do you feel in coming days Indianeeds more primary care or super speciality doctors?

Definitely, more primary care physicians. The way we are increasing postgraduate seats we will be left with few primary care physicians. Primary care needs much wider knowledge and astute clinical skills. The primary care physicians have to be considered at par with specialists like in UK where the GP is the most important person.

In the NHS, the GPs or primary care physicians are the best paid doctors in the whole system. This gives them the incentive to work more. But in India, primary care physicians are essentially left to fend for themselves with no government support and no social support. How can we encourage the youngsters to take up such a position?

10. Whether virtual seminars should be given new importance infuture curriculum.

Surely, the virtual seminars are a reality. The earlier a student learns it, better for the long run. The Massive Open Online Courses (MOOCs) are a reality. We need to integrate them into the learning process. Basic knowledge of computers, these communications portals, search engines and artificial intelligence is a must today. Electronic or online learning and face to face learning will now be used side by side. Such blended learning programmes will need strong institutional support and good internet connectivity. Patient care will not depend only on the ability to make a clinical diagnosis. Young doctors will have to be members of a healthcare delivery team with shared responsibilities and lot more use of technology.

11. What about virtual teaching methods:Should they becontinued even after the pandemic in over.

Absolutely. The virtual seminars are there to stay. The pandemic has been a major disruptor. However, as Abdul Kalam said, “Adversity always presents opportunities for in introspection”. They have significant cost saving, saving of time and freedom to switch on from home. Recording helps us to listen to them again. The cost of holding big conferences is enormous. As more portals develop these will become more interactive also.

12. Is training of senior teachers required about virtual *teaching method?*

Yes, to be digitally literate they will require training. Proper communication is very important. There should be no resistance to this change. They must transition to virtual student support and guidance using the e-learning platforms. The remote learning and online learning options need to be incorporated with ingenuity. If we do not exploit the potential of the various portals, we will only be using the basics. There is a need of simple articles in journals like JIMA and audio /video educational materials on these portals like Zoom, Google scholar etc.

In JIMA, we are planning to start a new monthly section on the use of current technology from January 2021. Please stay tuned.

13. Do you feel the doctor patient relationship has changed with the pandemic?

The pandemic has resulted in difficult times. The healthcare personnel have lost many colleagues. There is fear of their own risk and indirectly to the family. Uncertainly, crises and difficult times bring out the worst behaviour in some people. Due to all this, the doctor-patient relationship has been traumatised significantly.

On a positive note the pandemic has certainly brought healthcare to the focus of attention of the policy makers and the public. The IMA especially our President have represented the health care viewpoint very effectively on the national news networks. People now understand the difficulties of health care workers in a better manner. So, I would say there have been some positives also.

14. What measures should we take to improve the doctor patient relationship in future?

The doctor patient relationship was earlier viewed as one between a 'healer' and a 'sick person'. It is now viewed as an interaction between a 'care provider' and a 'service user'. It was earlier based on trust, loyalty and regards and so if improved recovery. Now the patient has become a 'consumer'. We must make the young doctors genuinely compassionate, caring and service oriented. The patients are better informed now, and we need to adapt. Transparency, open discussion, and patient participation in decision making has to be done. Anything hidden always raises doubt and should be avoided. The earlier 'Active-passive model' of the doctor patient relationship changed to a 'Guidance cooperation model'. Presently, it is a 'Mutual participation model' which places both at an equal level, we must let patients participate in the decision making and this will further improve the relationship. Besides this professionalism and good etiquettes need to be imbibed and practiced.

The cost of medical care is going up since effective but costly options are available. The patient should be given an idea of the exact cost that will be incurred and then allowed time to take a decision. These simple modifications will improve the doctor-patient relationship.

15. How the medical curriculum IMS (Indian Medical Service) will help to achieve this?

The Indian medical service system will ease the system of decision making. It will place doctors in the decision-making team and so obviously will be a great step forward in the right direction.

The IMS will help the doctors to have negotiating power equal to the bureaucracy in India. Now, doctors are their subordinates and must follow whatever the administrative bosses may order. Before independence, the doctors who were part of the IMS could take a lot of important decisions like starting a new department, increasing the number of beds in a hospital or recruiting research assistants. But now, even for these essential tasks, doctors have to depend on the administrative branch.

Thank you Dr Wander for your answers. We appreciate the time taken by you and we are sure that our readers will be benefited immensely.

Original Article

Maternal and fetal outcome in pregnancy with HbE Hemoglobinopathy in high prevalence area of North Bengal at Tertiary Health Care Facility

Madhusudan Haldar[1], Shamim Khandaker[2], Nabajibon Mondal[3], Shabana Munshi[4]

Introduction : This study is unique and first in the literature which compares feto-materanl outcome in HbE hemoglobinopathy mother with other anemic mother but without any hemoglobinopathy in the HbE high prevalence area of North Bengal as this group present in pregnancy as a special scenario.

Aims : Main objective of this study is to compare the feto-maternal outcome of pregnancy in HbE variant antenatal anemic women with respect to other antenatal anemic women with normal hemoglobin variant.

Methodology : It is a prospective cohort study. Anemic antenatal mothers are screened for HbE hemoglobinopathy by HPLC.They are grouped into Case group (HbE variants) and control group (anemic but with normal Hb variant).They are followed up till termination of pregnancy for detection of antenatal, intranatal, postnatal complication and neonatal or pregnancy outcome. Multiples variables are analyzed and compared with each group.

Results : The main outcome from this study is mean Hb concentration is significantly lower in HbE variant mothers than normal Hb variant antenatal anaemic mothers with more need for blood transfusion in postpartum period. Maternal hospital stay is also more in HbE variant mothers. Incidence of prematurity, fetal distress, and low APGAR score baby are high in HbE variant mothers. Neonatal respiratory distress syndrome and SNCU admissionare more in HbE variant mothers. Low birth weight baby is not significantly high in HbE variant mothers inspite of prematuirity.

Conclusion : In high prevalence area of HbE hemoglobinopathy adverse feto-maternal outcome is expected and regular antenatal check-up with monitoring for fetal growth and institutional delivery with good SNCU facility for newborn care is paramount for optimal feto-maternal outcome.

[*J Indian Med Assoc* 2020; **118(11):** 28-32]

Key words **: Anemia in pregnancy, Hemoglobinopathy HbE.**

Hemoglobinopathies are a diverse group of inherited disorders of hemoglobin production and function. They are the most common single-gene disorders that remain distributed in various frequencies throughout the world. In general, they can be classified broadly in two groups. One group is, disorder that result from structurally altered hemoglobin molecules (like sickle cell anemia) and another, that arises from numerical imbalance of otherwise normal globin chain synthesis (like β-thalassemia).

Cumulative gene frequency of haemoglobinopathy in India is 4.2%[1]. While the general incidence of thalassemia trait and sickle cell haemoglobinopathies in India varies between 3-17% and 1-44%[2] respectively because of consanguinity and caste and area endogamy, some communities show a very high

[1]MD (O&G) (JIPMER); Associate Professor, Department of Obstetrics and Gynaecology, North Bengal Medical College, Sushrutanagar, Darjeeling 734012

[2]MS (G&O), FNB (High risk pregnancy & perinatology), FNB (Reproductive Medicine), Assistant Professor, Department of Obstetrics and Gynaecology, North Bengal Medical College, Sushrutanagar, Darjeeling 734012 and Corresponding Author

[3]MS (G&O), Medical Officer, Department of Obstetrics and Gynaecology, Subdivision Hospital, Malbazar, NH 17, Jalpaiguri 735221

[4]DGO, DNB (G&O); RMO *cum* Clinical tutor, Dept of O&G, North Bengal Medical College, Sushrutanagar, Darjeeling 734012

Received on : 18/08/2020

Accepted on : 05/10/2020

Editor's Comment :

- **HbE hemoglobinopathyis associated with adverse feto-maternal outcome.**
- **Affected mother is more anaemic with more need for blood transfusion in postpartum period.**
- **Incidence of prematurity, fetal distress, and low APGAR score baby are high in HbE variant mothers.**
- **Neonatal respiratory distress syndrome and SNCU admissionare more in HbE variant mothers.**
- **Institutional delivery with good SNCU facility for newborn care is paramount for optimal feto-maternal outcome.**

incidence, making these diseases a major public health problem in our country[2,3].

HbE is the commonest abnormal hemoglobin variant in North-Eastern Region with prevalence of 7-50% and 1-2% in West Bengal[4]. Hemoglobin E disorder falls under the first category; structural defect in globin chain. It ($\alpha_2\beta_2^{26\ glulys}$) is a variant of hemoglobin, resulting from single β chain substitution of lysine for glutamic acid at position 26 codon of globin chain molecule[2]. Hemoglobin E is inherited. Hence there remains a chance of vertical penetration to her offspring.

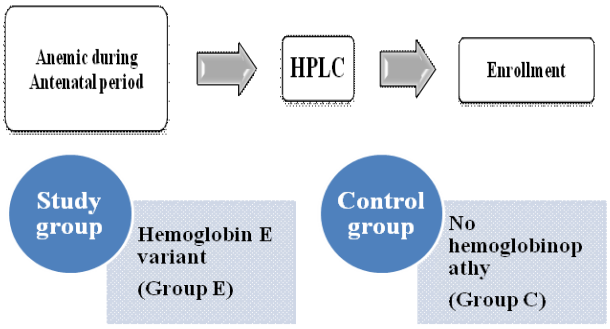
North Bengal comprises of four Sub-Himalayan districts of West Bengal is ethnically distinct not only from the rest of India but also from the rest of West Bengal. It is multi-ethnic and besides being inhabited by Bengalis, it is home to different population group like Rajbangsis, Marwaris and Hilly people like Nepalese, Bhutanese, Sherpa, Lepcha and many tribal populations like Santhals, Oraws and many others. In the plains of Darjeeling district, located in northern part of West Bengal, the Rajbangsis form a major chunk of the local inhabitants. The Rajbangsis are known to have a high prevalence of HbE mutation, though there is no published data till date. Subjects having HbE, either in homozygous or heterozygous state is otherwise normal but the probability of combining with β thalassemia trait can give rise to hemoglobin E-beta thalassemia. HbE-beta thalassemia can manifest as thalassemia minor, intermediate or even the grievous thalassemia major.

Obstetricians in these regions often face the pregnancies complicated by severe anemia, irrespective of any haemoglobinopathies. Moreover, being a zone highly prevalent with HBE, antenatal anemic women in scheduled visit occasionally revealed HBE trait or disease when advised for routine Hb electrophoresis. These causes confusion among the clinicians, as there is not enough data till date to estimate the severity and treatment of these anemic antenatal women with hemoglobin E. The purpose of this study lays on this context.

Thus, the main objective of this study is to compare the feto-maternal outcome of pregnancy in HbE variant antenatal anemic women with respect to other antenatal anemic women with normal hemoglobin variant.

Methodology :

It is a prospective cohort study done at Gynecology & Obstetric Department of North Bengal Medical College and Hospital during 1year period from June 2013- May 2014. All antenatal mothers are screened for Hb% and if they found to have anemia depending on cutoff value of Hb% 10gm/dl; they are selected in the cohort and advised for HPLC study. It is simple, rapid, sensitive, reliable method for detection of Hb variant. After that they are grouped into Case group (group E) include HbE variants and control group(group C) include anemic but normal Hb variant.After enrolment into specific group they are follow up till termination of pregnancy for detection of antenatal, intranatal, postnatal complication, mode of delivery and neonatal or pregnancy outcome. Multiples variables are analyzed and compared with each group.



Inclusion criteria for case:

a) Exclusive HbE variants

b) With other haemoglobinopathy in combined with HbE variant

Exclusion criteria for case:

a) Anemic women with unkown HbE status

b) Lost to follow up

c) Presence of other haemoglobinopathy without HbE variants

d) Expected date of delivery after study period

e) Critically ill moribund patient due to other chronic cause like chronic renal disease, heart disease, uncontrolled DM

Based on feasibility in North Bengal Medical College and Hospital we consider following statistical test values confidence level 95%, relative precision 20%, anticipated proportion of pregnancy complicated by anaemia with normal Hb variant 70%. Minimum sample size based on this is approximately 67 in each group [sample size determination in health study; SK Lwanga; Epidemiological and Statistical methodology; WHO table 8d]. In this study we finally taken 70 candidates in each group considering expected dropout.

Primary outcome of the study is to determine and compare antenatal, intranatal and postnatal complications in anaemic antenatal women with HbE variants versus anaemic women without haemoglobinopathies and to compare neonatal

outcome of women with HbE variants and women without hemoglobinopathy.

After completion of meticulous follow up all the characteristics are placed in master charts separately for HbE variant mother (group E) and normal Hb variant mothers (group C). Data was then entered in SPSS 16 for analysis (SPSS Inc, Chicago, IL, USA). Statistically significant is consider when P value is <0.05.

Results

Total number of cases in each group is 70. Majority of pregnancy is in 20-26 years women and almost equal in both groups that is 74.24% & 72.85% in group E and group C respectively. The age distribution in both the groups is comparable. More incidence of HbE variant is seen in high socio-economics status group. On the contrary, anemic but normal Hb variant mothers are in relatively lower socioeconomic status group as in those group of women incidences of nutritional anemia is relatively high.

Most of the mothers is primigravida (68.57% and 68.28% in HbE variants and normal Hb variant respectively). This is likely because of social factor that in 1st pregnancy most of the mothers attended in hospital than in subsequent pregnancy. Along with the fact that primigravida mothers more commonly referred to this tertiary hospital from peripheral hospital than multigravida mothers.

Mean Hb% in HbE variant mother was 8.20 gm% with standard deviation 1 and in anaemic normal Hb variant mother 8.64 gm% with standard deviation 0.7. This difference is statistically significant (P 0.002). Among the women with HbE variants most are HbE trait (AE) [58.57%]. No case of combination of HbE variants with sickle cell disease (SE) found. Only one case (1.42%) of HbE-β thalassemia found. Rest 40% is HbE disease (EE). Finding of study by Ong. HC *et al*[5] on Malayasian aborigine shows relative prevalence of different variants as follows: 71.2% with HbE trait abnormality, 17.6% with Hb E homozygous disease, and 11.2% with HbE-β thalassemia disease. The high frequency homozygous HbE (EE) in our study is probably due to area endogamy and poor premarital and pre-conceptional counseling.

Mean gestational age 37.28 with standard deviation 2.22 in study groups and 37.96 with standard deviation 2.23 in control groups. Total number of preterm deliveries was 24.61% in HbE variant & 13.43% in normal Hb variant respectively (P 0.04) (Table 1). In the study by Luewan S *et al*[6] there is three fold increased rate of preterm birth but in the study by Ong HC *et al*[5] there is no such increase rate of preterm birth is noticed. Table 1 also shows comparison of different modes of delivery and onset of labour process between two groups; the difference between them are not statistically significant.

Table 1

	Group E		Group C		P value
Mean Gestational age at delivery	37.28 wks with SD 2.2		37.96 wks with SD2.3		0.04
Gestation at time of delivery					
Preterm delivery	16	24.61%	9	13.43%	0.04
Term delivery (37-40wks)	42	67.74%	52	78.78%	
Postdated (>40wks)	4	6.45%	5	7.57%	
Mode of delivery					
Vaginal delivery	32	49.23%	42	62.68%	0.28
Forceps delivery	11	16.92%	8	11.94%	
LSCS	22	33.84%	17	25.37%	
Onset of labour					
Spontaneous labour	41	63.07%	50	74.62%	0.25
Induction of labour	17	25.15%	14	20.89%	

Antenatal complications like Preeclampsia, Heart failure, Antepartum haemarrhage, prelabour and/or preterm rupture of membrane, oligohydramnios, intrauterine growth restriction, gestational diabetes mellitus, urinary tract infection is not increase significantly in HbE variant mother in compared to normal Hb variant (Table 2). Study by Ong HC[5] revealed no increased in preeclampsia in HbE variant patients in compared to normal variant. So this study, to some extent support this event.

Study by Luewan S et al[6] heralded that increased incidence of IUGR in HbE variant mothers which is contradicted by this study. In the study by Ong HC[5] mean birth weight was significantly lower inspite of no increaserd prematuirity, this might be due to intra-uterine growth restriction, but it was not clearly mentioned in their study.

Incidence of fetaldistress was significantly high in HbE variant (27.58%) than normal Hb variant mothers (12.5%). [P 0.01] The probable explanation for this is cumulative effect of increased incidence of prematuirity,

Table 2

Antenatal complication	Group E (n= 65)		Group C (n=67)		P value
	Number	%	Number	%	
Preeclampsia	14	21.53	8	11.94	0.14
Heart failure	3	4.28	2	2.85	0.65
APH	5	7.69	2	2.98	0.23
PPROM	5	7.69	4	5.97	0.69
IUGR	5	7.69	3	4.48	0.43
Oligohydramnios	11	16.92	11	16.42	0.93
GDM	1	1.53	0	0	0.27
UTI	5	7.14%	3	4.28%	0.46

induction of labour and maternal complication like PIH, PROM, dysfunctional labour, abruptio placente in HbE variant mothers.

Although, percentage of dysfunctional labour (17.24%) is more in study group than control group (15.6%) but not statistically significance. Incidence of Abruptio placente, PPH, subinvolution, retained placenta is slightly high in HbE variant mothers that is 3.44%, 20%, 4.61%, 1.53% respectively compared to normal Hb variant mothers 1.56%,10.44%, 2,98%, 2.98% respectively; although the differences are not at statistically significant. Incidence of sepsis in HbE variant (2.85%) is higher than normal Hb variant (1.42%) mothers (P 0.56).Only 2(3.22%) cases had lactational problem after live birth in HbE mothers.

Total cases of blood transfusion in HbE group is 21(30%) which is significantly higher (P 0.07) than normal Hb variant anemic pregnant women (12 cases, 17.12%). Most of the transfusion re quired in post-partum period. No cases of reaction occurred in HbE variant mothers and there is also no major transfusion reaction. Mean duration of hospital stay is 5.18 day with standard deviation 3 in HbE variant mothers and in normal Hb variant mothers it is 4.3 days with standard deviation 3 (P 0.05).

Total live birth was 62(88.57%) and 66(94.28%) in HbE variant and normal Hb variant respectively (P 0.23). Incidence of abortion (7.14% vs 4.28%; P 0.46) and IUFD (2.85% vs 1.42%; P 0.55) was not significantly increased in HbE variant mother than control group. Also, in the study by Frischer H *et al*[7] pregnancy wastage is not increased among HbE mothers.

Among live birth babies; Mean APGAR score of HbE variant mothers at 1st is 5.51 (SD 1.6) and & at 5th min 8.64 (SD 1.8). This different in both groups is statistically significant (P 0.04). More newborn found to be mild to severely depressed in HbE variant mothers than normal Hb variant mothers (Table 3). Possible explanation for this difference may be due to more incidence of fetal distress, resulting in premature birth and low birth weight baby.In a prospective study by B Mahamuda *et al*[8] in Bangladesh mentioned significant increased incidence of lower gestational age baby with low APGAR score at 1st and 5th min depending of severity of anaemia. Another study by Nisha Shah *et al*[9] found significant high incidence of prematurity in anaemic mothers than normal mothers.

Mean birth weight is 2.623kg with standard deviation 0.6 in HbE variant mothers. It is 2.721kg with standard deviation 0.5 in normal Hb variant mothers. Mean bitrh weight is calculated in each groups excluding abortion but including still birth and IUFD. Maximum percentage of birth weight are in >2.5-3.5kg that is 61.23% & 77.27% in HbE and normal Hb variant mothers. But birth weight 1.5-2.5kg more frequent in HbE variant mothers than normal Hb variant mothers, 32.26% &16.67% respectively. But this difference is not statistically significant.

SNCU admission of newborns in HbE mothers is statistically significant (41.9% vs 24.2%; P=0.01).Regarding neonatal complication, only respiratory distress syndrome is significantly high in HbE variants mothers than normal Hb variant mothers. Other complications like jaundice, sepsis, meconium aspiration syndrome, necrotising enterocolitis & hypoglycemia are more in HbE variant mothers but not statistically significant (Table 4). Slightly increase percentage of perinatal death in HbE variant mother but it is not statistically significant (9.2% vs 5.9%; P= 0.48). This is likely due to advanced neonatal management in SNCU despite high frequency of neonatal morbidity in HbE variant mothers. The high incidence of neonatal morbidity likely due to increased frequency of preterm birth, fetal distress, low birth weight baby.

Conclusion

This study compares feto-materanl outcome in HbE hemoglobinopathy mother with other anemic mother but without any hemoglobinopathy in the HbE high prevalence area of North Bengal as this group present in pregnancy as a special scenario.

The main outcome from this study is mean Hb concentration is significantly lower in HbE variant

Table 3

Mean APGAR score	Group E (n=62)	Group C (n=66)	P value
1st min	5.51 (SD=1.6)	5.93 (SD=1.2)	0.04
5th min	8.64 (SD=1.8)	9.13 (SD=1.4)	0.04

Table 4

Complication	Group E (n=62)		Group C(n=66)		P value
	number	%	number	%	
Jaundice	16	25.81	11	16.67	0.21
Sepsis	10	16.13	7	10.61	0.35
Respiratory distress	8	12.90	2	3.03	0.03
Meconeum aspiration syndrome	3	4.84	1	1.52	0.28
Necrotizing enterocolitis	1	1.61	1	1.52	0.96
Hypoglycemia	1	1.61	0	0	0.29
SNCU admission	26	41.9	14	21.2	0.01
Perinatal death	6	9.23	4	5.96	0.48

mothers than normal Hb variant antenatal anaemic mothers with significantly more need for blood transfusion in postpartum period for HbEvariant mothers. Maternal hospital stay more in HbE variant mothers than normal variant mothers for pregnancy event. Incidence of prematurity, fetal distress, and low APGAR score baby are significantly high in HbE variant mothers than normal Hb variant mothers.Neonatal respiratory distress syndrome, SNCU admission are more in HbE variant mothers.Low birth weight baby is not significantly high in HbE variant mothers inspite of prematuirity.

In high prevalence area of HbE hemoglobinopathy adverse feto-maternal outcome is expected and regular antenatal check-up with monitoring for fetal growth and institutional delivery with good SNCU facility for newborn care is paramount for optimalfeto-maternal outcome.

Limitations: This study is a prospective cohort study with comparison between to groups of anemic mothers where one group in anemic due to HbE hemoglobinopathy and other group is anemic due to other causes. But the different causes of anemia in control group of mothers is not addressed, so that group is heterogenous. In this study, outcome of normal mothers without anemia is not compared with HbE mothers with anemia.

References

1 Sarnaik SA — Thalassemia and related hemoglobinopathy. India J Pediatr 2005; **72:** 319-24.
2 Balgir RS. The burden of haemoglobinopathies in India and the challenges ahead. *Curr Sci* 2000; **79:** 1536-47.
3 Balgir RS — The genetic burden of haemoglobinopathies with special reference to community health in India and challenges ahead. *Indian J Hemat Blood Transfus* 2002; **20:** 2-7.
4 Piplani S — Hemoglobin E disorder in north east India. J Assoc Physician India 2000;48(11):1082-4.
5 Ong HC — Haemoglobin E Variants and pregnancy in Malaysian aborigines. *Acta Haematol* 1974; **52(4):** 220-2.
6 Luewan S, Srisupundit K, Tongsong T — Outcomes of pregnancies complicated by beta-thalassemia/hemoglobin E disease.Int J Gynaecol Obstet. 2009 Mar; 104(3):203-5.
7 Frischer H, Bowman J — Hemoglobin E on oxidatively unstable mutation. *J Lab Clin Med* 1975; **85:** 531.
8 Mahamuda B, Tanira S, Feroza W, Perven H, & Shamim A — Effects of maternal anaemia on neonatal outcome: a study done in the specialized urban hospital set up in Bangladesh. *Bangladesh Journal of Medical Science* 2011; **10(3):** 177-80.
9 Shah N, Upadhyay C, Sahota R — Neonatal Outcome In Anemic Mothers: a Prospective Study. *Journal of Evolution of Medical and Dental Sciences* 2013; **2(43):** 8355-9

Original Article

Study of cardiac manifestations in patients with Human Immunodeficiency Virus Infection in West Bengal

Sirshendu Pal[1], Rupsha Dutta (Pal)[2], Subhas Chandra Hazra[3]

This case control study was done on 40 human immunodeficiency virus infected patients of North Bengal Medical College and Hospital compared with a healthy matched control group. The study was conducted to assess the cardiac chamber anomalies along with changes in pericardium. It was also aimed to check for lipid abnormalities and compare them with echocardiographic abnormalities and to document the relationship between CD_4 counts and echocardiographic abnormalities. Age and sex distribution and opportunistic infections were also studied. The mean age was found to be 34.15 years while maximum number of patients was in the age group 31- 40 years. Males outnumbered the females. Tuberculosis was the commonest opportunistic infections followed by Candidiasis. 85% of patients were asymptomatic from the cardiac point of view. It was obvious that total cholesterol, HDL cholesterol and LDL cholesterol of the study group were significantly lower than the control group though this was not the case with triglyceride levels. The study showed a positive correlation between CD_4 count and total cholesterol, HDL cholesterol and LDL cholesterol while inverse relation was seen with triglyceride and VLDL cholesterol. Pericardial effusion was the commonest echocardiographic finding. Low HDL cholesterol and LDL cholesterol were more significantly associated with pericardial effusion while low total cholesterol and high triglyceride were more significantly associated with diastolic dysfunction. Thus lipid levels could serve as markers for cardiac dysfunction where echocardiography is not available.

[*J Indian Med Assoc* 2020; **118(11):** 33-7]

Key words **: Lipids, CD_4 counts, Echocardiography, HIV.**

In 1981, when the world was alerted to the first case of Acquired Immunodeficiency Syndrome (AIDS), no one could have imagined that it would claim more than 20 million lives in a matter of 20 years. The first report described 5 young homosexual men in whom a rare disease, *Pneumocystis carinii* pneumonia had developed. Each patient had abnormal ratios of lymphocyte sub-groups and was actively shedding cytomegalovirus[1]. In 1983, Human Immunodeficiency Virus was isolated from a patient with lymphadenopathy, and by 1984, it was demonstrated clearly to be the causative agent of AIDS.

Cardiac involvement is more frequent in the more advanced stages of infection and in patients with lower CD_4 counts. During the 1990s, the disease was transformed for many patients specially in industrialized nations from a predictably fatal infection to a chronic condition requiring daily medication and occasional visits to the doctor's chamber[2].

North Bengal Medical College and Hospital, Sushrutanagar, Darjeeling 734012
[1]MD (Med), Senior Consultant Physician
[2]MD (Path), Assistant Professor and Corresponding Author
[3]MD (Med), Professor
Received on : 12/09/2019
Accepted on : 15/09/2020

Editor's Comment :

- **Low LDL levels and low HDL levels were more significantly associated with pericardial effusion while low total cholesterol and high triglycerides were more significantly associated with diastolic dysfunction. Thus lipid levels could be used as markers for cardiac dysfunction where echocardigraphy is not available.**

Aims and Objectives

1. To study cardiac chamber anomalies including left or right ventricular hypertrophy, and left ventricular systolic and diastolic dysfunction.
2. To note changes in the pericardium, myocardium and endocardium.
3. To check for lipid abnormalities and compare them with echocardiographic abnormalities.
4. To decipher any relationship between CD_4 counts and echocardiographic abnormalities.

Materials and Methods

Study Area :

North Bengal Medical College and Hospital, Sushrutanagar, Darjeeling.

Study Population :

Human Immunodeficiency Virus positive patients residing in North Bengal.

Selection Criteria :

1. Age > 20 years.
2. Sex - Male and Female
3. Western Blot confirmed cases after preliminary ELISA was positive.
4. Cardiac manifestations not attributable to any other cause.

Exclusion Criteria :

1. Addiction to alcohol or cocaine.
2. Family history of cardiomyopathy, pericarditis or storage disorder.
3. History of drug intake such as procainamide, hydralazine, phenytoin, methysergide, doxorubicin, etc.
4. History of zidovudine and protease inhibitor group of antiretroviral drugs intake.
5. History of radiation exposure.
6. History of relevant trauma.
7. Patients suffering from acute myocardial infarction, uraemia, neoplasia or other confounding illnesses.
8. Pregnant and peripartum women.
9. Electrolyte abnormalities.

Sampling :

Random.

Study Group :

40 human immunodeficiency virus infected patients with or without symptoms.

Control Group :

Healthy matched control of 20 individuals not infected with human immunodeficiency virus.

Duration of Study :

1 year (2017-2018).

Identification data was collected and detailed history taken. This was followed by general examination and systemic physical examination. Routine investigations and special tests were done. Screening was done for opportunistic infections . Principle of flow cytometry was used for CD_4 counts.

Statistical Analysis :

Mean and standard deviations were calculated. Tests of significance used were a) Standard error of difference between two means b) Standard error of difference between two proportions c) Paired t-test d) Chi-square test e) Coefficient of correlation.

Observations

In our study group, 8 patients were symptom free. Mean age was 34.15 years. Maximum number of patients was in the age group 31- 40years. In each decade, males outnumbered the females (Table 1).

Table 1 — *Distribution of patients according to age*

Class interval	Frequency
21-30	16
31-40	18
41-50	3
51-60	2
61-70	1

It was more common in goldsmiths(n=8) and drivers(n=5). In our study group, 80% of the patients were suffering from opportunistic infections. The commonest opportunistic infection was Tuberculosis (27.5%) followed by Candidiasis (20%) (Table 2).

Table 2 — *Opportunistic Infection*

Opportunistic Infection	No. of patients	% of patients
Candidiasis	8	20
Tuberculosis	11	27.5
Pneumonia Inc. PCP	3	7.5
Bacillary Dysentery	2	5.0
Genital Herpes	1	2.5
Syphilis	1	2.5
Toxoplasmosis	1	2.5
Cryptococcal Meningitis	1	2.5
Sinusitis	1	2.5
Hepatitis	1	2.5
Taenia Corporis	1	2.5

There was a significant difference between the total cholesterol level of the study and the control group ($t<0.01$).

The correlation co-efficient (r) between CD_4 count and total cholesterol was 0.31 ie, there was a positive correlation. As CD_4 count diminished, Tc (Total cholesterol) also diminished and vice-versa. However, there was no statistically significant difference in CD_4 counts between patients with low cholesterol and those without low cholesterol, though there was a positive correlation between cholesterol levels and CD_4 count. This slight apparent paradox may be explained by the fact that most of our cases were newly detected or within the first few years of detection. It is well known that hypocholesterolaemia is an early manifestation of Human immunodeficiency virus infection and CD4 count might not have decreased proportionately to that extent.

By Chi-square test, diastolic dysfunction was significantly more in HIV infected patients with low Total Cholesterol ($P<0.001$). Similarly, low total cholesterol was significantly associated with pericardial effusion. However, there was no significant difference between the two groups with respect to systolic dysfunction ($P>0.05$).

Paired t-test showed that there was no significant difference in the triglyceride levels of the study and control groups. This was perhaps because increases in triglyceride levels occur at a later stage of HIV infection while most of our cases were newly detected or were within the first few years of detection.

The correlation coefficient (r) between CD_4 count and TG was -0.3 ie, there was a negative correlation between the two. However, there was a statistical

difference in the CD_4 cell counts between patients with high TG levels and those with normal TG levels. Patients with high triglyceride had significantly more evidence of diastolic dysfunction (P<0.02). Pericardial effusion was significantly more common in the high triglyceride group. However, systolic dysfunction was not affected by the triglyceride levels.

HDL-cholesterol levels in the study group were significantly different from the control group (t<0.01). The correlation coefficient (r) between CD_4 count and HDL was +0.42, indicating a positive correlation between the two. There was a statistically significant difference in the CD_4 levels of the low HDL and the normal HDL level groups. Patients with low HDL levels were significantly more likely to have diastolic dysfunction as compared to those with normal HDL levels (P<0.01). Pericardial effusion was significantly associated with the low HDL group and the association was stronger than that with diastolic dysfunction (P<0.001). Again there was no significant difference between the low and the normal HDL groups with regard to systolic dysfunction.

The LDL- cholesterol levels in our study group were significantly different from those of the matched controls (t<0.01). The correlation coefficient (r) between CD_4 count and LDL was +0.38 indicating a positive correlation between the two. Diastolic dysfunction was significantly more common in those with low LDL than in those without so (P<0.01). Low LDL was significantly associated with pericardial effusion and the association was stronger as compared to diastolic dysfunction (P<0.001). However, there was no significant difference between the low and the normal LDL levels as far as systolic dysfunction was concerned.

Distribution of patients with echocardiographic manifestations in particular CD_4 range :

81.48% patients with CD_4 counts less than 200/µl had echocardiographic manifestations while only 7.69% of patients with CD_4 counts greater than 200/µl had echocardiographic manifestations. Since observed difference is more than 2 times the standard error of difference, the difference is statistically significant and not merely due to chance.

Discussion

Mean Age :

George J *et al*[3] conducted a study on 60 HIV infected patients and found a mean age of 30.3 years. K.Kothari *et al*'s[4] study of 30 patients found a mean age of 32.76± 8.11 years. 34.9 ± 12 years was the mean age in the study by Sircar et al[5]. Our study group had a mean age of 34.15 +/- 9.39 years.

Gender :

In almost all the studies including ours, there is a male preponderance. The exact reason is not known but perhaps females being home bound have less scope of high risk behavior.Also there may be a bias of doing HIV test more in male patients. Bogaert's J et al[6] from Rwanda, Africa reported one such study on 2824 adults of whom 1578 were men and 1246 women. (Ratio 1.26:1). A study in Edinburgh, U.K by Brettle et al[7] enrolled 680 patients of whom 476 were men and 204 were women, giving a ratio of 2.3:1.

Clinical Manifestations :

In a study by Fink *et al*[8], none of the 15 patients had clinical evidence of myocardial disease. However,on echocardiogram, almost all patients had cardiac dysfunction. Similarly, Levy et al[9], discovered cardiac abnormalities in 53% of his patients, though clinicians suspected none as having cardiac disease. Blanchard *et al*[10] found echocardiographic abnormalities in both symptomatic (52%) and asymptomatic (40%) patients. In our study, patients were asymptomatic from cardiologic point of view in 85% cases.

Lipids :

We compared our study group to a matched control group without HIV infection. It was obvious that total cholesterol, HDL cholesterol and LDL cholesterol of our study group were significantly lower than the control group. Hypocholesterolemia has been documented in various studies the world over[11, 12]. Authors opine that hypocholesterolemia occurs early in the course of HIV infection. This is well endorsed by our study comprising of mostly newly detected cases or cases within 1-2 years of detection.

Triglyceride levels in our study group were not significantly different from the control group (t>0.05). This was perhaps because hypertriglyceridemia occurs in the advanced stages of the disease as seen in studies by SA Mullamithai and A R Pazare[12]. Our study group comprised mostly of newly detected cases.

Low HDL levels as reported in our study were also reported from France[11] and Brazil[13]. However, a study from TNM College, Mumbai[12] did not find statistically different HDL levels compared to controls.

Our finding of low HDL is corroborated by C Fernandez- Miranda *et al*[14] and J. Constans *et al*[15]. Our study showed a positive correlation between CD_4 cell count and total cholesterol, HDL cholesterol and LDL cholesterol while inverse relation was seen with triglyceride and VLDL cholesterol. Similar conclusions were drawn by A Treitinger and C. Spada *et al*[13]. J

Ducobu and MC Payen also opined that lipid changes are proportional to the lowering of CD_4, which reflects the severity of infections [11].

Echocardiographic Abnormalities :

In our study group, 24 patients (60%) showed echocardiographic manifestations though only 6 (15%) had cardiac symptoms. Among them systolic dysfunction was present in 8 (20%), while diastolic dysfunction in 15 (37.5%). Systolic dysfunction was mild while diastolic dysfunction moderate in 3 (7.5%) and severe in 1 (2.5%). 2 patients (5%) had both systolic and diastolic dysfunction. Mitral regurgitation was present in 4 cases (10%) while tricuspid regurgitation in 7 cases (17.5%). 2 patients suffered from hypokinesia of which 1 was global in distribution. There were 2 cases of atrial septal defect which were perhaps incidental findings. Pericardial effusion was the commonest finding accounting for 40% of the patients.

A study by G. Minardi *et al* from Italy[16] on HIV positive subjects showed a cardiac involvement in 75% of HIV infected patients; 35% had myocardial dysfunction, 37% pericardial disease, 31% infective pericarditis. H.M.Steffan *et al*[17] studied 128 patients (28%): small to moderate pericardial effusions (n=34) and left ventricular dilatation (n=5).

CD_4 Count and Echocardiography :

81.48% of our patients with CD_4 counts less than 200/µl had echocardiographic manifestations compared with only 7.69% of patients with CD_4 count more than 200/ µl. There was a statistically significant difference between the two. GL Werneck and E. T. Mesquita et al from Brazil reported that patients with a more advanced infection (those with a CD_4 count less than 500/mm^3) had a significantly abnormal LV systolic function and a higher incidence of pericardial effusion and mitral regurgitation[18].

Lipids *versus* Echocardiographic Findings :

Hypocholesterolemia (≤130mg/dl) was significantly associated with diastolic dysfunction (P<0.001) and pericardial effusion (P<0.02). Significant association of high triglyceride (>150mg/dl) with diastolic dysfunction (P<0.02) and pericardial effusion (P< 0.05) was evident. Low HDL cholesterol level (<35mg/dl) had a significant association with diastolic dysfunction (P<0.01) and pericardial effusion (P<0.001). Low LDL cholesterol level (<100mg/dl) was significantly associated with diastolic dysfunction (P<0.01) and pericardial effusion (P<0.001).Thus low HDL cholesterol and LDL cholesterol are more significantly associated with pericardial effusion than diastolic dysfunction, while in low total cholesterol and high triglyceride it is just the opposite.

Thus total cholesterol and triglyceride could serve as markers for diastolic dysfunction while HDL cholesterol and LDL cholesterol could serve as markers for pericardial effusion where echocardiographic facilities are not available. However, more studies specially large scale ones with high statistical power are required.

Limitations :

Small study group of 40 patients limited to newly detected patients or patients within the first 1 or 2 years of detection. Also we had to depend mostly on our indoor patients for our study.

Conclusion :

Cardiac complications are frequently encountered in the HIV infected population. Cardiac care providers should implement appropriate preventive, screening and therapeutic strategies to maximize survival and quality of life in this increasingly treatable chronic disease. All HIV infected patients should undergo echo to identify sub-clinical cardiac dysfunction and implement proper primary and secondary prevention strategies. Lipid profiles should also be done.

Funding : None

Conflict of Interest : None

References

1 Pneumocystis pneumonia – Los Angeles, Morb. Mortal. Wkly. Rep. 1981 June 5; **30:** 250-52.
2 Sepkowitz Kent A — AIDS- The First 20yrs. *N Engl J Med* 2001**; 344:** 1764-72.
3 George J, Hamide A, Das A K, Amarnath, RS Rao — JIPMER Clinical and Laboratory Profile of 60 patients of AIDS: A South Indian Study. South East Asian Journal Trop. Med. Pub. Health, 1996. Dec. **27 (4):** 686-91.
4 K Kothari, S Goyal — Clinical Profile of AIDS. *JAPI* 2001; 49:
5 Sircar Kumar SD, Kreiger B P — CD_4 lymphocyte counts and mortality in AIDS patients requiring mechanical ventilator support due to *Pneumocystis carinii* pneumonia. *Chest* 1998; **113:** 430-33.
6 Bogaerts J, Rouvroy D — AIDS associated *cryptococcal* memingitis in RWANDA; 1983-1992. Epidemiologic and diagnostic features. *J Infect Dis* 1999; **39(1):** 32-7.
7 Brettle RP, Foreman A, Poverty S — Clinical features of AIDS in Edinburg City Hospital cohort. *Int J STD AIDS* 1996; May-Jun **7(3):** 190-6.
8 Fink T Reichak N, Sutton MG — Cardiac abnormalities in Acquired Immunodeficiency Syndrome. *Am J Cardiol* 1984; **54:** 1161-63.
9 Levy WS, Simon GH, Rios JC — Prevalence of cardiac abnormality in Human Immunodeficiency Virus Infection. *Am J Cardiol* 1989; **63:** 86-9.
10 Blanchard DG, Hagenhoff C, Chow LC, *et al*— Reversibility of cardiac abnormalities in HIV infected individuals: A serial echocardiographic study. *J Am Coll Cardiol* 1991; **17:** 1270-76.
11 Ducobu J, Payen MC — Lipids and AIDS. *Revue Medicale de*

Bruxelles 2000; **21(1):** 11-7.
12 Mullamitha SA, Pazare AR — Study of lipid profile in Human Immunodeficiency Virus Infection. *Journal of the Association of Physicians of India* 1999; **47(6):** 622-24.
13 Treitinger A, Spada C, da Silva LM, Amaral J A, Abdalla DS — Lipid and acute-phase protein alterations in HIV-1 infected patients in the early stages of infection: correlation with CD_4 + lymphocytes. *Brazilian Journal of Infectious Diseases*. 2001; **5(4):** 192-99.
14 Fernandez- Miranda C, Pulido F, Carillo JL, Larumbe S, Gomez Izquierdo T, Ortuno B, Rubio R, del Palacio A — Lipoprotein alterations in patients with HIV infection: relation with cellular and humoral immune markers. *Clinica Chimica Aeta* 1998; **274(!):** 63-70.
15 Constans J, Pellegrin JL, Peuchant E, Dumon MF, Pellegrin I, Sergeant C, Simonoff M, Brossard G, Barbeau P, Fleury H, *et al* — Plasma lipids in HIV- infected patients: a prospective study in 95 patients. *European Journal of Clinical Investigation* 1994; **24(6):** 416-20.
16 Minadi G, Di Segni M, Boccardi L, Pucci E, Giovanni E — Echocardiographic evaluation of HIV- positive subjects [Italian]. *Giornale Italiano di Cardiologia*.1991; **21(3):** 273-80.
17 Steffen HM, Schrappe- Bacher M, Muller R, Salzberger, B Fatkenheur, G. Geisler S, Degenhaedt S, Griebenow R — Cardiac involvement within the scope of HIV-1 infection: preliminary results of Echocardiography study. [German]. *Zeitschrift fur Kardiologic* 1990; **79(2):** 83-8.
18 Werneck GL, Mesquita ET, Romeo Filho LJ, Ribeiro M L — Doppler echocardiographic evaluation of HIV- positive patienys in different stages of the disease. *Arquives Brasileiros de Cardiologia* 1999; **73(2):** 157-68.

Original Article

Healing of Chronic Wounds — are PDGF or Collagen granules better and cost effective than Normal Saline ?

Shamita Chatterjee[1], Arnab Mitra[2], Anirban Chatterjee[3]

Introduction : Managing chronic wounds is challenging, often requiring prolonged dressings and reconstructive surgery. Conventional dressings alone with normal saline (NS) may require significant time to heal. Newer dressing materials like recombinant human platelet derived growth factor (rhPDGF) and Collagen granules can reduce healing time and morbidity. A study was designed to compare effectiveness of rhPDGF and Collagen granules against NS, in terms of rate of wound contraction, reduction in wound complications and cost effectiveness.

Materials and Methods : Ninety patients with chronic wounds were randomised into three cohorts: conventional dressing (NS), rhPDGF and Collagen granules. Wounds were categorised into three groups based on their size. Wound area was recorded at the beginning of the study and then weekly for four weeks. Data regarding wound size reduction, percentage of wound contraction, and presence of wound complications were recorded and analysed.

Results : Majority patients were middle aged with male (75%) predominance. Most wounds were in the lower limb (76%). Diabetic ulcers (43.3%) were the commonest aetiology. rhPDGF and Collagen both showed statistically significant wound reduction (irrespective of wound size) compared to NS dressings and showed complete healing within 4 weeks. Pain and wound discharge was three times less with rhPDGF and five times less with Collagen. Both Collagen and rhPDGF are costlier than NS but the reduced time to healing makes it cost effective in the long run.

Conclusion : Newer agents like rhPDGF and collagen granules can help to reduce both the time taken for wound healing as well as its complications.

[*J Indian Med Assoc* 2020; **118(11):** 38-43]

Key words **: Chronic wound healing, rhPDGF, Collagen granules, normal saline.**

Wound care has evolved significantly in the past century from use of conventional dressing with normal saline (NS), and povidone iodine to the use of sophisticated wound dressing materials, hyperbaric oxygen chambers and the very recent regenerative dermal substitutes. At present, several therapies involving the administration of growth factor and collagen granules are being investigated to accelerate the wound healing process. Advanced wound management techniques are needed in chronic or non-healing wounds due to burns, diabetes mellitus or venous ulcers. These wounds are found to have lacunae in various stages of healing and have unusually elevated or depressed levels of cytokines, growth factors or proteinases[1]. Our study was conducted with the objective of comparing the effectiveness of recombinant human platelet derived growth factor (rhPDGF) and collagen granules in healing of chronic wounds and evaluate their role in promoting reduction in wound size.

Editor's Comment :

- **Managing chronic wounds is challenging.**
- **Conventional dressing with normal saline alone take significant time to heal.**
- **Newer agents like rhPDGF and Collagen Granules reduce both time taken for wound healing as well as its complications.**

Aims and Objectives

To compare the efficacy of rhPDGF and Collagen granule-based dressing with that of control group (conventional dressing using NS), by measuring the rate of reduction of wound size as a percentage of surface area of wound.

The end point of the study was to assess the % of wound contraction weekly for first four weeks.

The study also looked at the complications ie, wound discharge and pain between the three groups

[1]MBBS, MS (General Surgery), FMAS, FAIS, Associate Professor, Department of General Surgery, NRS Medical College, Kolkata 700014 and Corresponding author

[2]MBBS, MS (General Surgery), Senior Resident, Department of General Surgery, Burdwan Medical College, Burdwan 713104

[3]MBBS, MS(Ortho), DNB(Ortho), MNAMS, Orthopaedic Surgeon, Medica Superspecialty Hospital, Kolkata 700099

Received on : 20/10/2018

Accepted on : 10/12/2018

and cost effectiveness of using rhPDGF and collagen granules.

Materials and Methods

The study included 90 patients in the age group of 15 to 70 years with different types of chronic non-healing wounds of >90 days duration. Written informed consent of the patients and institutional ethical committee approval was obtained. The patients were randomized into three groups according to their attendance in the Out-Patient Department (OPD); every 1st case was allotted to rhPDGF arm, 2nd case to collagen granule arm and 3rd case to conventional dressing (NS) arm. Detailed history and thorough clinical examination was done. Baseline investigations for haemoglobin, serum albumin, and serum blood glucose (fasting and post prandial) levels were performed.

Criteria for inclusion in the study were any chronic ulcer (>3 months) in patients irrespective of its anatomic size and site. Wound aetiology varied from diabetic ulcer, atherosclerotic ischemic ulcer, traumatic ulcer, trophic ulcer to non - healing wounds of superficial burn. Exclusion criteria were: patients with uncontrolled diabetes (fasting blood glucose level above 130 mg/dl and post prandial above 180 mg/dl), serum albumin <3mg/dl, patients having underlying vasculitis, osteomyelitis, fracture or malignancy and on immunosuppressant therapy. Patients with atherosclerotic ischemic ulcers underwent arterial Doppler study and those with an ankle brachial pressure index (ABI) <0.9 were excluded from the study.

Wound swab was taken from all patients for bacterial culture and sensitivity. In cases of infected wounds, local and/or systemic antibiotics were administered. After control of infection they were included in the study.

Clinical assessment of wound was performed at initiation of treatment and at each dressing change for all groups. Local application of rhPDGF gel, collagen granule and NS dressings were done daily. The results were recorded on a weekly basis. Any necrotic tissue was removed by meticulous debridement using sterile techniques as and when necessary, particularly at the beginning. The presence or absence of allergic reaction was ascertained within 48 hours of first dressing in all the three groups.

Wounds were classified into three groups based on longest dimension at the beginning of study

- < 5cm
- Between 5cm - 10 cm
- > 10 cm

The wound area was calculated by multiplying two of the longest dimensions of the wound and was recorded at the end of every subsequent week for four weeks. Following this, the percentage reduction in wound surface area with respect to initial area was obtained. This assessment of wound size was repeated once every week.

Preventive measures such as offloading of foot using sticks, crutches or special shoes, and supportive treatment by ensuring adequate nutrition and hydration were used in all three groups.

Most patients were initially admitted for necessary investigation and wound debridement. After this phase they were followed up on weekly basis in the outpatient clinic. Few patients with very small ulcers were managed entirely on OPD basis.

Complications like persistent discharge from the wound and local pain was also recorded. The presence and extent of wound discharge was noted and recorded on a weekly basis for each of the three groups. Persistence of local pain at the wound site was also evaluated. The overall cost of treatment between the three agents was calculated at the end of four weeks and compared.

Results

Data was compiled and analysed using mean values, standard deviation and standard error. Chi Square test and unpaired- t test was used to test the association of different study variables. Odds ratio (OR) with 95% Confidence Interval (CI) was calculated to measure the different risk factor. Significance level was set at 0.05 and confidence interval was at 95 % level. Statistical significance for comparing wound reduction rate in between the various agents was done using one way ANOVA and Mann–Whitney U test. SPSS 20 software was used for the analysis.

The mean age of the patients treated with rhPDGF gel and Collagen granules were 45.00 ± 12.36 years and 45.17 ± 12.25 years respectively. The mean age of the patients in the control group (NS) was 41.53 ± 13.43. Most of the patients of study population were males (75.6%).

Maximum number of wounds were in the lower limb (76%) followed by upper limb (12%), back (11%) and anterior chest wall (1%). The group wise distribution is given in the table below (Table 1).

Diabetic ulcer was the commonest aetiology of chronic wound amongst both males and females of the study population, comprising 43.3% of the total patients. The aetiological distribution is shown in Figs 1a & 1b.

Wounds less than 5 cm had mean surface area of

Table 1 — *Anatomical location wise distribution of wounds across the treatment groups*

Location of Wound	Aetiology	NS	PDGF	Collagen
Lower Limb	Diabetic	12	14	13
	Traumatic	1	3	5
	Atherosclerotic	7	3	7
	Pressure	1	Nil	Nil
	Burn	Nil	2	Nil
Upper Limb	Traumatic	4	Nil	2
	Burn	1	3	1
Back	Pressure	3	5	2
Anterior Chest Wall	Burn	1	Nil	Nil

11.19 ± 3.88 cm2 at the initiation of study. Wound reduction using rhPDGF gel or Collagen granules was better than NS in wounds of all the three groups and was statistically significant with p value <0.05. All wounds less than 5 cm size healed using rhPDGF gel or Collagen granules by the end of 4weeks.

But the wounds in the control group (NS) had a mean reduction in percentage of surface area by 68.72 ± 7.09 % at the end of 4th week. The reduction in size of the wound after 4 weeks using rhPDGF gel and collagen granule as compared to NS dressing was statistically highly significant (p <0.001). However, no statistical difference in wound reduction rate was noted between rhPDGF gel and collagen granules over the 4 weeks duration.

In wounds between 5 to 10 cm sizes, the mean surface area of wounds at initiation of study was 38.93 ± 13.85 cm^2. When rhPDGF gel and collagen granules were applied to these wounds, the mean reduction in percentage of surface area were 77.49 ± 19.13 % and 90.49 ± 8.51%. In the control group (NS) mean reduction was found to be 56.37 ± 7.05% at end of 4th week. The reduction in size of the wounds after 4 weeks using statistical analysis amongst rhPDGF vs

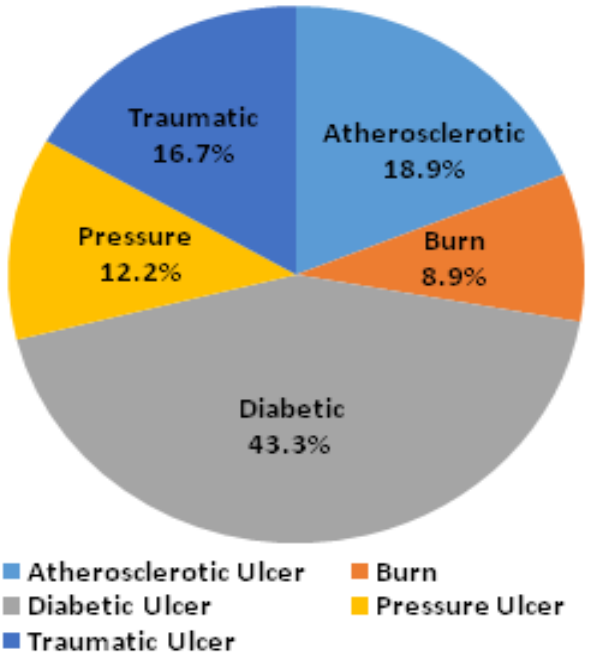


Fig 1a — Aetiological distribution of wounds

NS and collagen vs NS was found to be significant, with p=0.002 and p<0.001 respectively. But it was observed that the wounds treated with collagen granules had a better reduction as compared to rhPDGF gel in 1st, 2nd and 3rd week with p <0.05. In the 4th week, difference in mean reduction in percentage of surface area between rhPDGF gel and collagen granule was not statistically significant with p=0.061.Thus, in wounds of size 5 to 10cm, wound reduction using collagen granules was greater as compared to rhPDGF gel and was statistically significant in the first three weeks.

In wounds >10 cm size, the mean surface area of wounds at initiation of study was 109.14 ± 64.10cm^2. When rhPDGF gel and collagen granules were applied

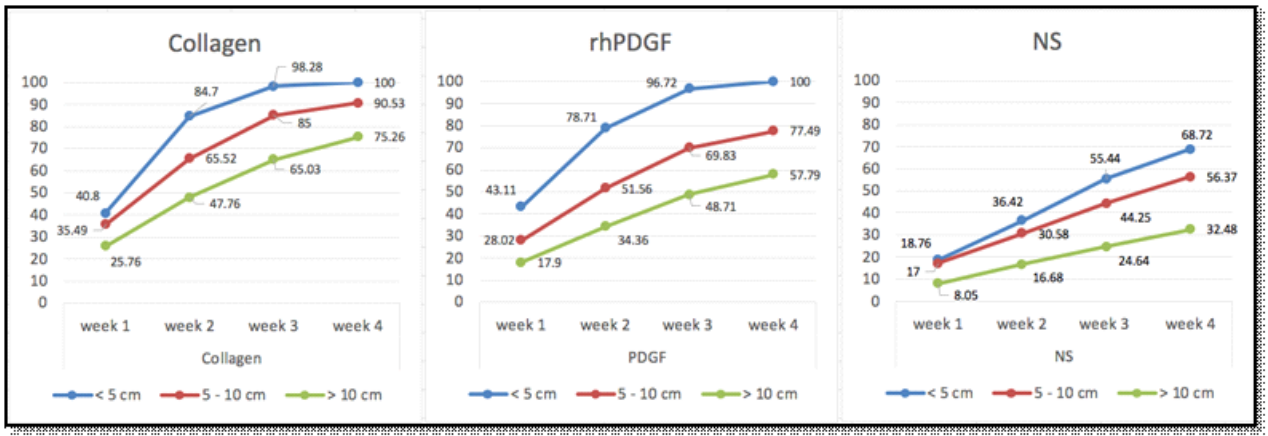


Fig 1b — Aetiological distribution of wounds with respect to the three treatment groups

to these wounds, the mean reduction in percentage of surface area at the end of 4weeks were 57.79 ± 16.39 % and 75.26 ± 17.28% respectively. In the NS group, mean reduction was found to be 32.46 ± 10.38%. The percentage reduction in size of the wounds using rhPDGF gel and collagen granule as compared to NS was found to be highly significant with p<0.001 in both the cases. Also it was seen that percentage reduction in wound size was statistically significant using collagen granule as compared to rhPDGF gel at the end of 4 weeks with p=0.002.Thus, in wounds >10 cm size, collagen granules caused greater reduction than rhPDGF gel in all the four weeks, which was statistically highly significant with p value <0.001.

Table 2 — *Occurrence of wound complications using various agents*

Agent Used	Persistent Wound Discharge	Odds Ratio (in comparison to NS)	Persistent Local Pain	Odds Ratio (in comparison to NS)
rhPDGF gel	5 (16.6%)	2.89	3 (10.0 %)	3.27
Collagen granule	3 (10.0%)	5.21	2 (6.7%)	5.09
Normal Saline	11 (36.7%)		8 (26.7%)	

It was also found that the rate of reduction of wound depth was generally proportionate to the rate of reduction of wound size by using rhPDGF gel and collagen granule dressing.

Persistent wound discharge at end of 4weeks was 3 times less using rhPDGF gel (Odds ratio= 2.89) and 5 times less using collagen granules (Odds ratio= 5.21) as compared to conventional dressing using NS. (Table 2)

Similarly, persistence of pain at wound site after 4 weeks, was 3 times less in case of rhPDGF gel (Odds ratio= 3.27) and 5times less in case of collagen granules (Odds ratio= 5.09).

Cost of therapy using collagen granules was cheaper as compared to rhPDGF gel.

Cost of therapy using Normal Saline was much less as compared to either of the above two agents.

Though the initial cost of therapy using rhPDGF gel and collagen granules was high with respect to NS dressing, it was found to be overall cost effective due to faster healing, reduction in treatment time which resulted in improved quality of life among patients and quicker resumption of normal, productive life.

Discussion

Though basic principles of wound healing have been known since centuries, ideal wound dressing is not yet a clinical reality. But novel advances are being made towards reaching that goal.

rhPDGF is a cationic, heat stable protein stored in alpha granules of circulating platelets.2It is the first major human serum polypeptide growth factor shown to be chemotactic for cells migrating into the healing wound, such as neutrophils, monocytes and fibroblast[3,4]. It is a potent mitogen[5] for cells of mesenchymal origin and enhances proliferation of fibroblast and arterial smooth muscle cells. rhPDGF stimulates many metabolic processes including general protein and collagen synthesis as well as collagenase activity. These properties suggest that rhPDGF, delivered from platelets at the site of injury may play an important role in the initiation of the repair process of wounds. Furthermore, rhPDGF was the first growth factor to be approved for the treatment of human ulcers[6].

Collagens are prolineand glycine-rich proteins that are fibrous with long, stiff, triple stranded helical structure comprising of three a-chains. It forms an important structural component in connective tissue and constitutes 25% of total protein mass in mammals. The major collagen molecules that give tensile strength to skin are heterotrimeric collagen type I, formed by two a 1(I) chains and one a 2(I) chain and homotrimeric collagen type III, formed by three a 1(III) chains.

The importance of collagen in healing has been appreciated for a long time because the end result of a healed wound is a scar composed of collagenous fibres covered by epithelium. Previously, collagens were thought to function only as a structural support; however, it is now evident that collagen and collagen-derived fragments control many cellular functions, including cell shape and differentiation, migration, and synthesis of several proteins[7]. The role of collagen in improving wound healing is by stimulating fibroblast activity. Findings suggest that cell contact with precise extracellular matrix molecules influence cell behaviour by regulating the quantity and quality of matrix deposition[8].

Our results indicated that rhPDGF gel and collagen granules are far superior, causing 2 to 3 times faster reduction in wound size than conventional dressing (NS) in all three categories of wound at the end of 4 weeks, and this was statistically highly significant with p<0.001(Fig 2). Further analysis showed that baseline ulcer size was probably an important covariate: the difference in the rate of reduction in wound size between rhPDGF gel and collagen granule appeared to be larger in patients with ulcer size >5 cm size. Collagen granules performed better than the rhPDGF gel in the larger size wounds.

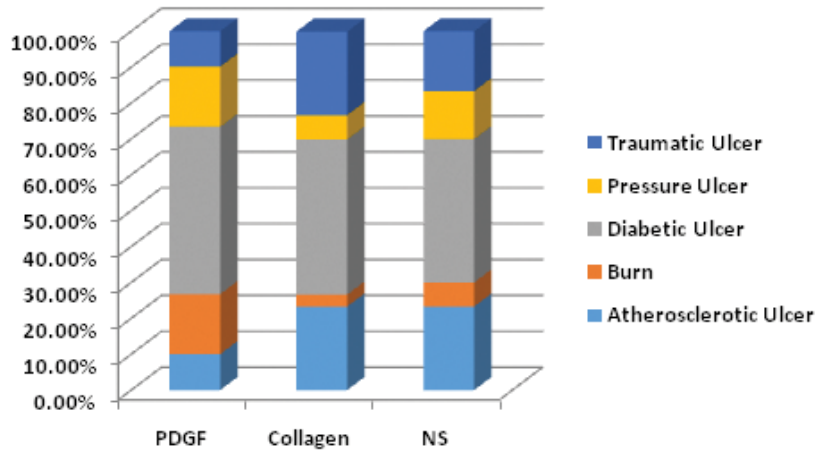


Fig 2 — Percentage reduction in wound area with respect to different treatment groups over 4 weeks

Percentage reduction in wound area using rhPDGF gel and Collagen granules was greater than normal saline for all classes of wound aetiology at the end of 4 weeks. Since the cases were randomly distributed, there was unequal distribution of cases in different etiological groups (Table 3). Thus, a definite assumption for rate of wound healing using these agents for a particular wound aetiology could not be made. This is a weakness of our study.

Our study revealed that chances of persistent wound discharge at end of 4weeks was 3 times less using rhPDGF gel (Odds ratio= 2.89) and 5 times less using collagen granules (Odds ratio= 5.22) as compared to conventional dressing using NS. Similar outcomes were obtained in case of persistence of local pain at wound site after 4 weeks, with 3 times less in case of rhPDGF gel (Odds ratio= 3.29) and 5times less in case of collagen granules (Odds ratio= 5.09). So, the overall patient satisfaction was more using rhPDGF gel and collagen granules due to decreased wound related complications, less hospital stay, ultimately leading to early mobilization. These findings are comparable to those reported in literature[9-13].

The use of rhPDGF gel and collagen granules are more cost effective for the treatment of chronic ulcers than conventional treatment modalities, despite their higher initial cost[14]. This may be attributed to a combination of factors. First, expenses incurred in more prolonged treatment, such as hospital visits and the need for additional dressings, can be avoided when healing completes in a shorter period. Second, rapid and complete ulcer healing may reduce the incidence of significant morbidities (such as amputation or infection) and premature mortality. Consequently, the financial burden associated with these complications would be reduced. Finally, the value of improved quality of life in patients with healed ulcers and the reduction in financial burden for patients who return to work cannot be ignored.

Table 3 — *Average cost of therapy using rhPDGF gel and Collagen granules*

Size of Wound	Agent Used for Dressing	
	rhPDGFgel[a]	Collagen granules[b]
< 5 cm	2 tubes (cost =Rs 2190/-)	1 to 2 vial (cost = Rs760 /-)
5 to 10 cm	3 tubes (cost = Rs 3285/-)	3 to 4 vial (cost = Rs1520/-)
> 10 cm	3 tubes or more	4 vial or more

a. Cost of 1 tube of rhPDGF gel containing 7.5 gm is Rs. 1095.
b. Cost of 1 vial of Collagen Granules containing 5ml is Rs. 380.

Limitations of the Study :

This was a short duration study conducted only over 4 weeks. The wound was studied in only two dimensions. Wound volume measurement rather than area could have been a more accurate approach of judging results. A larger sample size would have increased the power of the study. Different aetiologies of wounds were included and randomised into groups thus creating unequal groups with respect to the treatment agent used.

Conclusion

Chronic wounds are a challenge to wound care professionals and consume a great deal of healthcare resources around the globe. With better understanding of pathophysiology of wound healing and increasing number of available options a paradigm change has occurred in the approach to wound healing and measuring outcomes.

The results of our study reveals that overcoming the factors contributing to delayed healing are key components of a comprehensive approach to wound care. Novel approach using growth factors which promote angiogenesis like rhPDGF gel and those that promote tissue matrix formation like Collagen granules show statistically significant wound contraction at 4 weeks following topical application, when compared to conventional dressing using Normal Saline. These agents also reduce major wound complications and drastically minimize the chances of persistent wound discharge and local pain.

Although individually rhPDGF gel and collagen granules scores over Normal Saline dressing over the same time interval, when compared with each other there is significant improvement in wound contraction by using Collagen granules than rhPDGF gel in larger wounds. Though they are expensive than normal saline, overall the cost benefit ratio tilts in favour of using these agents as wound morbidity is decreased and quality of life improved among patients. More evidence for the efficacy of current therapies is required for their appropriate use.

Funding : None

Conflict of Interest : None

References

1 Lazarus GS, Cooper DM, Knighton DR — Definitions and Guidelines for assessment of wounds and evaluation of healing. *Arch Dermatol* 1994, **130 (4):** 489-93.

2 Leong M, Phillips LG — Wound Healing. In Townsend CM, Beuchamp RD, Evers MB, Mattox KL et al editors – Sabiston Textbook of Surgery, 19th ed. Philadelphia, Elsevier Saunders. 2012: 151-177.

3 Seppa H, Grotendorst G, Seppa S, Schiffman E, Martin GR — Platelet-derived growth factor is chemotactic for fibroblasts. *J Cell Biol* 1982, **92:** 584-8.

4 Deuel TF, Senior RM, Huang JS, Griffin GL — Chemotaxis of monocytes and neutrophils to platelet-derived growth factor. *J Clin Invest* 1982; **69:**1046-9.

5 Bowen-Pope DF, Ross R — Platelet-derived growth factor II. Specific binding to cultured cells. *J Biol Chem* 1982, **257:** 5161-71.

6 Nagai MK, Embil JM — Becaplermin: recombinant platelet derived growth factor, a new treatment for healing diabetic foot ulcers. *Expert Opin Biol Ther* 2002; **2(2):** 211-8.

7 Park SN, Lee HJ, Lee KH, Suh H — Biological characterization of EDC-crosslinked collagen-hyaluronic acid matrix in dermal tissue restoration. *Biomaterials* 2003; **24:** 1631-41.

8 Vyas KS, Vasconez HC — Wound Healing: Biologics, Skin Substitutes, Biomembranes and Scaffolds. *Healthcare* 2014; **2(3):** 356-400.

9 Robson MC, Phillips LG, Thomason A — Recombinant Human Platelet-derived Growth Factor-BB for the Treatment of Chronic Pressure Ulcers. *Annals of Plastic Surgery* 1992; **29(3):** 193-201.

10 Smiell JM, Wieman TJ, Steed DL, *et al* — Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. *Wound Repair Regen* 1999; **7(5):** 335-46.

11 Donahue VM, Chrzan JS, Rosenblum BI, Giurini JM, Habershaw GM, Veves A — Evaluation of a collagen-alginate wound dressing in the management of diabetic foot ulcers. Advances in Wound Care: *the Journal for Prevention and Healing* 1998; **11(3):** 114-9.

12 Singh O, Gupta SS, Soni M, Moses S, Shukla S, Mathur RK — Collagen Dressing Versus Conventional Dressings in Burn and Chronic Wounds: A Retrospective Study. *J Cutan Aesthet Surg* 2011; **4(1):** 12-6.

13 Chalimidi KR, Kumar Y, and Kini UA -Efficacy of Collagen Particles in Chronic Non Healing Ulcers: *J Clin Diagn Res* 2015; **9(6):** PC01–PC03.

14 Albert S — Cost-effective management of recalcitrant diabetic foot ulcers. *ClinPodiatr Med Surg* 2002; **19(4):** 483-91.

Original Article

Lithium Monitoring in a VA Hospital : A Quality Improvement Project

Anindita Chakraborty[1], Musa Yilanli[2], Nicole Stromberg[3]

Background : Lithium has established efficacy in the treatment of bipolar affective disorder and is one of the few medications known to reduce the risk of suicide. Due to its narrow therapeutic index, drug levels are needed to monitor for toxicity. Long term lithium treatment increases risk of hypothyroidism, hyperparathyroidism and progressive renal insufficiency. As per VA/DoD clinical practice guidelines for management and treatment of bipolar disorder, maintenance therapy requires serum lithium monitoring every 6 months as well as annual Creatinines, TSH and CBCs with differential counts.

Aims :To develop a program to improve the blood monitoring of patients who are on lithium to 75% over an 8-month period at the VA Hospital in Detroit.

Methods : A retrospective audit was conducted in August 2016 of blood monitoring for all patients who were taking lithium at the VA hospital in Detroit and compared it to published guidelines. We then implemented a series of educational programs and reminders to improve the adherence rate. A re-audit was completed in March 2017.

Results : A significant improvement in all suggested monitoring was observed after the reminders and informative educational materials had been delivered. Serum lithium monitoring went up by 28% and overall maintenance monitoring standards went up by 31%.

Conclusions : We were able to demonstrate improvement in the level of adherence in all of the Guideline recommended monitoring parameters at one VA Hospital with the use of educational material and reminders. This program may be practical for dissemination to other hospitals.

[*J Indian Med Assoc* 2020; **118(11):** 44-7]

Key words **: Lithium, Quality Improvement, Bipolar Disorder.**

Bipolar affective disorder is a chronic, recurrent disorder with a lifetime prevalence of approximately 1-3%, it affects men and women equally with a mean age of onset of 19 years[1].

The hallmark of bipolar disorder is episodes of mood elevation and/or depression. The main subtypes of bipolar disorder include bipolar I and bipolar II. Type I with mania and usually recurrent major depression and type II with recurrent major depression and hypomania. Bipolar disorder has an episodic course with varying degrees of intensity and severity, often with prolonged periods of depression and associated comorbid anxiety and substance use. The suicide rate for bipolar disorder is phenomenally high, and patients are at risk of premature death due to medical illness[2]. Treatment of bipolar disorder was revolutionized with the introduction of lithium in the 1970s and since then, it remains standard of care in the treatment of acute mania and prophylaxis of both bipolar mania and depression. Long term treatment with lithium has also shown to reduce

[1]MD, Department of Child and Adolescent Psychiatry, Wayne State University School of Medicine and Corresponding author
[2]MD, Department of Child and Adolescent Psychiatry, University of Arkansas for Medical Sciences
[3]MD, Clinical Assistant Professor, Wayne State University School of Medicine. John D Dingell VA Medical Center, Detroit, Michigan
Received on : 15/07/2020
Accepted on : 13/09/2020

Editor's Comment :

- **Lithium has established efficacy in the treatment of bipolar disorder as well as in preventing suicidality in affective disorders.**
- **Lithium has a narrow therapeutic index (0.6-1.2 mEq/L) and can lead to acute toxicity with symptoms such as confusion, ataxia, fasciculations, cardiovascular collapse and death.**
- **Chronic use has been linked to deterioration in renal function as evidenced by decreasing glomerular filtration rate. The incidence hypothyroidism is six-fold higher in patients on lithium as compared to the general population.**
- **Per the VA/DoD clinical practice guidelines safe and effective treatment with lithium requires monitoring lithium levels every 6 months, as well as annual creatinines, TSHs and CBCs with differential counts.**
- **Inadequate monitoring could be due to physicians not placing laboratory orders or patients failing to get their blood drawn.**
- **Adherence to monitoring guidelines may be improved with simple targeted interventions such as EMR reminders and physician and patient education programs.**

the risk of both completed suicide and lethality of suicide[3]. However, since lithium has a narrow therapeutic index (0.6-1.2 mEq/L), drug levels are needed to monitor for toxicity. Chronic use has been linked to deterioration in renal function as evidenced by decreasing glomerular filtration rate. The incidence of hypothyroidism is six-fold higher in patients on lithium as compared to the general population. Lithium is associated with hypercalcemia/hyperparathyroidism[4]. It can also cause increase in white cell lines and platelets[5]. To ensure safe and effective use of lithium, clinical practice guidelines (Table 1) recommend periodic, routine serum monitoring of lithium levels, thyroid stimulating hormone (TSH), and renal function[6].

Despite the recognized need and availability of guidelines local audits tend to find lithium monitoring inadequate. For instance, one retrospective audit[7] found that that 7% of patients did not have a lithium level measured, for over a year after lithium was started, and another retrospective audit[8] showed that 1/3 of the patients had no record of results for urea and electrolytes or TSH in the last year. In 2016, the American Association of Poison Control Centers cited 6,901 reports of lithium toxicity cases; 157 were considered to have major medical outcomes and 3 deaths occurred[8]. In the same year, the Veterans Health Administration (VHA) in America, released a bulletin[10], after a patient who had not had serum lithium level drawn for years and was admitted to the intensive care unit with lithium toxicity. The bulletin noted that 24% of patients prescribed lithium at a local Veterans Affairs (VA) Hospital had not had a lithium level drawn in the past year. The bulletin highlighted the use of VA/DoD (Veterans Affairs/Department of Defense) guidelines for lithium monitoring, where patients must have a documented serum lithium level in the past 6 months, and an evaluation of renal function, thyroid function and complete blood count (CBC) in the past year[11].

This prompted us to examine our lithium monitoring habits at our VA hospital in Detroit. Upon reviewing the National VA Psychotropic medication safety database, we found that adherence to lithium monitoring guidelines at the Detroit VA, was below the national average. This prompted us to initiate a Quality improvement (QI) project aimed at improving lithium monitoring habits at the Detroit VA.

Aims

We aimed to increase adherence to serum monitoring guidelines in patients on lithium to 75% over a 8-month period at the VA Hospital in Detroit, Michigan, USA.

Materials and Methods

Our project is based on the "Plan, Do, Study, Act" framework[13], which is a cyclical 4 step problem solving model, widely implemented in quality improvement projects (Fig 1).

Our project was conducted between August 2016 and March 2017, at the VA Hospital in Detroit, Michigan. Of note, the VA Hospital system is the largest integrated health care system in the United States, serving Veterans or persons who have served in the United States military.

First, a retrospective Electronic Medical Record (EMR) audit was done on all patients with prescribed lithium over the past year. Each patient's last lithium levels, TSH, creatinine and CBCs were checked to see if they were completed per VA/DoD monitoring guidelines. This was recorded categorically as "completed" or "not completed" on Microsoft excel. Since our project was based at a VA Hospital, we chose to apply the VA/DoD guidelines.

Failure to adhere to guidelines was defined as being prescribed lithium but with incomplete implementation of lithium monitoring

Table 1 — *Clinical Practice Guidelines for safe and effective use of Lithium*

Guideline	Serum Lithium	Renal	Endocrine	Tests
APA	Every 6 months	During first 6 months: every 2-3 months Thereafter every 6-12 months	Duringfirst 6 months: once or twice thereafter every 6-12 months	Urea, Creatinine, TFT, ECG
BAP	Every 3-6 months	Every 12 months	Every 12 months	Creatinine, eGFR, TSH
NICE	First year : Every 3 months Thereafter Every 6 months	Every 6 months	Every 6 months	BMI, Urea, Electrolytes, Calcium, eGFR, TSH
ISBD	Every 3-6 months	Every 3-6 months	At 6 months and thereafter yearly	TSH, serum calcium, urea, creatinine, weight
CANMAT	Every 3-6 months	Every 3-6 months	At 6 months and thereafter yearly	TSH, serum calcium, urea, creatinine, weight
VA/DOD	Every 6 months	Every 12 months	Every 12 months	CBC, TSH, Creatinine

APA: American Psychiatric Association; BAP : British Association for Psychopharmacology; NICE : National Institute for Health and Care Excellence; ISBD : The International Society for Bipolar Disorders; CANMAT: Canadian Network for Mood and Anxiety Treatments; VA/DOD: Veteran Affairs / Department of Defense [Table Modified from Malhi et al. (2017)]

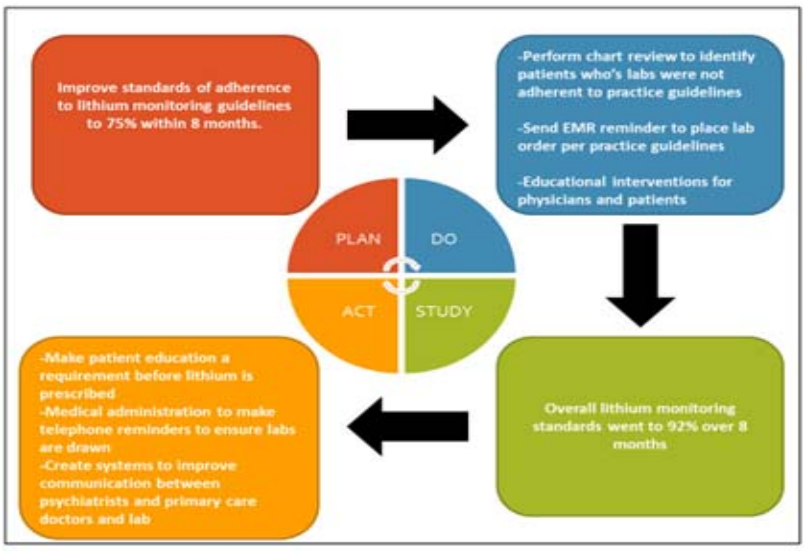


Fig 1

guidelines. Based on EMR review, our QI team determined that barriers to adherence were either physician related, patient related, or procedure related. Patient related barriers included failure to get blood drawn following physician lab orders and failure to attend follow up appointments. Physician related barriers included failure to order laboratory studies per guidelines. (Physicians refer to Psychiatrists as well as primary care physicians (PCPs). Procedural barriers refer to either inadequate communication of test results between labs as well as inadequate communication about lithium monitoring between clinical teams.

As physician and patient barriers were more common and easier to address, we designed the following interventions: an electronic notification reminding physicians that patients' labs were due. These notifications were added manually to the patients' electronic chart, essentially "flagging" certain patients that were delinquent on their labs. Physicians were also provided paper educational materials on VA/DoD guidelines. Interventions for patients included mailing paper educational information, with information on lithium toxicity as well as monitoring schedules with emphasis on getting lab tests in a timely manner. Interventions were placed once, and then after 8 months, and post-audit data was recorded from the EMR. Procedural barriers were not addressed at this time. This project did not require any funding and therefore, there was no conflict of interest.

Results

Of 107 patients, prescribed lithium,42 (39.3%) did not have adequate lithium monitoring. Of these 42 patients, 61% had completed all recommended labs per guidelines, 65% had a lithium level drawn, 80% had a TSH, 86% had a creatinine, 86% had a CBC per guidelines. While our pre-intervention analysis included 42 patients, over the span of the project, 7 patients (17%) were dropped ie, 5 stopped receiving lithium, 1 was incarcerated and 1 was transferred to another VA Hospital. Therefore, post audit analysis was conducted on 35 patients only.

Post intervention, adherence to all VA/DoD guidelines increased from 61% to 92%. Specifically, TSH increased to 96%, CBC increased to 98% and serum creatinine increased to 100% (Fig 2). The disparity in the above numbers is because, while some physicians ordered all labs at once, some did not. That would account for the disparity reflected in Fig 2. Of note, this did not affect the analysis of our data.

At baseline physician barriers were noted in 12 cases, patient barriers noted in 21 cases and procedural barriers noted in 9 cases. Post intervention, in 7 out of 12 cases, physicians placed orders per guidelines, and in 14 out of 21 cases patients obtained blood draws.

Discussion

Although there are evidence-based guidelines for the monitoring and prevention of lithium toxicity, optimal

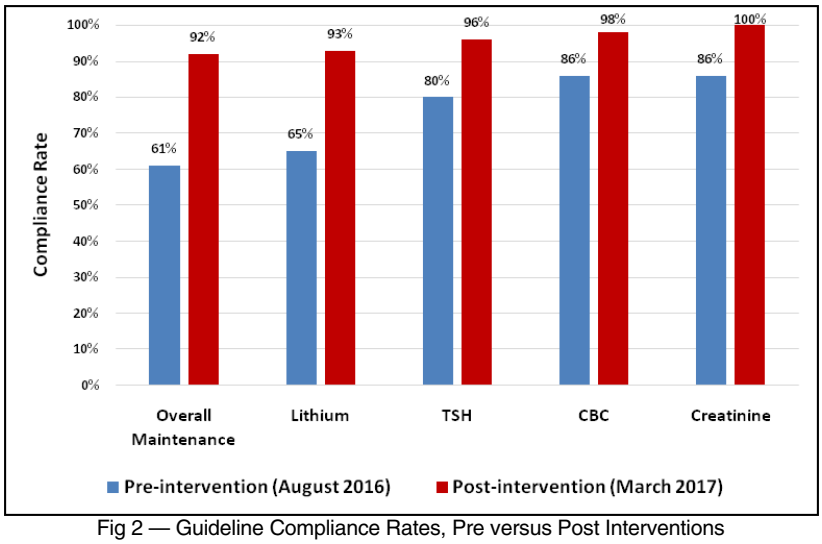


Fig 2 — Guideline Compliance Rates, Pre versus Post Interventions

serum monitoring has been a challenge. Our QI program was able to raise adherence to therapeutic drug monitoring per guidelines to 92% over a period of 8 months. Our interventions were simple and targeted towards prescribers and patients separately.

The EMR reminders and physician education were most helpful, in that, they led to lab orders being placed per guidelines.However, as they were placed simultaneously it was difficult to discern which was more effective. Due to our success, our EMR reminder was permanently embedded as an automatic pop up for all patients being prescribed lithium.

To improve current standards, future interventions will need to be introduced at every step of administering lithium, including initiation, monitoring and follow up. Patient education must be introduced at every level. Use of QI tools such as patient lithium level log-books may be beneficial. Collaboration between Psychiatrists, primary care doctors, laboratories and medical administration is key. Primary care doctors, often monitor kidney and thyroid function and may pick up lithium toxicity early. Since our patient barriers were primarily related to missing follow up, administrative staff may provide telephone reminders, asking that patients with active lithium prescriptions get their labs drawn. A central lithium registry will improve communication and help trend lithium monitoring trends in a better manner.

Limitations

Limitations to our program include a small sample that was population and locality specific (veterans only). Its setting in a VA Hospital with access to a national VA Psychotropic medication safety database and an EMR with the option of electronic notifications, make it difficult to generalize to other settings. Using our local (VA/DoD) guidelines made comparison of our findings with other audits difficult. Even though all patients had active lithium prescriptions, some had no lithium levels drawn in the past year. This made us wonder if these patients needed lithium monitoring at all. Individual factors such as psychiatric diagnosis, non-compliance, special populations may influence clinical decision making, suggesting that guidelines may not resemble real-world scenarios. In other words, although our QI project raised adherence to monitoring guidelines, this is unlikely to be associated with improved outcomes[15].

Conclusion

In conclusion, we showed that quality of health care practice may be improved by simple, low cost interventions such as EMR reminders and education programs. However, enhancing current practices may require better patient education programs and collaboration between physicians and other stake holders. Finally, feedback from more QI cycles is needed to see if our interventions are sustainable.

Disclosures and Acknowledgements :

Drs Chakraborty, Yilanli and Stromberg report no conflicts of interest.

References

1 Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA, Viana MC, Andrade LH, Hu C, Karam EG, Ladea M — Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. *Archives of general psychiatry* 2011 Mar 7; **68(3):** 241-51.

2 Baldessarini RJ, Tondo L — Suicide risk and treatments for patients with bipolar disorder. *JAMA* 2003 Sep 17; **290(11):** 1517-9.

3 Tondo L, Hennen J, Baldessarini RJ — Lower suicide risk with long term lithium treatment in major affective illness: a meta analysis. *Acta Psychiatrica Scandinavica* 2001 Sep; **104(3):** 163-72.

4 Gitlin M — Lithium side effects and toxicity: prevalence and management strategies. *International Journal of Bipolar Disorders* 2016 Dec; **4(1):** 27.

5 Tisman G, Wu S-JG — Haematological Side-Effects of Lithium. In: Johnson FN, editor. Handbook of Lithium Therapy [Internet]. Dordrecht: Springer Netherlands; 1980 [cited 2019 Mar 26]. p. 338–44. Available from: https://doi.org/10.1007/978-94-011-7197-7_37

6 Malhi GS, Gessler D, Outhred T — The use of lithium for the treatment of bipolar disorder: Recommendations from clinical practice guidelines. *J Affect Disord* 2017; **217:** 266-80.

7 Butler JA, Taylor DM — A survey of lithium monitoring and prescribing patterns. *Int J Psychiatry Clin Pract* 2000; **4(2):** 135-8.

8 J Glover K — How safe is lithium prescribing? Audit of a local prescribing framework and patient survey. *Psychiatric Bulletin* 2005 Mar 1; **29:** 98-100.

9 Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, Banner W — 2016 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th Annual Report. *Clin Toxicol (Phila)* 2017 Dec; **55(10):** 1072-252.

10 https://www.pbm.va.gov/PBM/vacenterformedicationsafety/nationalpbmbulletin/Lithium Safety_NATIONAL_PBM_BULLETIN_072516_FINAL_with_disclaimer.pdf

11 VA/DoD Clinical Practice Guideline for Management of Bipolar Disorder in Adults.May2010. [cited 2020Jan19]. Available from: www.healthquality.va.gov/guidelines/MH/bd/bd_305_full.pdf

12 National Academies of Sciences, Engineering, and Medicine. Evaluation of the department of veterans affairs mental health services. National Academies Press; 2018 Mar 29. p.234-235.

13 Langley GJ, Moen RD, Nolan KM, Nolan TW, Norman CL, Provost LP — The improvement guide: a practical approach to enhancing organizational performance. John Wiley & Sons; 2009.

14 Collins N, Barnes TR, Shingleton-Smith A, Gerrett D, Paton C — Standards of lithium monitoring in mental health trusts in the UK. *BMC Psychiatry* 2010 Dec; **10(1):** 80.

15 Kilbourne AM, Post EP, Bauer MS, Zeber JE, Copeland LA, Good CB, Pincus HA — Therapeutic drug and cardiovascular disease risk monitoring in patients with bipolar disorder. *Journal of Affective Disorders* 2007 Sep 1; **102(1-3):** 145-51.

Original Article

Prevalence, Demographics and Risk Factors of Intracranial Stenosis in Ischemic Stroke Patients Admitted at a Teaching Government Hospital in Central Gujarat

Ashka Shah[1], Himanshu Rana[2], Chirag Rathod[3], Anavi Sheth[4]

Introduction : Ischemic Strokes (IS) occur when an artery of brain is occluded by thrombosis or embolus.It can be caused either by large artery atherosclerosis, cardioembolic source, small vessel disease and in some rare cases such as hypercoagulable state or in few cause can't be determined (cryptogenic stroke). We chose to compare Intracranial Arterial Stenosis (ICAS) IS with non-ICAS IS patients to determine whether particular risk factors,demographics or clinical characteristics were particularly associated with ICAS.

Material and Method : We collected data of 153 stroke patients admitted at GMERS General Hospital, Gotri, Vadodara for three months from March 2018-May 2018.Out of which 50 IS patients passed our inclusion criteria. Their history, laboratory values and imaging. MRA and CTA imaging results were assessed and recorded. Statistics was carried out using Excel, MedCalc and Graph Pad Prism.

Results : In our study, out of 73 Stroke patients, 21 (29%) were diagnosed as stenotic and classified as ICAS. The remaining IS were classified as Non-ICAS. Among the IS patients (N=50), ICAS accounted for 21 (42%); females had a dramatically lower Time since onset (TSO) than males, with few arriving within one hour. Majority (71.4%) of the males iarrived after 24 hours while half (53%) of the females arrived after 24 hours to the hospital. The TSO was longest in rural lower-middle class patients (mean 20 days). On comparison of age,median age was higher in ICAS than non-ICAS patients.High neutrophil count was found both in ICAS as well as Non-ICAS groups and neutrophil to lymphocyte ratio (NLR) was different between both the groups.Tobacco and Alcohol abuse, Diabetes Mellitus were major risk factors.Cardiac disorder were seen in very few patients whereas Past Stroke event had occurred in several of the IS patients, with no significant differences observed in the two groups (ICAS and non-ICAS) studied.

Conclusion : Demographics, risk factors and laboratory values were obtained from all the patients. Higher proportion of males was observed in all IS patients, Lower-middle class patients had the longest TSO. There was no significant difference in risk factors. Significant difference in neutrophilia was striking and showed strong inverse relationship to lymphocytes in ICAS IS patients and moderate inverse relationship in non-ICAS IS patients. [*J Indian Med Assoc* 2020; **118(11):** 48-52]

Key words **: Ischemic Stroke, Intracranial Arterial Stenosis (ICAS), Non-ICAS, MRI and MR Angiography, Treatment.**

Ischemic Stroke is an episode of neurological dysfunction caused by focal brain, spinal cord or retinal infarction[1]. Ischemic Strokes (IS) occur when an artery to the brain is blocked (occluded), typically by occlusion of the vessel by thrombosis or migration of a blood clot (embolus). This deprives the brain cells supplied by that artery of essential oxygen and nutrients[2].

Stroke has a high fatality rate in India[3,4] and Intracranial Arterial Stenosis (ICAS) is known to be a common cause of IS in the Asian population[5]. ICAS has a prevalence of 20-53% depending on the population being studied[3-6]. There is limited awareness

[1]Third MBBS Student, GMERS Medical College, Gotri, Vadodara 390021
[2]MD (Medicine), Associate Professor of Medicine, Baroda Medical College, Vadodara 390001 and Corresponding Author
[3]MD (Medicine) Associate Professor of Medicine, GMERS Medical College, Gotri, Vadodara 390021
[4]Third MBBS Student, GMERS Medical College, Gotri, Vadodara 390021
Received on : 07/12/2019
Accepted on : 12/09/2020

Editor's Comment :

- **Time Since Onset plays a major role in delayed treatment in Rural and Lower-middle class population.**
- **Diabetes Mellitus, Tobacco, Alcohol and cardiac illness forms a major risk group.**
- **Early recognition of the risk factor, awareness of stroke and early treatment shall be helpful.**

in India[7] and particularly in Gujarat[6] about the symptoms and risk factors of stroke. Indian population is diverse ethically as well as socio economically and so, could be exposed to different modifiable and non-modifiable risk factors. In a developing country such as India, communicable and chronic diseases pose a combined burden and pose additional challenges from socio-economic and availability of resources perspective[7].

Knowing the risk factors, demographics and prevalence of ICAS helps in better diagnosis and subsequently prognosis, outcome and management of the patients. Furthermore, ICAS IS is known to be associated with higher rates of recurrent stroke[8,9]. So, it is important to identify, diagnose and treat the patients early as well as develop a better understanding of the etiology. It would be of great benefit to understand the factors that might influence the etiology of stroke in a larger future study and thus help in the proper management (aggressive medical therapy, management of risk factors and/or intervention such as percutaneous transluminal angioplasty and stenting), as well as prevent recurrence[10-12]. Only few study found in Gujarat area.

So, the overall objective of the study was to determine the prevalence of IS and also to identify specific risk factors associated with ICAS among all patients admitted with IS at a Government Hospital.

Materials and Methods

Study Design : The study design was prospective and analytical for all IS patients. A Case Record Form was prepared by the investigator.

Study Setting : Tertiary care teaching hospital (GMERS General Hospital)

Ethics : All ethical guidelines will be followed as per ICMR. The study protocol was approved by the institutional ethics committee and guidelines were adhered to throughout the study. All data was collected and analyzed by the investigator.

Inclusion and Exclusion criteria : All patients were admitted in the medicine department with stroke were included. Patients included were all those with strokes and in which Magnetic Resonance Angiography (MRA) and/or Computed Tomography Angiography (CTA) imaging of intracranial vessels was performed. Patients were excluded if MRA/CTA had not been performed.

Participants or guardian of all participants were explained about the nature of study in detailed. And written informed consent was taken.

Sample Size: In present study, total 153 patients with stroke were assess. Out of that total 50 patients could be included according to inclusion and exclusion criteria.

Study Procedure : A Patient Study ID number was assigned to every patient and we collected data on Age, Gender, Height, Weight, Waist, BMI, BP, Residence (Rural/Urban), Socio-economic Status, Education, Diet (Vegetarian or Non-Vegetarian), Stroke date/time, Time since onset. Socioeconomic Status was classified according to the modified Kuppuswamy scale[13].

Additionally, the following risk factors were assessed based on prior history and laboratory results/ blood pressure and were noted in the questionnaire: Diabetes Mellitus, Hypertension, Exercise, Smoking/ Tobacco abuse, Alcohol, Family History of Stroke, Cardiac disorder, Past Stroke event. Laboratory analyses (Hb, CBC, Blood glucose) were included in the study to determine any risk factors which may not have been evident in the history. MRA and CTA were performed by the hospital-affiliated imaging facility for the patients enrolled in the study. Interpretation of the imaging results was done under guidance of qualified Radiologists and Neurophysicians.

Strokes were classified into subtypes based on Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification[2]. MRA and CTA imaging results were assessed and recorded. The cross-sectional nature of this study limited our data to one time point, which included imaging, history and laboratory values.

Data Analysis: Data was collected and tabulated using Microsoft Excel. All data analysis and tabulation was performed using Excel, MedCalc and Graph Pad Prism. Means and Median values along with Standard deviations were calculated. Categorical data was analyzed using univariate and multivariate Chi Square analysis or Fisher's exact test. Continuous variables were analyzed using unpaired t-tests and linear regression. Results were considered significant if the p value was less than 0.05.

Results

In Fig 1, the percentage of patients that present with ICAS among the IS patients.

Tables 1 and 2 show the comparative demographics, clinical characteristics and risk factors of ICAS patients and non-ICAS patients. No significant difference was seen between the two groups for all parameters except Neutrophils, which were significantly higher in the non-ICAS group. Lymphocytes trended towards higher mean in ICAS, although it was not significant at $p<0.05$. Males were clearly predominant in the ICAS group (67%).

In Fig 2, comparison of age (medians shown by

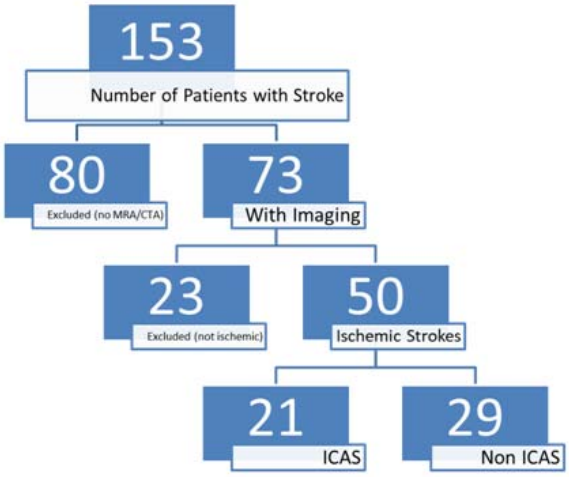


Fig 1 — the percentage of patients that present with ICAS among the IS patients

Table 1 — *History and Risk Factors*

Demographics	ICAS (N=21)	Non-ICAS (N=29)
Males/Females	14/7	21/8
age (median)	65	55
age (mean)	62	55
education		
None	4	7
Upto 5th Standard	6	9
5th-10th Standard	6	5
10th pass to 12th pass	3	4
Graduate	2	4
residence		
Rural	9	12
Urban	12	17
Socio-economic status		
Lower	11	16
Lower-Middle	5	6
Middle	5	5
Upper-Middle	0	2
Vegetarian	13	23
Time since onset (mean)	4.7days	3.1days
Diabetes Mellitus	6	15
Hypertension	11	20
Past H/O Stroke	10	14
Tobacco	7	8
Alcohol	3	5
Cardiac History	10	18
Respiratory history	5	2

horizontal line) is shown for both groups. Although median age was higher in ICAS than non-ICAS patients, no statistically significant difference was seen. In Fig 3, the mean time since onset (TSO) in days is plotted on the y axis, with error bars showing standard deviation, against the stroke subtype and gender on the x axis. Males had longer mean TSO than females. This held true irrespective of whether the stroke was ICAS or non-ICAS IS. In addition to the gender differences seen in TSO, we observed a difference based on socio-economic status as well. Individuals belonging to the lower-middle socio-economic strata showed the longest TSO, as shown in Fig 4. This held true for both rural and urban residing patients. However, the rural lower middle class patients showed the highest TSO at 20 days. Diabetes Mellitus, Hypertension, Past history of Stroke in ICAS patients were not mutually exclusive risk factors, as shown in the Venn diagram in Fig 5. Tobacco and Alcohol abuse although prevalent (Table 1) in both ICAS and non-stenotic patients, did not show any remarkable difference. However, of the ICAS patients with history of Diabetes Mellitus, over 80% also had history of Tobacco and/or Alcohol abuse. Cardiac and Respiratory disorder were seen in very few patients whereas Past Stroke event had occurred in several of the IS patients, with no significant differences observed in the two groups (ICAS and non-ICAS) studied.

Table 2 — *Laboratory Values (means)*

Demographics	ICAS (N=21)	Non-ICAS (N=29)	p-value
Hb	12.81	12.80	0.981
PCV	38.94	39.60	0.497
MCV	84.81	87.28	0.490
MCH	27.51	28.54	0.466
MCHC	32.33	32.74	0.268
Total RBC	4.79	4.50	0.224
Total WBC count	10719	10181	0.647
Neutrophils	68.9	74.8	0.028
Lymphocytes	20.5	16.8	0.102
Eosinophils	3.8	2.7	0.179
Monocytes	6.2	5.6	0.272
ESR	45.6	55.5	0.531
PLT	2.7	3.1	0.396

Fig 6 shows the inverse correlation seen between neutrophils and lymphocytes in stenotic and non-stenotic IS patients. The regression analysis showed strong inverse linear correlation (R2=0.89) between neutrophils and lymphocytes in stenotic and a moderate inverse correlation in non-stenotic patients; the slope was also more negative in ICAS.

Discussion

In present study demographics appeared similar to those reported in other studies from South India and event same region[3,6]. In a multinational study published in 2013, data was compared from Prospective Hospital Stroke Registries in China (n = 752 acute stroke patients), Germany (n = 96054), India

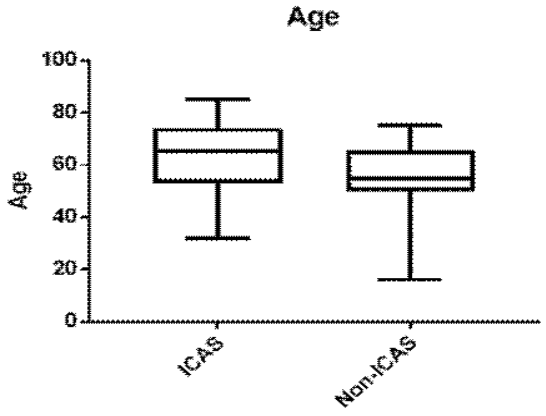


Fig 2 — comparison of age among ICAS and non-ICAS patients

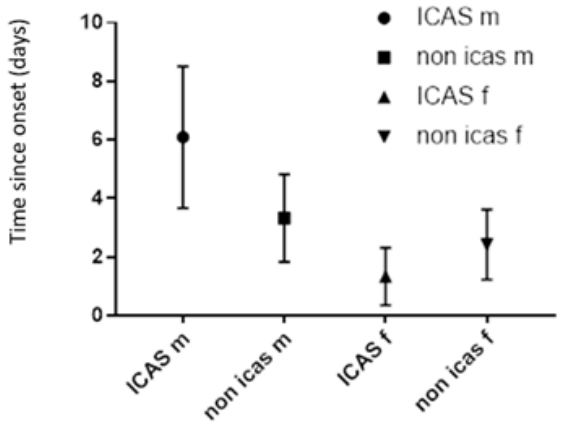


Fig 3

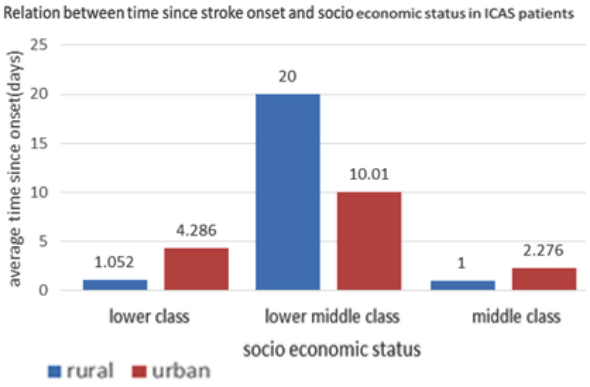


Fig 4 — Relation between time since stroke onset and socioeconomic status in ICAS patients

(n = 1500), and Iran (n = 1392) to determine gender distribution of stroke patients and associated factors[14]. Gender distribution was highly different between countries. For example, whereas India and China showed a male preponderance, Iran had more females in their stroke patient population. In the current study, a gender difference was apparent in our sample of patients – there were more men who were admitted with IS than women, both in ICAS and non-ICAS patient categories.

The present study shows among all IS patients, females had a dramatically lower Time since onset (TSO) than males, with few of them arriving within one hour. Majority (71.4%) of the males in our study arrived after 24 hours while half (53%) of the females arrived after 24

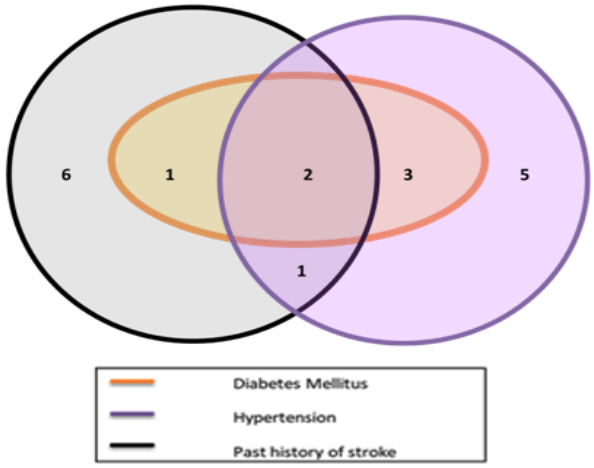


Fig 5 — Diabetes Mellitus, Hypertension, Past history of Stroke in ICAS patients

hours to the hospital. This may indicate a possible heightened awareness of the critical nature of stroke among the small proportion of women that reached the hospital. Further, the TSO was longest in rural lower-middle class patients (mean 20 days). This length of time is much longer than that reported by other studies in our region and elsewhere[3,5,6,15]. This sheds light on a major area for improvement for timely care of patients in a Government Hospital setting. Future directions of our study would be to increase stroke awareness in the community.

An observation that stood out in this study was the large number of patients with a high neutrophil count both in ICAS as well as Non-ICAS groups. In addition to the unusually high count of neutrophils in several patients, we also noted a statistical difference in the mean neutrophils between the ICAS and non-ICAS groups. We also assessed the neutrophil to lymphocyte ratio (NLR) but there was no statistical significance between the NLR of the 2 groups. Previously, high neutrophils have been shown to be

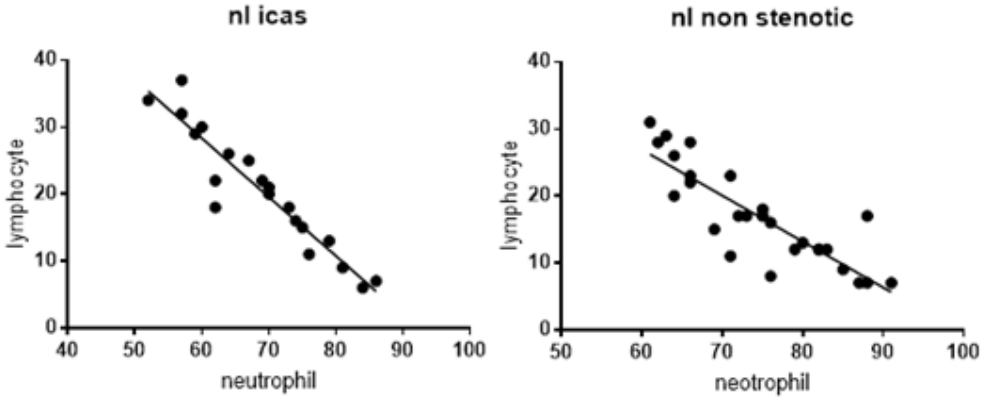


Fig 6 — correlationbetween neutrophils and lymphocytes in stenotic and non-stenotic IS patients.

associated with recurrent strokes[15]. This relationship warrants further investigation in future studies comparing ICAS and Non-ICAS and neutrophil involvement. ICAS IS association with higher rates of recurrent stroke[8,9] is dependent on the time window following first event and unfavorable outcome is more likely in older patients[6,16]. It is important to identify, diagnose and treat the ICAS IS patients early as well as develop a better understanding of the etiology to improve outcome.

This study provides insight for future investigators who can focus on taking a proactive approach to implement preventive measures. In-hospital psychological, medical and follow-up care may not be a feasible option for many patients and their families, and community involvement in Stroke prevention and care might be a better way to tackle this issue. The constraints to arriving at the hospital in time as well as the costs associated with in performing required tests and retaining patients until treatment is complete is a major hurdle that needs to be addressed. Stroke awareness campaigns would be of great benefit for long term involvement of the community in prevention and care.

The major limitation of the study is less sample size which is mainly because the total duration of the study. As most of the patients admitted belonged to lower socio-economic strata, imaging was not available/done for all patients owing to their economical limitations. That also decrease recruitment rate in the study.

In conclusion higher proportion of males was observed in all IS patients, however the small number of females admitted all came in a much smaller time window following onset than males. Lower-middle class patients had the longest TSO, both from rural and urban residential areas. No significant differences were obtained for most risk factors and laboratory values that were assessed owing to small sample size. Significant difference in neutrophilia was striking, and showed strong inverse relationship to lymphocytes in ICAS IS patients and moderate inverse relationship in non-ICAS IS patients.

References

1 Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MS, George MG, Hamdan AD, Higashida RT, Hoh BL — An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013 Jul; **44(7):** 2064-89.

2 Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh 3rd EE — Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993 Jan; 24(1): 35-41.

3 Ram R, Kaul S, Alladi S, Afshan JS, Prabha TS, Kohat A, Tandra S, Rani JY — Risk factors, vascular lesion distribution, outcome and recurrence of strokes due to intracranial atherosclerosis: one year data from Hyderabad stroke registry. *Annals of Indian Academy of Neurology* 2017 Oct; **20(4):** 387.

4 Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Mukherjee CS, Chaudhuri A, Hazra A, Roy J — A prospective community-based study of stroke in Kolkata, India. *Stroke* 2007 Mar 1; **38(3):** 906-1

5 Wang Y, Zhao X, Liu L, Soo YO, Pu Y, Pan Y, Wang Y, Zou X, Leung TW, Cai Y, Bai Q — Prevalence and outcomes of symptomatic intracranial large artery stenoses and occlusions in China: the Chinese Intracranial Atherosclerosis (CICAS) Study. *Stroke* 2014 Mar; **45(3):** 663-9.

6 Vaishnav AG, Vaishnav RA — Symptomatic Intracranial Atherosclerosis: Natural History of Medical Management Beyond the Hyperacute Stage of Ischemic Stroke in the Post-SAMMPRIS Era. *Journal of Stroke Medicine* 2018 Jun; **1(1):** 68-72.

7 Pandian JD, Sudhan P — Stroke epidemiology and stroke care services in India. *Journal of Stroke* 2013 Sep; **15(3):** 128.

8 Kaul S, Alladi S, Jabeen SA, Bandaru VCSSR, Ankem U, Mekala S, *et al*— Intracranial Atherosclerosis is the Most Common Stroke Subtype: Ten-year Data from Hyderabad Stroke Registry (India). *Annals of Indian Academy of Neurology* 2018; **21:** 209-13.

9 Gorelick PB, Wong KS, Bae HJ, Pandey DK — Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. *Stroke* 2008 Aug 1; **39(8):** 2396-9.

10 Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, Sila CA — Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *New England Journal of Medicine* 2005 Mar 31; **352(13):** 1305-16.

11 Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, Janis LS, Lutsep HL, Barnwell SL, Waters MF, Hoh BL — Stenting versus aggressive medical therapy for intracranial arterial stenosis. *New England Journal of Medicine* 2011 Sep 15; **365(11):** 993-1003.

12 Liu L, Wong KS, Leng X, Pu Y, Wang Y, Jing J, Zou X, Pan Y, Wang A, Meng X, Wang C — Dual antiplatelet therapy in stroke and ICAS: subgroup analysis of CHANCE. *Neurology* 2015 Sep 29; **85(13):** 1154-62.

13 Saleem SM — Modified Kuppuswamy scale updated for year 2018. *Indian J Res* 2018; **7(3):** 6-7.

14 Foerch C, Ghandehari K, Xu G, Kaul S — Exploring gender distribution in patients with acute stroke: A multi-national approach. Journal of research in medical sciences: *The official Journal of Isfahan University of Medical Sciences* 2013 Jan; **18(1):** 10.

15 Zhu B, Liu H, Pan Y, Jing J, Li H, Zhao X, Liu L, Wang D, Johnston SC, Wang Z, Wang Y — Elevated neutrophil and presence of intracranial artery stenosis increase the risk of recurrent stroke. *Stroke* 2018 Oct; **49(10):** 2294-300.

16 Chimowitz MI, Kokkinos J, Strong J, Brown MB, Levine SR, Silliman S, Pessin MS, Weichel E, Sila CA, Furlan AJ, Kargman DE — The warfarin-aspirin symptomatic intracranial disease study. *Neurology* 1995 Aug 1; **45(8):** 1488-93.

Original Article

Bacterial Profile with Antimicrobial Sensitivity Pattern of Different Pyogenic Infections Treated in a Tertiary Care Hospital at Kolkata

Rina Das[1], Tanushree Mondal[2], Bimal Kumar Mandal[3], Dibakar Haldar[4]

Background : It is pertinent that in order to mitigate the burden and its associated complications of pyogenic infections, a robust antimicrobial therapy is the need of the millennium. The world is very badly hit by the recent era of antibiotic resistance. This has posed an impediment to the treatment options which has been much been curtailed.

Objective : To identify the spectrum of causative organisms from pus cell, to find out pattern of antibiotic susceptibility of most predominant microbial agents. Methodology: A descriptive Cross-sectional study was carried out from 26th July 2016-25th July 2018 in the Department of Microbiology, Calcutta National Medical College, Kolkata involving all the 90 and 370 specimens of Pus and Wound swab collected via recommended procedure from the patients attending OPD and admitted in IPD and sent for culture and sensitivity testing. Specimen belonged to post-surgical complicated cases were 140 and rest of the samples were not related to surgery. Results: Culture was positive in 54.12% with slight dominance of male gender and in 21-40 years age group. Maximum comprised of Staphylococcus aureus species of organisms (43.48%) which showed high sensitivity to the drugs Erythromycin, Vancomycin, Doxycycline with one fourth Methicillin resistant strain. The second predominant organism was the gram-negative species Klebsiella sp. (23.91%) found to have maximum sensitivity to Colistin, Imipenem, Amikacin, Levofloxacin and Gentamicin.

Conclusion : In clinical practice Pyogenic skin infections are mainly resistant to one or more of the antibiotics, thereby limiting the treatment options. It is pertinent to have an antibiotic policy of health facilities for treatment of patients and reducing resistance.

[*J Indian Med Assoc* 2020; **118(11):** 53-8]

Key words **: Pyogenic infection, Bacteria, Antimicrobial, Sensitivity.**

Those so-called Pyogenic infections are usually characterized by local inflammations, the cause of which has been attributed to be due to pyogenic bacteria that can produce the accumulation of dead leukocytes and infectious agents commonly known as pus. Such infections of the human skin and soft tissue infections are caused during or after trauma, burn injuries and surgical procedures resulting in production of pus[2]. One of the most common causes of health care infection is the Surgical site infection with a reported rate of 2 to 20%[3]. A team led by World Health Organization researchers found developing countries carry much higher infection rates than the developed world and it is said "poor nation face: greater hospital infection burden"[4]. In India, the wound sepsis ranges from 10% to 33% in its occurrence[5,6].

Wound infections are contributed both by aerobic and anaerobic bacteria leading to significant morbidity, prolonged hospitalization which have great economic

[1]MBBS, MD Associate Professor, Department of Microbiology, CNMC, Kolkata 700014

[2]MBBS, MD, FAIMER Fellow CMC-Ludhiana, PhD Scholar, MAPC Associate Professor, Department of Community Medicine, MC, Kolkata & Assistant Director of Medical Education, Government of West Bengal and Corresponding Author

[3]MBBS, MS Associate Professor, Department of ENT, Raiganj GMC, Raiganj (MS) 733134

[4]MBBS, MD, Professor, Department of Community Medicine, BSMC, Bankura 722102

Received on : 28/07/2020

Accepted on : 29/09/2020

Editor's Comment :

- **Antibiotic Resistance has been a great challenge over the years. This has been aggravated by several factors like sell of OTC Drugs, Self-medication etc. In this new era of Emerging and Re-emerging infections, it is of utmost importance to be very vigilant on Antibiotic Policy.**
- **In this regard, every sample of Pyogenic Infection in tertiary care hospitals must be screened for bacterial profile with antimicrobial sensitivity pattern. this will not only reduce the burden of additional health costs, but can also help in developing a SOP of a robust antimicrobial therapy. Antibiotic stewardship is the call for the new Millennium.**

implication[7]. The emerging antibiotic resistance among pathogenic bacteria is viewed as serious threat to the public health worldwide. It has been observed that pus infections are mainly caused by Multidrug-resistant Gram-negative bacterial strains such as *E coli*, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Gram-positive methicillin-resistant Staphylococcus aureus (MRSA) and that too due to irrational prescribing habit[8-10]. As a result of emergence of multidrug-resistant bacteria, the treatment options have become limited in nature[10,11]. Few studies have shown a predictable bacterial profile and their antibiogram in certain areas[12]. Those clinicians who wants to initiate empirical treatment to his patients while laboratory culture reports are awaited can employ this strategy[13,14]. Thus our study mainly intended to develop a reliable data base about the bacterial profile.

Objectives :

1. To identify the spectrum of causative organisms of infection from the pus cell
2. To find out the pattern of antibiotic susceptibility of most predominant causative organisms

Materials and Methods

Our study is a descriptive Cross-sectional study which was undertaken in the Department of Microbiology, Calcutta National Medical College, for a period of over two years (26th July 2016- 25th July 2018) involving all 850 specimens of Pus and Wound swab which were sent for culture and sensitivity testing. Specimens collected from out-patient-department (OPD) were 90 in number and 370 were drawn from in-patient-department (IPD). From cases with post-operative complications 140 samples were collected and rest of the samples was not related to surgery of any kind.

Study tools and Reagents: Swab stick, sterile test tubes, Petri plates, inoculating loops, spirit lamps, cotton, incubator, microscope, glass slide and cover slip, blood agar, MacConkey agar, Mueller Hinton agar, Gram stain reagents, antimicrobial discs.

Control stains: Staphylococcus aureus ATCC 25922 and E. coli ATCC25923.

Specimen collection: A complete medical history with reference to onset, duration and progress of lesion and other relevant history was obtained. Then the specimens were collected by maintaining all aseptic measures, after cleaning the area around the lesion with 70% ethanol. Samples of pus were collected by a sterile swab stick or in sterile test tube. No sample was taken for anaerobic culture.

Culture of pus sample: Specimens were transported within two hours of collection. This was followed by processing on blood agar and MacConkey agar media by streaking method. Simultaneous gram staining was done directly from samples. His procedure was soon followed by incubating the culture plates at 37°C for 24 to 48 hours. The growth was noted from the colony and it was stained by gram staining. Following that, the biochemical tests were performed based on the organism.

Gram stain: The pus cells and the bacterial morphology, arrangement and the number of different types of organism were noted from direct stain. The colony morphology and strain from colony was correlated with previous direct stain.

Biochemical tests for gram positive bacteria were catalase, slide coagulase, tube coagulase and for gram negative isolates of test Indole, TSI, Citrate, Urease, Oxidase tests were performed routinely.

Using antimicrobial discs on Mueller Hinton agar applying the Kirby Bauer disc diffusion method (according to CLSI guideline), the sensitivity pattern was recorded.

Collected data were compiled in Micro soft excel and described by estimating various proportions. Displaying of data was achieved via tables and charts. The study was carried out after obtaining approval of the Institutional Ethics Committee.

Results

Total 850 specimens of pus were collected and processed with slight higher male preponderance (52.94%). Out of 850 pus samples, 460 (54.12%) showed growth with a male-female ratio of 1.09:1.0 (52.17% *versus* 47.83%). Around nine percent (8.69%) of the isolates were polyorganism. Majority of the culture positive participants belonged to the age group of 21-40 years closely followed by 41-60 years comprising of 43.48% and 34.78%, respectively (Table 1).

In this study gram positive organisms were found predominate with S (43.48%) on the top followed by gram negative Klebsiella species (23.91%).

Antibiotic susceptibility percentage: Analysis revealed that one fourth of the S aureus isolates showed resistance to Methicillin having sensitivity towards Linezolid and Vancomycin. The S aureus sensitive to Methicillin was also found to have good sensitivity to Doxicycline, Gentamycin, Levofloxacin and Vancomycin combination (Table 2).

In the study the most predominant species of organisms were found to be S aureus (43.48%) which showed high sensitivity to the drugs Erythromycin, Vancomycin, Doxicycline. (Table 3)

The second predominant organism was the gram negative species Klebsiella sp (23.91%) which was followed by Acinetobactor sp (13.04%) , Pseudomonas

Table1 — *Distribution of participants showing growth of organism as per age group and Gender (N=460)*

Age (Yr) Group	Male No (%)	Female No (%)	Total No (%)
1-20	30 (6.52)	50(10.87)	80(17.39)
21-40	90(19.57)	110(23.91)	200(43.48)
41-60	110(23.91)	50(10.87)	160 (34.78)
61-80	10(2.17)	10(2.17)	20(4.34)
Total	240(52.17)	220(47.83)	460 (100)

Table 2 — *Distribution of participants showing growth of Gram positive S aureus with its antibiotic sensitivity (n=200)*

Strain	Frequency (%)	Antibiotics to which Sensitive
S aureus (MRSA)	50 (25.0)	LZD, VAN
S aureus (MSSA)	150 (75.0)	DOX, GEN, LVX.VAN

MR/SSA= Methicillin resistant/sensitive S aureus,
LZD = Linezolid, VAN = Vancomycyn, DOX = Doxicycline,
GEN = Gentamycin, LVX=Levofloxacin,
LVX.VAN = combination of Levofloxacin & Vancomycin

aeroginosa (6.52%) and *E Coli* (4.35%). The gram-negative species were found to have maximum sensitivity to the drugs like Colistin, Imipenem, Amikacin, Levofloxacin and Gentamicin (Table 4).

Discussion

Age group :

Khanam RA *et al* observed in their study that around four out of every ten participants (42.0%) belonged to the age group of 20 to 40 years in concurrence to 43.48% in the present study[2]. From their study done at Kathmandu Razza MS *et al* also concluded that the maximum prevalence of the infection was prevalent in the age group 21-40 years[15].

Gender distribution :

The present study shows that males were found to be predominant (52.94%) as well as among the culture positives (52.17%) too. Khanam RA *et al* also reported higher proportion (56.1%) of male specimen[2]. Rao DVMVSVR *et al* observed that among the culture positive cases 58.82% were male[13]. Similar observations also made by Kamble P *et al* (67.0%), Mudassar S *et al* (64%), Mohammed A *et al* (59.10%), Muluye D *et al* (54.8%), Sudhaharan S *et al* and Khan I *et al* (59%)[16-21].

Culture positivity :

Analysis of the present study revealed culture positivity in 54.12% of all specimens and 8.69% showed polymicrobial growth. In a study by Sangwan J et al. that worked on 438 pus samples, about 72.6% of the culture showed positivity, surgical wards (39.7%) being the major contributor. Out of positive samples 82.3% were monomicrobial and 17.7% polymicrobial[1]. In majority (61.8%) of the cases aerobic culture was positive as observed by Khanam RA *et al*[2].

Kamble P *et al* reported growth in 92.0% of specimen out of which 85.87% cases showed monomicrobial[16]. In a study conducted by Rao DVMVSVR et al. about 89.47% of the cases yielded positive culture of which 95.09% was revealed to be pure bacterial isolates[13]. Sen M *et al* showed 59.38% samples to have single growth[22]. Kumari Pilli H P *et al* reported 21% culture positivity[23]. Shama M *et al* reported 73% culture positivity[24]. 83.9%. of the reported bacterial case was positive in a study by Mohammed A *et al*[18]. Muluye D *et al* found 70.2% culture positivity[19]. Another study by Sudhaharan S *et al* revealed that mono-microbial infections were found in 93.2% patients whereas combined infections with growth of two pathogens in 6.8%[20]. In their study Subha M *et al*[25]. observed 59.92% culture positivity having concurrence to the observation of growth in 61.11% of isolates made by Ghosh A *et al*[26].

Table 4 — *Distribution of participants according to antibiotic susceptibility of gram negative bacteria (GNB)*

Antibiotic[@]	Sensitivity of Bacteria to antibiotic (R:S)				
	Citrobacter koseri	Klebsiella sp.	E coli	Acineto-bacter sp.	Pseudomo-nassp.
AMC	100:0		100:0	—	—
LVX	—	—	—	—	100:0
AMK	0:100	57:43	50:50	75:25	0:100
CPM	—	—	—	—	100:0
CAZ	—	—	—	—	100:0
CTX	100:0	86:14	50:50	100:0	—
CTR	100:0	100:0	100:0	100:0	—
COT	—	57:43	100:0	75:25	—
CST	—	0:100	50:50	0:100	0:100
GEN	0:100	86:14	50:50	75:25	0:100
IMP	0:100	29:71	0:100	100:0	0:100
PTZ	100:0	57:43	0:100	50:50	100:0
PIB	—	—	—	—	0:100

[@]AMK =Amikacin, CPM = Cefexime, CAZ = Ceftazidine,
CTX = Cefotaxime, CST = Colistin, IMP = Imipenem,
PTZ = Piperacillin-tazobactum, PIB = Polymyxin B

Table 3 — *Distribution of participants according to antibiotic susceptibility of gram-positive bacteria (GPB)*

Organisms	Sensitivity of bacteria to antibiotics (R:S*)									
	GEN	HLGEN	CLIND	ERY	LVX	AMC	VAN	LZD	COT	DOX
S aureus	40:60	—	20:80	80:20	100: 0	40: 60	40:60	100: 0	90:10	20:80
Enterococcus	—	100: 0	100: 0	50:50	100: 0	100: 0	0:100	0:100	—	100: 0

R = Resistant, S = Sensitive, ERY = Erythromycin, LVX = levofloxacin, GEN = Gentamycin,
HLGEN = High level Gentamycin,CLIND = Clindamycin, AMC = Amoxicillin-Clavulanate,
COT = Cotrimoxazole

Isolates :

In our study, the most predominant species of organism was found to be S aureus (43.48%). Sangwan J *et al* observed S aureus to be the commonest isolate (24.2%) followed by Pseudomonas (21.4%), *E coli* (14.8%), Proteus spp (8.8%), Citrobacter spp (8.2%), Enterococcus (6.6%), Klebsiella spp (6.1%) and Streptococcus (2.2%). MRSA was 25.0% in the present study, compared to 48.9% found in another study[1]. Mudassar S et al. reported that among the culture positive pus samples S aureus accounted for 42%, P aeruginosa 19%, *E coli* 18%[17]. S aureus was found to the most predominant isolate (34%) followed by Klebsiella species (13%) in another study[18]. Muluye D and his associates found that majority (63.9%) were gram positive and around one third (36.1%) were gram negative. S aureus accounts 32.9% isolates, Coagulase Negative staphylococci [CONS] (14.7%), Streptococcus spp. (11.6%), Escherichia coli (9.5%), Klebsiella spp. (6.3%)[19]. From the observation of their study Shama M *et al* reported predominance (89%) of gram-negative isolates[24]. Predominance of S aureus was noted also by Subha M *et al* (26.32%) in their study[25]. Another study by Ghosh A *et al* showed that incidence of MRSA was half[26].

According to Khanam RA *et al* S aureus was the most prevalent (25.0%) isolated bacteria from pus followed by E coli, Pseudomonas, Acinatobactor species and Klebsiella species contributing to 16.5%, 14.6%, 4.7% and 0.9% isolates respectively[2]. Similarly, Mantravadi H B *et al*[12] revealed similar results of S. aureus as commonly occuring pathogen (37.2%) similar to studies by Rao DVMVSVR *et al*[13], Tiwari P *et al*[27], Lee CY *et al*[28] and Mahmood A[29]. However, Agnihotri N *et al* found Pseudomonas species to be more prevalent than S aureus [30] Another study conducted by Basu S *et al*[31] showed that Pseudomonas and E coli spp to be the most prevalent pathogens in wound infections which is in contradiction to the present study results. In a study conducted in Kathmandu Raza MS *et al* found *E coli* to be the most commonly occurring pathogen[15].

Gram Negative dominance :

In our study half isolates belonged to gram Negative bacteria (GNB). Overall, similar results have been reported by Khanam RA *et al*[2]. Mohammed A *et al* observed more than half (57%) of the isolates as GNB[18]. According to Sudhaharan S *et al* GNBs were isolated in 68.3%, *E coli* being the major one (38.6%); gram positive bacteria (GPB) were isolated in 31.6% of cases and S aureus was commonly occuring organism (91.7%) out of which 43.34% was MRSA[20]. Subha M *et al*,[25] Ghosh A *et al*,[26] Basu S *et al*[31] and Zubair M *et al*[32] also reported Pseudomonas and *E coli* spp. to be the widely prevalent pathogen in wound infections.

Sensitivity pattern :

In present study the most predominant isolate S. aureus showed high sensitivity to Erythromycin, Vancomycin, Doxycycline. The gram negative species dominated by Klebsiella sp (23.91%), Acinetobactor sp (13.04%), P aeroginosa (6.52%) and *E coli* (4.35%) were found to have maximum sensitivity to Colistin, Imipenem, Amikacin, Levoûoxacin and Gentamicin.

Khanam RA *et al* observed S aureus to have high resistance to penicillin (up to 84.5%), moderate sensitivity (58.3%) to Erythromycin while fair sensitivity to Vancomycins like clindamycin. Highest level of sensitivity was revealed towards high- end drugs such as Linezolid and Vancomycin.

While Streptococcus is sensitive to most of the drugs[2]. Rao DVMVSVR *et al* also found S. aureus highly resistant to Penicillin (84.62%), Erythromycin (84.62%), and sensitive to Clindamycin (65.38%) and Vancomycin (100%)[13]. The antibiogram in another study revealed that the S aureus was mostly susceptible to Vancomycin (89%) followed by Gentamicin (86%), Cefoxitin (82%), and resistant to Penicillin. The antibiogram of Pseudomonas revealed that it was more sensitive to Imipenem (97%) and resistant to Cotrimoxazole. Enterobacteriaceae were sensitive to Imipenem[17]. A study conducted at Peswar, Pakistan explored that Gram-positive isolates were resistant to Ampicillin (86.4%), Amoxicillin (83%), Penicillin (81.3%), Oxacillin (74.6%), and Tetracycline (59.4%), but Gram-negative isolates resistant to Amoxicillin (97.4%), Ampicillin (94.8%), Tetracycline (72.7%), Trimethoprim/sulfamethoxazole (66%), and Chloramphenicol (54.5%) were also noted[18].

In another study, 66.2% isolates were resistant to Tetracycline, followed by 59.8% for Ampicillin, 59.1% for Cotrimoxazole, 51.7% for Penicillin; least resistant being 6.3% for Gentamicin[19]. From Peswar study Khaan I et al. revealed that majority of isolates were observed to be resistant to three or more classes of antibiotics. S. aureus were resistant to Amoxicillin (82%), Ofloxacin (80%), Sparfloxacin (78%), Ciprofloxacin (71%), Levofloxacin (46%) and Gentamicin (36%). Sensitivity to Tygacil and Linezolid was universal, and isolates showed low resistance to sulzone (2%), Oxacillin (3%), Vancomycin (4%), Fusidic acid (5%), Clarithromycin (7%), Erythromycin (8%), Cefoxitin (9%), Amikacin (15%), Cefaclor (15%) and Cephradine (19%)[21].

According to Kumari Pilli H P *et al* S aureus showed

maximum sensitivity to antibiotics like Linezolid (83.3%) and Teicoplanin (50%)[23].

Antibiotic sensitivity pattern as explored by Shama M *et al* showed that Cefaperazone/ Sulbactum was highly effective drug against commonest gram negative isolates *E coli* (57.5%), followed by Proteus sp (31.5%) - Penicillin and Ampicillin were highly effective drugs[24]. Subha M *et al* showed MRSA was 17.5% and 100% sensitive to Vancomycin. Around one fifth (23.61%) of E coli and 25% of K pneumoniae ESBL producers. Imipenem and Meropenem were effective for majority of the gram negative isolates[25].

Study in Nigeria carried out by Taiwo S S *et al* revealed 99.6% resistance to Ampicillin and 33.1% to Oxacillin, 72.7% to Erythromycin but 100% sensitivity to Vancomycin and more than 98% to Linezolid. GNBs were highly resistant to b-lactams whereas Carbapenems are still reactive, however increasing resistance was observed to Meropenem[33].

Amongst the aminoglycosides Amikacin showed good sensitivity in spite of rising resistance to Gentamicin and Tobramycin. Drug combination such as Piperacillin plus Tazobactam and Cefoperazone plus Sulbactum was found to be good[2]. In their studies Taiwo SS *et al*[33], Rao DVMVSVR *et al*[13], and Basu S *et al*[31] also corroborated these findings.

Razza MS *et al* showed that all isolates of S aureus was sensitive to Vancomycin and Aminoglycosides. About two-fifth (41.66%) S aureus isolates was MRSA High resistance against Cephalexin (75% - 100%) and Ceftriaxone (25% - 100%) was detected among all gram negative isolates. Grossly 66.7% were multi-drug resistant isolates[15].

Limitations of the study : The study was conducted in one of the Medical Colleges of Kolkata which caters a small segment of the total patients turn out for treatment in all other health facilities in the capital city of West Bengal. So, the only constraint was in its external validity. Other factors of antibiotic resistance like duration and compliance to treatment, comorbidity, nutritional status of the patients etc. couldn't be taken into consideration in this small study. A large scale multicentre study encompassing all these correlates of antibiotic usage may be tried for drawing a reliable and valid inference.

Conclusion

Pyogenic infections are frequently encountered in day to day clinical challenges and most of them are resistant to one or more antibiotics, thus limiting treatment options. The finding of the present study is helpful to guide for developing antibiotic policy and empirical therapy and thus reducing morbidity of patients. A correct antibiotic strategy and the avoidance of inappropriate antimicrobial usage are mandatory to mitigate the containment of antibiotic resistance in the community, also keeping newer antibiotics in reserve for use only against strains that are resistance to the common antibiotics.

Conflict of Interest : None

Financial Assistance from outside sources : Nil

References

1 Sangwan J, Singla P, Mane P, Lathwal S, Malik AK — Prevalence and Antimicrobial Susceptibility Patterns of Aerobic Bacterial Isolates from Pyogenic Wound Infections at a Tertiary Care Institute in Haryana, India. *International journal of current Microbiology and Applies Sciences* 2016; **5(2):** 78-85.

2 Khanam RA, Islam MR, Sharif A, Parveen R, Sharmin I, Yusuf MA — Bacteriological Profiles of Pus with Antimicrobial Sensitivity Pattern at a Teaching Hospital in Dhaka City. *Bangladesh Journal of Infectious Diseases* 2018; **5(1):** 10-4.

3 Kaur K, Oberoi L, Devi P — Bacteriological profile of surgical site infections. *IAIM* 2017; **4(12):** 77-83.

4 Gangania PS, Singh VA, Ghirmire SS — Bacterial isolation and their antibiotic susceptibility pattern from post operative wound infected patients (Internet). *Indian J Microbiol Res* 2015 (cited on 21/12/2019); **2(4):** 231-5. Available at: https://www. innovativepublication. com/innovative-file?file= IJMR_2% 284% 29_231-235.pdf

5 Akimoto Y, Mochizuki Y, Omata H, Uda A, Shibutani j, Nishimura H, *et al* — Amoxicillin concentration in pus from abscess caused by odontogenic infection. *Gen Pharmacol* 1994; **25:** 111-3.

6 Koneman EW , Allen SD, Janda WM, Schreckenberger PC, Propcop GW, Woods GL, *et al* — Philadelphia Color Atlas and Textbook of Diagnostic microbiology, 6th edn Philadelphia, PA; Lippincott Williams and Wilkins, 2005. 624-62.

7 Bowler P G, Duerden B I, Armstrong D G — Wound microbiology and associated approaches to wound management. *Clinical Microbiology Reviews* 2001; **14(2):** 244-69. doi: 10.1128/cmr.14.2.244-269.2001.

8 Rice LB — Antimicrobial resistance in gram-positive bacteria. *The American Journal of Medicine* 2006; 119 (6, supplement 1):S11–S19. doi: 10.1016/j.amjmed.2006.03.012.

9 Misic AM, Gardner SE, Grice EA — The Wound Microbiome: modern approaches to examining the role of microorganisms in impaired chronic wound healing. *Advances in Wound Care* 2014; **3(7):** 502-10. doi: 10.1089/wound.2012.0397.

10 Iredell J, Brown J, Tagg K— Antibiotic resistance in *Enterobacteriaceae*: mechanisms and clinical implications. *British Medical Journal* 2016; 352 doi: 10.1136/bmj.h6420.h6420

11 Cerceo E, Deitelzweig S B, Sherman B M, Amin A N — Multidrug-resistant gram-negative bacterial infections in the hospital setting: overview, implications for clinical practice, and emerging treatment options. *Microbial Drug Resistance* 2016**; 22(5):** 412-31. doi: 10.1089/mdr.2015.0220.

12 Mantravadi HB, Chinthaparthi MR, Shravani V — Aerobic isolates in pus and their antibiotic sensitivity pattern: a study conducted in a teaching hospital in Andhra Pradesh. *Int J Med Sci Public Health* 2015; **4:** 1076-9. Available at: https://pdfs.semanticscholar.org/b9fb/ 3af935c819589d251fb73c5a1083a 84f98dc.pdf

13 Rao Raghav DVMVSV, Basu R, RoyBiswas D — Aerobic

Bacterial Profile and Antimicrobial Susceptibility Pattern of Pus Isolates in a South Indian Tertiary Care Hospital. *IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)* 2014; **13(3):** 59-62.

14 Trojan R, Razdan L, Singh N — Antibiotic susceptibility patterns of bacterial isolates from pus samples in a tertiary care hospital of Punjab, India (Internet). *Int J Microbiol* 2016: 1-4. doi:10.1155/2016/9302692 (cited 20/12/2019), Available at: https://www.ncbi.nlm.nih.gov/ pmc/ articles/PMC5107258/

15 Raza MS, Chander A, Ranabhat A — Antimicrobial susceptibility patterns of bacterial isolates in postoperative wound infections in a tertiary care hospital, Kathmandu, Nepal. *Open J Med Microbiol* 2013; **3:** 159-63

16 Kamble P, Parihar G, Kumar M, Mohanpuriya LR — Bacteriological study of pyogenic skin infection at tertiary care hospital. *IOSR Journal of Dental and Medical Sciences* 2016; **15:** 114-21.

17 Mudassar S, Khan SW, Ali M, Mahmood A — Aerobic Bacteriological Profile and Antimicrobial Susceptibility Pattern of Pus isolates in a Teaching Hospital, Lahore, Pakistan. *International Journal of Contemporary Medical Research* 2018; **5(4):** D1-D3. DOI: 10.21276/ijcmr.2018.5.4.8

18 Mohammed A, Seid ME, Gebrecherkos T, Tiruneh M, Moges F — Bacterial Isolates and Their Antimicrobial Susceptibility Patterns of Wound Infections among Inpatients and Outpatients Attending the University of Gondar Referral Hospital, Northwest Ethiopia. *International Journal of Microbiology* 2017; https://doi.org/10.1155/2017/8953829

19 Muluye D, Wondimeneh Y, Ferede G, Nega T, Adane K, Biadgo B, *et al* — Bacterial isolates and their antibiotic susceptibility patterns among patients with pus and/or wound discharge at Gondar university hospital. *BMC Research Notes* 2014; **7:** 619.

20 Sudhaharan S, Kanne P, Chavali P, Vemu L — Aerobic bacteriological profile and antimicrobial susceptibility pattern of pus isolates from tertiary care hospital in India. *J Infect Dev Ctries* 2018; **12(10):** 842-8. doi:10.3855/jidc.10473

21 Khan I, Sarwar N, Ahmad B, Azam S, Rehman N — Identification and Antimicrobial Susceptibility Profile of Bacterial Pathogens Isolated From Wound Infections in a Teaching Hospital, Peshawar, Pakistan. *Adv Life Sci* 2017; **5(1):** 8-12.

22 Sen M, Islahi S, Das A, Agarwal J — Antimicrobial susceptibility profile of Staphylococcus aureus isolated from pyogenic infections-Variations encountered at secondary and tertiary care level centres. *Int J Med Microbiol Trop Dis* 2019; **5(4):** 188-92.

23 Kumari Pilli HP, Rani PU, Vijayalakshmi P — Evaluation of microbiological profile and antibiogram of aerobic bacteria isolated from pus samples. *J Med Allied Sci* 2018; 8(1): 26-35. DOI: 10.5455/jmas.284747

24 Shama M, Murugesan K, Vijayan H — Isolation Identification and Antibiotic Sensitivity pattern of Pyogens from Pyogenic pathogens. *Biomedical & Pharmacology Journal* 2018; **11(1):** 463-8.

25 Subha M, Srinivasagam M — Microbial Profile and Antimicrobial Susceptibility Pattern of Pus Culture Isolates from a Teaching Tertiary Care Hospital, South India. *Int J Curr Microbiol App Sci* 2018; **7(4):** 1149-53. doi: https://doi.org/10.20546/ijcmas.2018.704.126

26 Ghosh A, Karmakar PS, Pal J, Chakraborty N, Debnath NB, Mukherjee JD — Bacterial incidence and antibiotic sensitivity pattern in moderate and severe infections in hospitalized patients. *J Indian Med Assoc* 2009; **107(1):** 21-2.

27 Tiwari P, Kaur S — Profle and sensitivity pattern of bacteria isolated from various cultures in a tertiary care hospital in Delhi. *Indian J Public Health* 2010; **54(4):** 213-5.

28 Lee CY, Chen PY, Huang FL, Lin CF — Microbiologic spectrum and susceptibility pattern of clinical isolates from the pediatric intensive care unit in a single medical center—6 years' experience. *J Microbiol Immunol Infect* 2009; **42(2):** 160-5.

29 Mahmood A — Bacteriology of surgical site infections and antibiotic susceptibility pattern of the isolates at a tertiary care hospital in Karachi. *J Pak Med Assoc* 2000; **50:** 256-9.

30 Agnihotri N, Gupta V, Joshi RM — Aerobic bacterial isolates from burn wound infections and their antibiograms—a fve-year study. *Burns* 2004; **30(3):** 241-3.

31 Basu S, Ramchuran Panray T, Bali Singh T, Gulati AK, Shukla VK — A prospective, descriptive study to identify the microbiological profle of chronic wounds in outpatients. *Ostomy Wound Manage* 2009; **55(1):** 14-20.

32 Zubair M, Malik A, Ahmad J — Clinico-microbiological study and antimicrobial drug resistance profle of diabetic foot infections in north India. *Foot (Edinb)* 2011; **21(1):** 6-14.

33 Taiwo SS, Okesina AB, Onile BA — In vitro antimicrobial susceptibility pattern of bacterial isolates from wound infections in University of Ilorin teaching hospital. *Afr J Clin Exp Microbiol* 2002; **3(1):** 6-10.

Image in Medicine

Bhoomi Angirish[1], Bhavin Jankharia[2]

Quiz 1

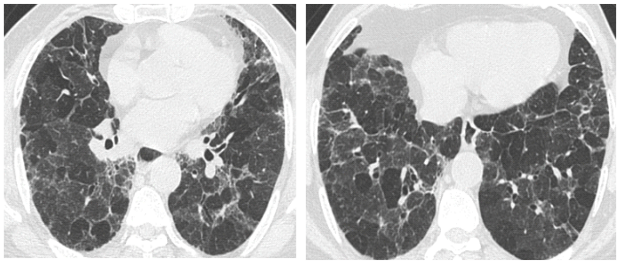
Axial CT scan images of 58 year old male presenting with dyspnea for many years.

Questions :

(1) What pattern is shown?

(2) What is the diagnosis?

(3) How do we classify hypersensitivity pneumonitis?



Answers :

(1) "Triple-density sign" - which includes ground glass opacities (high attenuation), patchy air trapping (low attenuation) and normal lung tissue. Previously it has been referred to as the “headcheese sign”.

(2) Fibrotic hypersensitivity pneumonitis (HP) - HP is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways. It typically results from an immune-mediated reaction provoked by an overt or occult inhaled antigen in susceptible individuals.

(3)HP was historically categorized as acute, subacute, or chronic. Now it is categorized as either fibrotic or nonfibrotic HP. The HRCT findings can further categorize these as “typical HP”, “compatible with HP” and “indeterminate for HP”. Ground glass, mosaic attenuation, ill-defined centrilobular nodules and air trapping are seen in non-fibrotic HP whereas coarse reticulation with parenchymal distortion, traction bronchiectasis, ill-defined centrilobular nodules, air trapping and triple-density sign are seen in fibrotic HP.

Quiz 2

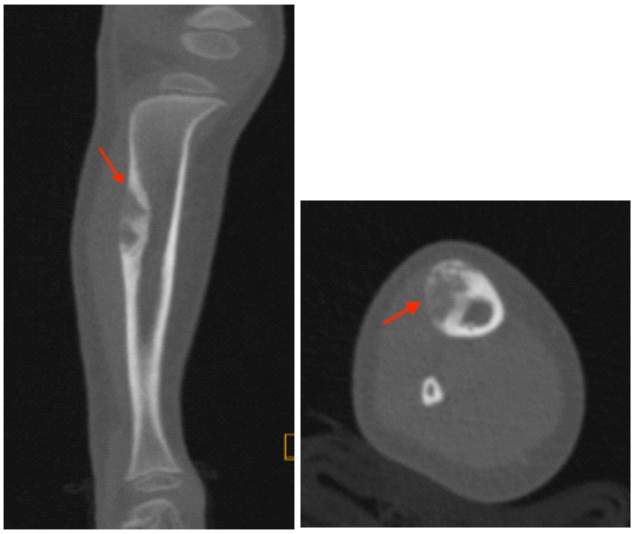
Coronal and axial CT scan images of 4 year old male presenting with swelling in leg since 4 months.

Questions:

(1) What is the diagnosis?

(2) What are the radiographic features of this lesion?

(3) What are the differential diagnosis?



Answers :

(1) An expansile osteolytic lesion with surrounding sclerosis is seen involving anterolateral cortex of diaphysis of tibia, with focal thinning of cortex and no obvious soft tissue component. An image guided biopsy was performed, which confirmed the diagnosis of **osteofibrous dysplasia**.

(2) Osteofibrous dysplasia is a benign fibro-osseous cortical lesion, that occurs exclusively in the tibia and fibula in mid-diaphysis. It has narrow zone of transition with surrounding sclerosis. Periosteal reaction or nidus is not associated with this lesion.

(3) Adamantinoma is a close differential as these are also common in tibial diaphysis, however they are locally aggressive tumours, which appear as expansile osteolytic cortical lesions whereas osteofibrous dysplasia show more ground glass texture on CT. Adamantinoma presents in 2nd to 3rd decade whereas osteofibrous dysplasia is common in younger age group. The other differential is ossifying fibroma.

Picture This by Jankharia, Mumbai, Maharashtra
[1]MD, DNB (Radiology)
[2]MD, DMRD (Radiology)

Student's Corner

Become a Sherlock Homes in ECG

M Chenniappan[1]

Series 6 :

ECG

"Confusion of Colours"

Routine ECG of 68 years old Male

1. **What are the ECG findings?**
2. **Why is this clue?**
3. **What are the practical implications?**

ECG FINDINGS :

This ECG shows sinus rhythm with left anterior fascicular block (LAFB) and PR interval in the upper limit. There is sudden appearance of Tall R wave in V3 (>V4) and sudden disappearance of R wave in V5. In V5 and V6 QRS complex is looking completely different. The unexpected appearance of R wave in one lead and sudden disappearance of R wave in another lead are suggestive of chest electrode malposition. Here electrode of V5 is placed in V3 position and electrode for V3 is placed in V5 position resulting in this unusual appearance and disappearance of R wave. This type of ECG change cannot be explained by electrocardiographic terms because the configuration of QRS in V5 and V6 is most often similar in normal ECG.

CLUE:

The ECG technicians most often do the error of misplacing electrodes either in limb leads or in the chest leads. To avoid this error chest electrodes are given in particular colours. So that the technician remembers the particular colours for the specific electrode and place it in a correct place. The colours for the chest electrodes are

V1 - Red V2 – Yellow V3 – Green
V4 – Brown V5 – Orange V6 – Purple

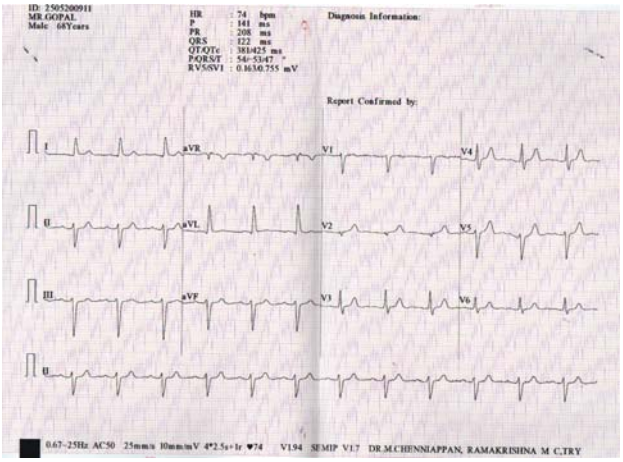
These colours can be remembered easily by the following method.

Electrodes V1 – V3 remember traffic signals (Red, Yellow, Green)

Electrodes V4-V6 remember the pneumonic "BOP"(Brown, Orange, Purple).

In this simple way technicians can identify the chest electrodes and place it in the correct place without looking at the letter in the electrode like V1,V2, etc, In this ECG, orange is placed in Green position and Green is placed in orange position resulting in abnormal QRS complexes in V3 and V5.That is why the clue of "Confusion of Colours" is given.

[1]Adjunct Professor, Dr MGR Medical University, Tamilnadu; Senior consultant cardiologist, Tamilnadu; Ramakrishna Medical Centre, Apollo Speciality Hospital, Trichy



PRACTICAL IMPLICATIONS :

Correct ECG recording is an essential prerequisite for the right interpretation of Electrocardiogram. So, the ECG technician/paramedics who record the ECG should be taught how to connect the electrodes in the limbs as well as how to place chest electrodes in the correct positions. Most often technicians make error because they do not look at the name of the letters inscribed on that particular electrode and in a hurry, they misplace the chest electrodes. If they are taught the positioning of the chest electrodes as well as the limb electrodes through the colours it is easy for them to place the electrodes in a correct position. Some of this wrongly recorded ECGs may give a wrong diagnosis like dextrocardia , Myocardial Infarction , Ventricular enlargement etc. and the patient may get inappropriate and incorrect treatment. So , educating the technicians in a simple way through colour coding of electrodes is an efficient method of making sure that the ECG is recorded properly.

Case Report

Case Report of Multiple Myeloma in a Young Age of 35 Year Old Male Patient

P K Agrawal[1], Faraz Ahmad[2]

Multiple myeloma is a neoplastic plasma cell disorder characterized by a clinical pentad, Anaemia, monoclonal protein in the serum or urine, bone lesion, hypercalcemia, renal insufficiency. Multiple myeloma, a disease of elderly, is extremely rare in those about 30 years of age. A patient with Multiple Myeloma diagnosed at age 35 is described. He presented with markedly reduced haemoglobin include systemic sequelae such as, anemia, fatigue, and weakness. He also complains of backache as there are early osteoporotic changes develops in the lumbosacral bone picture. On bone marrow examination hypercellularity is noted with Plenty of myeloma cells are diagnostic which includes plasmablast, mature plasma cells and intermediate differentiated cells. The Bence Jones proteinuria is not very commonly reported among young patients but in our patient the Bence Jones proteinuria was also present. As our patient profile with beta microglobulin is 4.2 with serum albumin 3 categorise in the second stage of multiple myeloma classification. In serum protein electrophoresis: M band detected in Gamma region. Despite the rarity of multiple myeloma among young patients, the clinical, radiological and laboratory features, among young patients, are similar to elderly patients and with early diagnosis and treatment a longer survival in noted in younger patients.

[*J Indian Med Assoc* 2020; **118(11):** 61-3]

Key words **: Multiple myeloma, Young person, Bone marrow, Plasma cells.**

Multiple myeloma is a neoplastic plasma cell disorder characterized by a clinical pentad, anaemia, monoclonal protein in both urine or serum, bone lesion/ bone pain, hypercalcemia, renal insufficiency.

With an exception of of monoclonal gammopathy (MGUS), it is the most common B cell disorder with an incidence of about 4.5 per 100,000 per year[1]. The median age at diagnosis is 65 years, extremely rare in those younger than 35 years while 2% are younger than 40 years of age. Multiple myeloma patients has risk of infections due to monoclonal gammapathy as well as reductions of CD4+T cells, natural killer cells and defects in complement system that leads to functional impairment and mortality of the patients.

There is no specific intervention in but there are many effective treatments that prolong and improve the quality of life in multiple myeloma patients.

Case Study

A 35 year patient name keno Ranjan, resident of West Bengal was admitted to the Department of medicine of Katihar Medical College, with a chief complains of weakness, backache, fatigue, myalgia, chest congestion for six months. He had been treated with oral analgesics, antibiotics without any improvements outside the hospital. There is a past history of pneumonia one year back.

Department of Internal Medicine, KMCH, Katihar 854105
[1]MBBS (Hons), MD (Gen Medicine), FICP, Professor & Head
[2]MBBS, MD (STD), Junior Resident (3rd year)
Received on : 13/07/2020
Accepted on : 02/11/2020

Editor's Comment :

- **This study represents a constellation of rare findings in patient with multiple myeloma.**
- **These cases showing unusual presentations,that shows the importance of good clinicopathological correlation to arrive at a correct diagnosis.**
- **Early diagnosis and management of such cases can decrease the morbidity and mortality.**

My patient is vegetarian by diet and there is no h/o of smoking or any addiction (Fig 1).

On admission, patient vitals are Heart Rate : regular 80 bpm, Respiratory Rate : 16 rpm, Temperature: 37°C, Oxygen Saturation : 98%, Weight: 45 Kg, Height: 5 ft 7 inches.

On examination, patient is alert.

Oriented and cooperative, Lean built, poorly nourished with severe pallor, mask facies of chronic disease with backache. On systemic examination chest is congested and spleen is mildly palpable and rest findings are normal. Patient is also giving h/o weight loss since last 6 months.

Laboratory Findings —

The complete hemogram showed sever anaemia - Hemoglobin 4.2 g/dl and high ESR 90 mm/hour, creatinine 1.4 mg/dl, normal electrolytes, LFT and CBG.

Imaging studies of Chest, Spine, Skull were normal.

Ultrasound abdomen showed bilateral renal cortical echoes increased but cortico-medullary relation is normal. Spleen : Measured 12.2cm enlarged in size with normal outline and echotexture.

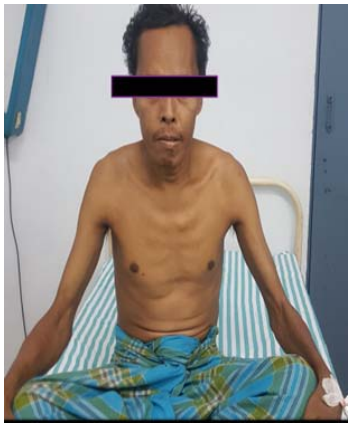


Fig 1

Bone marrow examination revealed plasma cell infiltration with hypercellular marrow with plenty of myeloma cells suggestive of multiple myeloma.

Serum protein electrophoresis : M band detected in Gamma region, Bence-Jones protein : in urine positive, β2 microglobulin : 4.2g/dl.

Discussion

Multiple myeloma is a condition of malignant plasma cell proliferation derived from a single B cell lineage[2,3]. These cells produce monoclonal immunoglobulins, most commonly either immunoglobulin G (IgG) or immunoglobulin A (IgA)[3].

As a gammopathy, multiple myeloma generally presents with recurrent infections secondary to humoral immune deficiencies, or with bone pain as a result of osteolytic lesions.

• There is B cell mutation which leads to bone marrow plasmacytosis, mostly 13q deletion and sometimes 17p deletion. Translocation of chromosome 11 and 14 responsible for interleukin 6 secretion that causes increase osteoclastic activity results in pathological fractures, backache, hypercalcemia, headache and punched out lesions.

The peak incidence of MM is in the seventh decade, whereas, it is a rare entity in young patients, with less than 2% cases occurring in patients under the age of 40 years and it is still rarer in patients who are younger than 30 years[4].

Here in our case report the patients age is 35 years and we were able to find all the classical features of MM.

Our patient presented with markedly reduced haemoglobin include systemic sequelae such as, anemia, fatigue, and weakness. He also complains of backache as there are early osteoporotic changes develops in the lumbosacral bone picture.

As the ESR of the patient is raised , Hematological analysis in Multiple Myeloma patients reveals rouleaux formation because of increased globulins.

Hyperviscosity symptoms appeared like generealised malaise, infection, somnolence and sluggish mentation typically experience by the patient because of high monoclonal protein in the blood.

Reviewing our case, the MCV is markedly raised on peripheral smear, we first consider megaloblastic anaemia in differential and start the line of treatment. After primary management, like blood transfusion, broad spectrum antibiotic therapy still the patient Hb level drops again and the patient symptoms did not shows signs of improvement. The patient again re-evaluated further approach for bone marrow had been done. On bone marrow examination hypercellularity is noted with Plenty of myeloma cells which are diagnostic of multiple myeloma which includes plasmablast, mature plasma cells and intermediate differentiated cells.

The Bence Jones proteinuria is not very commonly reported among young patients[7] but in our patient the Bence Jones proteinuria was also present. Total leukocyte count is with in normal limit .

Serum β2 microglobulin level is increased in MM and higher levels are also associated with poor prognosis.

The latest criteria to diagnose symptomatic Multiple Myeloma defined by the[5]

(A) : Bone marrow plasma cells 10% plus one of the myeloma defining events :

• Anemia with below a lower limit in hemoglobin of at least 20g/l below the normal limit or Hb less than 10g/dl.

• Hypercalcemia greater than 11 mg/d.

• Renal insufficiency with creatinine of more than 2 mg/dl

Bone lesion: one or more osteolytic lesion on skeletal radiography

(B) Any one or more of the following biomarker of malignancy bone marrow plasma cells > 60%

Serum involved: serum free light chain ratio (SFLC) >100

More than 1 focal lesion on MRI Studies.

For prognosis and management the

The stratification system divides Multiple Myeloma in three stages according to the level of serum protein and β2 level[5,6].

• STAGE I: serum β2 - microglobulin <3.5 mg/liter, serum albumin ≥3.5 g/dL

• STAGE II: serum β2 – macroglobulin 3.5 mg/liter, plus serum albumin 3.5 g/dl; or β2 microglobulin of 3.5 to <5.5 mg/l, irrespective of serum level of serum albumin

• Stage III: serum β2 - microglobulin ≥5.5 mg/liter.

As our patient profile with beta microglobulin is 4.2 with serum albumin 3 categorise in the second stage of this classification.

Serum protein electrophoresis: M band detected in Gamma region.

Avereage survival of patients with MM ranges between 2-3 years. In the study from Mayo clinic, the avereage survival of the patients was 87 months.

The life expectancy of the younger patients was considerably longer than that of patients of all ages with MM[7,8]. These results support the beneficial effect of a very young age on survival in patient with myeloma.

As initial therapy for the introduction of several newer induction regimens[8]. The most common induction regimens used today are thalidomide–dexamethasone, bortezomib based regimens, lenalidomide dexamethasone, three to four courses recommended before proceeding to stem cell collection[8]. As the patients in the kosi region is of very poor socio-economic status, bortezomib is not prescribed to the patient, dexamethasone and lenalidomide were used as we get a very good response and tolerance.

Dexamethasone of 40 mg PO daily on 1-4 days then on 9-12, then on 17-20th day of month plus 25 mg of lenalidomide on days 1-21 was advised in the first month. After the first month of treatment, patient profile is improved with beta2 microglobulin level comes down to 3.7 and Hb also improves to 7.0gm/dl, with the improvement we transfer the patient to the hametology centre for further workup.

Conclusion

Despite the rarity of multiple myeloma among young patients, the clinical, radiological and laboratory features, among young patients, are similar to elderly patients. Thus, multiple myeloma should be evoked even in young patients. It appears that there is no difference between younger and elderly patients on the presentation of the disease, although a longer survival has been reported among younger patients.

References

1 Kyle RA — Multiplemyeloma, an odyssey of discovery. *Br J Haematol.* 1035-44.

2 George ED, Sadovsky R — Multiple myeloma: recognition and management. *Am Fam Physician* 1999; **59(7):** 1885-94.

3 Kyle RA, Gertz MA, Witzig TE, Lust JA, Lacy MQ, Dispenzieri A, Fonseca R, Rajkumar SV, Offord JR, Larson DR, Plevak ME, Therneau TM, Greipp PR — Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003; **78(1):** 21-33.

4 Ishida T, Dorfman HD — Plasma Cell Myeloma in Unusually Young Patients: A Report of Two Cases and Review of Literature. *Skeletal Radiology* 1995; **24:** 47-51.

5 Ramón GS, María VM — Salamanca. España. *Med Clin (Barc)* 2007; **129:** 104-15.

6 Bart B, Alan M, Frits van R, Joshua E, Gareth JM, *et al* — Curingmyeloma at last: defining criteria and providing the evidence. National Center of Biotechnology Medicine Blood 2014; 124.

7 Blade J, Kyle RA, Greipp PR, et al — Presenting features and prognosis in 72 patients with multiple myeloma who were younger than 40 years. *Br J Haematol* 1996; **93:** 345-51.

8 Vincent Rajkumar S, Shaji Kumar — Multiple myeloma: diagnosis and treatment. *Mayo Clin Proc* 2016; **91:**101-19.

Case Report

Sheehan's Syndrome — A Case Report

M Sathish Kumar[1], P R Sowmini[1], S Sakthi Velayutham[1], Jeyaraj K Malcolm[1], R Viveka Saravanan[2], K Mugundhan[3]

Anterior pituitary infarction occurring in the postpartum period and the ensuing hypopituitarism is called Sheehan's syndrome. Postpartum hemorrhage is an important precipitating factor for Sheehan's syndrome. Here we describe a primigravida with severe postpartum hemorrhage who remained drowsy and failed to produce breast milk in the puerperium. Her MRI T2 & FLAIR revealed hyperintense and enlarged anterior pituitary gland consistent with anterior pituitary infarction. Her cortisol and prolactin levels were also low. After replacing corticosteroids her clinical condition improved. Failure to lactate, failure of return of menses in a puerperal woman along with typical MRI findings and low anterior pituitary hormone levels suggests Sheehan's syndrome. Assessing hormonal deficiencies and replacing them forms the cornerstone of management.

[*J Indian Med Assoc* 2020; **118(11):** 64-5]

Key words **: Sheehan's syndrome, Anterior pituitary, Postpartum hemorrhage.**

In 1937 Harold L Sheehan, a Pathologist at Glasgow Royal Maternity Hospital performed autopsy of women who died in late pregnancy. He found that nearly 12 out of 76 had destruction of anterior pituitary whose common clinical feature was hemorrhagic shock. He compiled his experience in a monograph titled 'postpartum hypopituitarism' which was published in 1982. He was also a man of modesty who had aversion to the term Sheehan's syndrome and preferred postpartum pituitary necrosis. His exemplary work on postpartum hypopituitarism has stood the test of time. Anterior pituitary infarct due to puerperal hemorrhage is called as Sheehan's syndrome[1]. Six percent of all hypopituitarism is attributed to Sheehan's syndrome. In India 3 percent of women above 20 years develop postpartum pituitary necrosis[2]. The clinical presentation of this entity can be acute (less common) or chronic. Here, we report a case of an acute presentation of Sheehan's syndrome in a young female who had massive postpartum hemorhage (PPH).

Case Report

A 25 year old primigravida with twin gestation of 34 weeks delivered dead born male babies via labour naturalis. She had abruption of placenta, leading to massive postpartum hemorrhage. Subsequently she developed features of HELLP syndrome and disseminated intravascular coagulation. Her clinical course was further complicated by acute pulmonary edema and acute kidney injury. She was intubated and ventilated soon after delivery and required inotrope support to maintain hemodynamics. She was transfused 10 units of blood and blood products including platelets and fresh frozen plasma (FFP). Initially she was conscious and oriented. General examination revealed severe pallor and anasarca. Her temperature was 102.2°F, pulse 118/min, and a supine blood pressure of 130/80 mm Hg. Systemic examination revealed normal heart sounds with bibasal crackles and a soft abdomen. There was trickling of blood with few clots per vaginally. On laboratory evaluation She had low hemoglobin (Hb -7 g/dl), raised urea levels (blood urea 110 mg/dl), liver enzyme (ALT 118 U/L), uric acid (18 mg/dl) and Lactate dehydrogenase (4300 U/L). Her electrolytes were within the normal range. She had prolonged prothrombin time (19 seconds) hence an elevated international normalized ratio (1.42).

On day 2 of post partum,her blood clots were evacuated under general anesthesia with ultrasound guidance. At the end of procedure she sustained sudden cardiac arrest but was resuscitated successfully. Around 3 litres of blood clots were removed and blood products were replaced along with uterotonic infusion. Post operatively, she continued to bleed per vaginally for which uterine massage, FFP transfusion and prostaglandin infusion were administered. After a few hours her bleeding stopped.

On day 6 of post partum, she still remained drowsy and somnolent. She was not able to move her limbs and her speech was very slow. She also had lactation failure. Computed tomography(CT)of brain revealed enlarged pituitary gland with prominent stalk (Fig 1). Magnetic resonance imaging (MRI) T2/FLAIR of brain showed hyperintense lesion in an enlarged pituitary gland (anterior portion) suggestive of anterior pituitary infarct. Hormonal

Editor's Comment :

- **Sheehan's syndrome should be suspected in a postpartum woman with massive uterine bleed following childbirth, hypotension, agalactorrhea, and failure of return of menses.**
- **Careful assessment and replacement of hormones is necessary to avoid life threatening consequences.**

Department of Neurology, Government Stanley Medical College and Hospital, Chennai 600001
[1]MD, DM, Assistant Professor of Neurology
[2]MD, DM, Associate Professor of Neurology
[3]MD, DM (Neuro), FICP, FRCP (Glasg), FACP (USA), Professor and Head
Received on : 10/10/2020
Accepted on : 30/10/2020

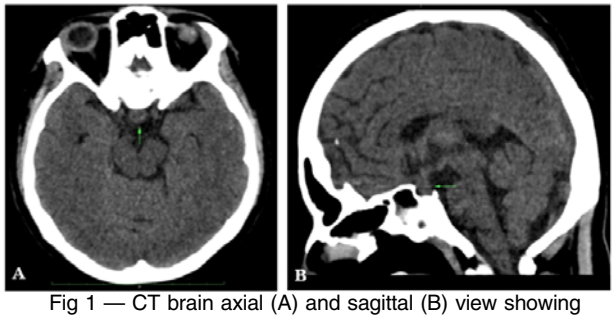


Fig 1 — CT brain axial (A) and sagittal (B) view showing enlarged pituitary with prominent stalk

assays including thyroid stimulating hormone (TSH), cortisol and prolactin were performed. Low prolactin (7.23 ng/ml) and cortisol levels (1.8 mcg/dl at 6 am) were noted. In the background of PPH, her reduced alertness, failure of lactation, low cortisol and prolactin levels along with MRI which was consistent with anterior pituitary infarction made us to diagnose Sheehan's syndrome. Corticosteroid was replaced (hydrocortisone 50 mg per day intravenous) along with hematinics and physiotherapy. After 48 hours of hormonal replacement her sensorium improved and was discharged on 14th day successfully.

Discussion

Sheehan's syndrome or postpartum pituitary necrosis results in anterior pituitary hormonal deficiency due to infarction of anterior pituitary. Postpartum hemorrhage, autoimmunity, coagulation abnormalities and small sellaturcica are some of the risk factors for developing postpartum pituitary necrosis. Our patient had postpartum hemorrhage which could have caused transient hypoperfusion of anterior pituitary resulting in infarction and necrosis in a physiologically enlarged gland. The production of growth hormone and prolactin is affected the most. In severe necrosis TSH and ACTH secretion is also affected. Diabetes insipidus is rare and can occur if the stalk is damaged[2]. The clinical spectrum varies from immediate postpartum circulatory collapse to mild central hypothyroidism manifesting many years later after the inciting event. Postpartum hypotension and hypoglycemia are the clinical clues in acute presentation. Failure to lactate is a feature of subacute presentation[3]. Secondary hypothyroidism and secondary adrenal insufficiency occurred in all 28 patients of Sheehan's syndrome studied by Sert et al whereas Banzal et al reported in 97 % and 90 % of his patients (n=30) respectively[4,5]. The secretion of prolactin and cortisol were affected in our patient as expected. Laboratory abnormalities usually reveal a normocytic anemia, hyponatremia and hyperlipidemia. Hypernatremia can occur if stalk is damaged. MRI findings include T1 hypointense and T2 hyperintense enlarged anterior pituitary which is consistent with infarction as noted in our patient. Irregular enhancement occurs with Gadolinium contrast. Sequential MRI will show atrophied pituitary resulting in empty sella. Lymphocytic hypophysistis is the most relevant differential diagnosis as it also occurs commonly in peripartum period. It's a nonneoplastic inflammatory condition in which lymphocytes infiltrate pituitary gland resulting in enlargement and impaired production of hormones. Uniform enhancement with gadolinium contrast

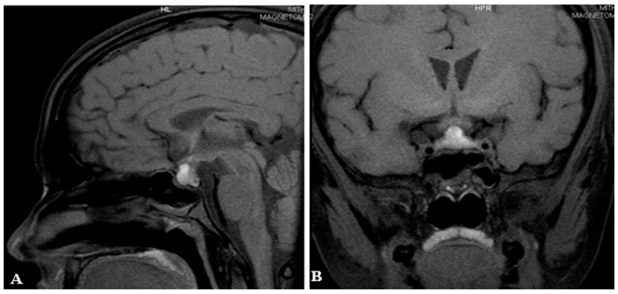


Fig 2 — MRI brain- FLAIR sagittal (A) and coronal view (B) showing enlarged and hyperintense anterior pituitary suggestive of anterior pituitary infarct

and cystic appearance in MRI will help in differentiating this entity from Sheehan's syndrome. Pituitary tumors usually exhibit uniform enhancement but can cause diagnostic confusion particularly if necrosis occurs[6].

Management of postpartum hemorrhage aggressively can prevent hypoperfusion of the pituitary. Cord clamping, controlled cord traction and usage of uterotonics are some of the techniques to avoid PPH[2]. Assessment of hormonal deficiency guides further management. Thyroxine supplement should be done only after corticosteroid replacement as thyroxine enhances the metabolism of steroids which may result in adrenal insufficiency. Gonadal steroids can be replaced in pre-menopausal women to maintain bone density and to improve quality of life. The benefit of growth hormone replacement is uncertain[1].

Conclusion

Sheehan's syndrome should be suspected in a postpartum woman with massive uterine bleed following childbirth, hypotension, agalactorrhea, and failure of return of menses. Diagnosis can be delayed as the timing of presentation and symptom range varies widely. MRI can help in diagnosing anterior pituitary infarction.Careful assessment and replacement of hormones is necessary to avoid life threatening consequences and also to improve the quality of life.

References

1 Tessnow AH, Wilson JD — The Changing Face of Sheehan's Syndrome. The American Journal of the Medical Sciences [Internet]. Elsevier BV; 2010 Nov; **340(5):** 402-6.

2 Karaca Z, Laway B, Dokmetas H, *et al* — Sheehan syndrome. *Nat Rev Dis Primers* **2:** 16092 (2016).

3 Matsuzaki S, Endo M, Ueda Y, Mimura K, Kakigano A, Egawa-Takata T, *et al* — A case of acute Sheehan'ssyndrome and literature review: a rare but life-threatening complication of postpartum hemorrhage. BMC Pregnancy and Childbirth [Internet]. Springer Science and Business Media LLC; 2017 Jun 14; **17(1):**

4 Sert, Murat & Tetiker, Tamer & Kirim, Sinan & Kocak, Mikail — Clinical Report of 28 Patients with Sheehan's Syndrome. Endocrine journal. 50. 297-301(2003).10.1507/endocrj.50.297.

5 Banzal S, Ayoola EA — Sheehan'ssyndrome in Saudi Arabia. *Int J Gynaecol Obstet* 1999; **66:** 181-2.

6 Kaplun J, Fratila C, Ferenczi A, Yang WC, Lantos G, Fleckman AM, *et al* — Sequential Pituitary MR Imaging in Sheehan Syndrome: Report of 2 Cases. American Journal of Neuroradiology [Internet]. *American Society of Neuroradiology (ASNR)* 2008 Feb 22; **29(5):** 941-3.

Pictorial CME

A Rare Cutaneous Manifestation of Type 2 Diabetes

Purbasha Biswas[1]

A 49 year old lady presented to the outpatient department of medicine for follow up of type 2 Diabetes after 6 months with reports of FBS=236 mg/dl, PPBS=312 mg/dl, glycated haemoglobin (HbA1C) 9.2%. She is a known diabetic for 7 years and was under oral hypoglycaemic agents which she was not taking regularly. She complained of red rashes, non-itching, on both her legs for last 10 days. There was no past history of surgical procedures, undue medicine intake, allergy to drugs or environmental agents. On examination, reddish brown papular rash with erythematous borders, non-tender (Fig 1) with reddish flakes were seen. There was no sign of atrophy or ulceration with preserved sensation without any evidence of diabetic neuropathy.

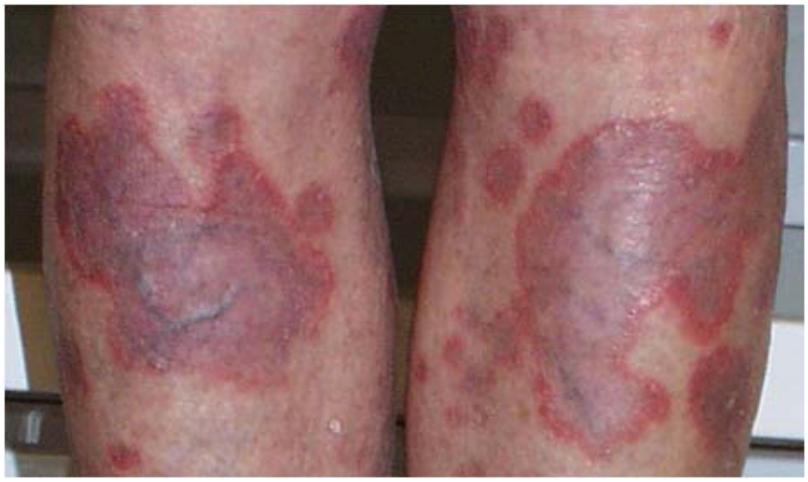


Fig 1

(1) What may be the provisional diagnosis of this presentation?

(2) What is the pathophysiology of this condition?

(3) What is the treatment of this condition?

Answers:-

(1) The characteristic appearance of the rash with preserved vibration perception over both feet, revealing absence of neuropathy in a background of poorly controlled type 2 diabetes is suggestive of NECROBIOSIS LIPOIDICA DIABETICORUM (NLD), a chronic disfiguring condition specially located above tibia, lesions of which may be single or multiple.

(2) Because of the strong relationship between diabetes and NLD, many studies have focussed on diabetic microangiopathy as being the leading etiology. Another theory is based on immunoglobulin deposition in the blood vessels causing an antibody-mediated vasculitis which initiate changes in the blood vessels and subsequent necrobiosis in NLD. Also defective and abnormal collagen fibrils, trauma, inflammatory and metabolic changes, abnormal glucose transport by fibroblasts are some other possible etiologies.

(3) Sometimes the lesions may resolve spontaneously when glycemic control is achieved. At times, it responds to topical cortisone creams with airtight dressings. Cortisone injections can also be used. Trauma should be avoided by protection of legs with stockings. Inhibition of platelet aggregation by a combination of Aspirin and Dipyridamole was proposed as the treatment for NLD. Stanozolol, an anabolic steroid with fibrinolytic activity and inositol nocotinates, a vasodilator, can be beneficial for NLD with slow improvement.

[1]MBBS, Postgraduate Trainee, Department of General Medicine, R G Kar Medical College and Hospital, Kolkata 700004

References

1 https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.dermatologyadvi sor.com%2Fhome%2Fdecision-support-in-medicine%2Fdermatology%2Fnecrobiosis lipoidica-necrobiosis-oidicadiabeticorum%2F&psig=AOvVaw0q6cUP9Mr3OaV_WAYmLLsK&ust=1605424103616000&source=images&cd=vfe&ved=0CAIQjRxqFwoTCOChgYG9ge0 CFQAAAAAdAAAAABAD

2 Kota SK, Jammula S, Kota SK, Meher LK, Modi KD — Necrobiosis lipoidica diabeticorum: A case-based review of literature. *Indian J Endocrinol Metab* 2012; **16(4):** 614-20. doi:10.4103/2230-8210.98023

From Archive

JIMA, Vol 27, No 3, AUGUST, 1956, P-98

time permitted to it to act in
digestion was not studied in
for it has long been recognised
eble in the stomach.
—Different preparations have
rding to their gastric evacua-
On studying the various con-
served that the reducing sub-
nach first, approximately half
other components. The order
reducing substances, other
n and then fats. The gastric
article was not directly pro-
position, e.g., emptying time
or milk and curd—having
sition was not equal.
m to be concerned in deter-
n from the stomach. After
cid peak the reducing sugars
he stomach indicating that
er the peak leading to some
c secretion. It appears that
s not the only determining
arian full meals the acidity
/10 acid per cent yet the
much longer than when
n, which brought about a
ion of 103 c.c. N/10 acid.
ices help to evacuate an
z evacuated the stomach
pauha from which the
Consistency of an article
mportant factor. Change
ed to commence soon.
liquefied within ½ hour.
chapati were aspirated
e after 2 hours and of
hours.
eached with usual meals
nged than what one is
esults of standard frac-
However, in the past
laid on the acid nature
mach and little atten-
ivity. When the food
is relaxed to accommo-
ncreasing the internal
ty stomach exhibits
ed rhythmic contrac-
conds—which are re-
ary to what is gene-
ty stomach is not a

gs, meat, cereals,
in 100 g. and also

stomachs
evacuation time
analysis and fluoroscopy
gastric
ated.

ACKNOWLEDGMENT

Our thanks are due to the Indian Council of Medical Research for their financial aid, to the Principal, Medical College, Baroda, for interest shown in the work and to the medical students who volunteered as subjects.

REFERENCES

ALVAREZ, W. C.—An Introduction to Gastroenterology, Harper Bros. Inc., N.Y., 1948.
BEAUMONT, G. E. AND DODDS, E. C.—Recent Advances in Medicine, 12th Ed., J. A. Churchill & Co. Ltd., London, 1952.
CANNON, W. B.—*Am. J. M. Sc.*, **137** : 480, 1909.
CARLSON, A. J.—*Am. J. Physiol.*, **31** : 151, 1912.
FERMI, C.—Quoted by Alvarez.
HAWK, P. B., REHFUSS, M. D. AND BERGHEIM, A.—*Am. J. M. Sc.*, **171** : 359, 1926.
PAVLOV, I.—The Work of Digestive Glands (Translated by Thompson), 2nd Ed., Griffin, 1910.
WILSON, H. J., DICKSON, W. H. AND SINGLETON, A. C.—*Arch. Int. Med.*, **44** : 787, 1929.
WOLF, S. AND WOLFF, H. G.—Human Gastric Function, Oxford Univ. Press, London, 1944.

SPECIAL ARTICLE

HAEMATOLOGICAL REACTIONS TO DRUGS

J. B. CHATTERJEA, M.D. (CAL.),

School of Tropical Medicine, Calcutta.

The highly specialised haemopoietic system is highly dynamic as well. The normal blood picture in the human system is maintained by two opposing forces of 'new' blood formation and 'old' blood destruction balancing each other in dynamic equilibrium. Under normal conditions approximately 40 ml. of 'old' blood is replaced daily by an equal amount of 'new' blood. Like many other essential organs, the bone marrow has got the potential capacity of working eight to ten times its routine work. This high reserve of bone marrow is essential to maintain normal blood picture against the manifold baneful influences of haemorrhages, infections, toxins, toxic drugs and various other haemotoxic agents to which the human system so often falls a prey. As long as the haemotoxic agent is mild and the period of exposure relatively short, the bone marrow rises

From Archive

JIMA, Vol 27, No 3, AUGUST, 1956, P-99

to the occasion and overcomes the crisis without any significant deleterious effect. If, on the other hand, the haemotoxic agent is a severe one and the period of exposure fairly long, the resultant damage to the bone marrow is always considerable and in extreme cases may lead to irreversible aplasia. In between the two extreme forms of minimum and maximum damage there may be all gradations of haemodepression representing a spectrum of haematologic dyscrasia, characterised by various types of cytopenia.

During recent years there has been a considerable increase in these types of haematological reactions, a large number of which have been attributed to the various recently introduced drugs. The brilliant series of chemotherapeutic and antibiotic drugs that are now available for the control of infectious diseases have been a boon to mankind. One limitation of these specific drugs as also of other potent drugs is their undesirable side effects on blood and bone marrow. Chloramphenicol is an example in point. The possibility of serious haemopoietic depression reported to ensue from prolonged and repeated chloramphenicol therapy has compelled the cautious physician to restrict its use to a great extent. The cytopenias following the use of drugs like sulphonamide, aminopyrine, butazolidin, trimethadione and thiouracil have been very much discouraging to clinicians.

The first suggestion indicating the possibility of chemicals affecting the bone marrow appeared to have emerged from the use of benzene. Selling (1910) clearly demonstrated that in experimental animals benzene could induce varying degrees of bone marrow aplasia with proportionate peripheral cytopenia. Osler and subsequent workers sought to utilise this myelodepressant action of benzene in the treatment of leukaemia. The toxic reactions of benzene, however, far outweighed its possible usefulness. The disease, agranulocytic angina (Schultz, 1922), brought into bold relief the role of drugs in the causation of disease. Careful works of Kracke and Parker (1934), Madison and Squier (1934), Dameshek and Colmes (1936) and Plum (1937) demonstrated that agranulocytic angina was a manifestation of aminopyrine toxicity.

Influence of Drug Composition on Its Toxicity

Kracke and Parker (*loc. cit.*) were the first to point out that the chemical structure of a drug plays a significant role in determining its deleterious effect on blood and bone marrow. They asserted that the association of benzene ring with either N, NH or NH_2 group usually makes a drug toxic particularly to the leucopoietic tissue. Analysis of the chemical structure of a large series of drugs with known haemotoxic properties corroborated the view of Kracke and Parker (*loc. cit.*). Dameshek (1954) carefully reviewed the chemical structure of haemotoxic drugs and concluded that almost all of these drugs have a central benzene ring structure and a varying number of combinations with N, NH or NH_2 grouping. Chloramphenicol was introduced to the medical profession in 1949. In the same year Smadel pointed out the nitrobenzene radical in the drug and warned the profession of its possible haemotoxicity (Smadel, 1949 ; Dameshek, 1952). Numerous reports up-to-date indicate that chloramphenicol has a depressant action on the bone marrow. Agranulocytosis following the new drug chlorpromazine has similarly, been ascribed to the presence of nitrobenzene linkage in its structural formula (Yules and Baker, 1955). Dameshek (1954) pointed out that the highest toxicity is shown by drugs with the largest number of 'N' groupings in their structure such as aminopterin and triethylene melamine. The two anti-epileptic drugs, troxidonum and methoin have somewhat similar structures but the latter with two nitrogens is more toxic than the former with one nitrogen. Aminopyrine with three nitrogen atoms in its molecule is very toxic. It has been suggested that all drugs with a nitrobenzene radical are potentially myelotoxic. This is, however, not universally true and there are exceptions, notable among which is phenobarbitone.

Mechanism of Haemotoxicity

In general there are two ways in which drugs induce blood and bone marrow changes.

First is the direct destruction of the formative tissue in the bone marrow or of the formed elements in the peripheral blood. Benzene, nitrogen mustard, aminopterin, and chloramphenicol owe their toxicity to the direct destructive action they possess against the bone marrow. Under certain conditions bone marrow might be inhibited presenting a picture of maturation arrest. These drugs probably act by inhibiting enzyme systems which are indispensable for the growth and maturation of haemic cells or by biologically competing with nutritional factors needed for the same purpose. Megaloblastic anaemia may develop during therapy with folic acid antagonists due obviously to depletion of folic acid in the system. Megaloblastic anaemia that has been reported during therapy with the anti-epileptic drug, phenytoin sodium, may be explained on the basis of folic acid deficiency developing due either to absorption or utilisation defect (Israels and Sharp,

From Archive

JIMA, Vol 27, No 3, AUGUST, 1956, P-100

1950; Badenoch, 1954; Hawkins and Meynell, 1954). Recently Girdwood and Laneman (1956) reported development of megalobastic anaemia in a patient while under treatment with primidone and phenobarbitone. There was no response to cyanocobalamin, but a good response to folic acid.

Many of the haemotoxic drugs like phenyl hydrazine, quinine and sulphonamides possess a direct haemolytic action on the red cells. In experimental animals a wide variety of drugs and chemicals have been employed to study the changes in erythrocytic morphology preceding haemolysis (Fertman and Fertman, 1955). Many of these haemolytic drugs produce characteristic intra-erythrocytic inclusion bodies variously designated as Heinz body, Heinz-Ehrlich body, inner body, innenkörperchen, innerkörpern. These inclusion bodies represent globules of haeme-containing protein denatured by the drugs. Demonstration of Heinz body in a case of anaemia constitutes a valuable sign in favour of the diagnosis of haemolytic anaemia. In addition, many of these toxic drugs also tend to produce methaemoglobinaemia or sulphhaemoglobinaemia. It has been suggested that methaemoglobin which precedes and accompanies the formation of Heinz bodies might catalyse the reaction of denatured haemoglobin. Another allied reaction to these drugs is porphyrinuria. The relevant literature on drug-induced porphyrinuria with the various noxious drugs including, sulphonal, barbiturate, sulphonamide, antipyretics, phosphorus, lead, arsenicals and alcohol has been reviewed by Dobriner and Rhoads (1940).

The second mechanism is mediated through specific antibodies which destroy the blood cells and/or inhibit their production in the bone marrow. Such antibodies against blood cells have, however, been demonstrated in cytopenic states independent of drugs (Harrington *et al*, 1953; Stefanini *et al*, 1953; Moeschlin *et al*, 1954). Grandjean (1948) was probably the first to show that a drug could cause thrombocytopenia on an immunologic basis. He demonstrated that plasma of a certain patient recovering from thrombocytopenia induced by quinine caused a decrease in the platelet count *in vitro* in the presence of quinine. Most convincing and unequivocal evidence was produced by Ackroyd (1949). He clearly showed that thrombocytopenia induced by allylisopropylacetyl carbamide was due to the development of a specific 'lytic' type of antibody which needed complement for its activation. Careful studies by Larson (1953), Plitman and Stefanini (1953), Bigelow and Desforges (1952) and Barkham and Tocantins (1954) indicated that thrombocytopenia due to quinidine was also mediated through the development of specific antibodies which were agglutinating and/or lytic in type.

Investigative works of Moeschlin and Wagner (1952) and of Dausset *et al* (1954) regarding the pathogenesis of agranulocytosis due to aminopyrine clearly suggest an immunologic basis. The sequence of events that lead to an immunologic disturbance may be as follows: The offending drug itself or one of its intermediate metabolic products possibly combines with a particular blood cell and the combination which may be further modified in the system acts as an auto-antigen. A highly specific auto-antibody develops which does not react with the blood cells directly but only in the presence of the offending drug. The reaction, in general, is active both *in vitro* and *in vivo*. Complement may be necessary for the activation of some of these reactions. The drug (partial antigen or hapten) is apparently needed to "couple" the agglutinating or lytic antibody with the specific blood cell against which sensitisation has developed.

The haemotoxicity appears to affect particularly some individuals who show a constitutional or hereditary susceptibility to a particular drug, a predisposition which is commonly attributed to allergy. Children who have comparatively unstable haemopoietic system are probably more susceptible to the various drugs. A list of the more commonly used drugs that have so far been reported for haemocytopenic reactions is appended in Schedules 1 and 2. The peripheral blood in all these cases showed cytopenia of varying grades and composition. The bone marrow pattern was, however, variable being either one of maturation arrest or of hypoplasia. The different categories of haematological reactions as reported with the various drugs are shown in Schedule 1—A to D.

Drugs and chemicals which are known to damage blood and blood forming organs may be also potentially leukaemogenic. Lignac (1932) produced various types of leucocytic proliferation in mice by prolonged administration of benzene. Mallory, Gall and Bricklay (1939) while critically reviewing all the available evidences could not exonerate benzene as a leukaemogenic agent. Hydrocarbons are certainly carcinogenic. Experiments of Law (1941) and of Shay *et al* (1952) show that hydrocarbons may induce leukaemia in experimental animals. A very strong presumptive evidence in favour of the speculation that myelotoxic drugs are potentially leukaemogenic is provided by the effect of irradiation on the bone marrow. Irradiation certainly tends to depress the normal haemopoietic tissue. Incidence of leukaemia in radiologists is at least eight times higher than that in a comparable group of physicians (March, 1944

From Archive

JIMA, Vol 27, No 3, AUGUST, 1956, P-101

and 1950; Ulrich 1946). Haematological studies on the atom-bomb casualties show that while the incidence of aplastic anaemia was very high immediately after explosion, the incidence of leukaemia was thirteen times higher in the epicentre of the blasted area at Hiroshima than at the periphery (Amano, 1952). These evidences show that while immediate reaction to myelotoxic and haemotoxic drugs is essentially one of depression, the remote and cumulative effect of prolonged therapy may occasionally in a susceptible subject be manifested by a proliferative disorder.

It appears that the haemopoietic system is quite sensitive and sometimes selectively so, to many drugs and chemicals which are foreign to the human system. While the haemodepressive reactions to some of these may be minor and insignificant and while tolerance to some of these agents may be slowly acquired in course of time, there remain some to which tolerance is never acquired and to which the haemopoietic system will always react unfavourably. This brings into bold relief the necessity of ensuring the safety of any new drug by carefully investigating its immediate as well as remote effect on blood and bone marrow.

Prevention of Haemopoietic Depression

Drugs known to be potentially toxic to the blood and bone marrow elements should not be prescribed unless there are impelling indications for their use. Indiscriminate use of sulphonamides, antibiotics, analgesics, and sedatives cannot be too strongly condemned. Potent drugs should be withheld as long as the indications are equivocal and as long as safer therapeutic alternatives are available. Drugs with a 'benzamine' radical should be viewed with suspicion. New drugs awaiting full assessment of their therapeutic values and haemotoxic limitations should be used with particular caution. While under treatment with potentially toxic drugs the physician should be particularly vigilant for other side effects like, fever, skin rashes, arthralgia and gastro-intestinal symptoms. These side effects which may be overlooked as indefinite signs and symptoms may herald blood and bone marrow reaction. Periodic haematological check-up is also imperative when therapy is likely to be prolonged. Particular attention should be paid to the neutrophil which is not infrequently the first element to be affected. Timely withdrawal of these drugs can alone avert more serious crisis.

Ordinary skin tests for foretelling the drug sensitivity have not always proved useful. The employment of a test dose of the suspected drug and attempt to reproduce the blood dyscrasia are neither safe nor feasible. Pathogenicity and toxicity tests as ordinarily scheduled in experimental animals have not always proved adequate for the purpose. Only the test of time and the careful accumulation of statistically assessed observations can provide necessary data for proper appraisal of the safety or otherwise of a drug.

Management of Haemodepressive Reactions

The drug known or suspected to be the cause of mischief should be immediately withheld. The details of management will depend on the type of cell affected and degree of cellular depletion. The general principles may be enunciated here. When the symptomatology springs from rapidly developing haemolytic anaemia, blood transfusions are indicated. When neutropenia is the main problem, penicillin is the sheet anchor to sustain the patient against the infections which always tend to thrive in neutropenic states. When thrombocytopenia and consequent haemorrhagic manifestations are disturbing features, fresh blood transfusions especially in non-wettable containers, should be given. Steroid hormones have proved useful in the cytopenic states developing on an immunologic basis. In conditions of hypoplastic marrows, these hormones are worth giving a trial. Cobalt chloride in a dosage of 100 to 150 mg. daily has occasionally proved useful. The haematinics, iron, folic acid, vitamin B_{12}, and various other vitamins are usually of no use. Folic acid or folinic acid is indicated only in cases where the reactions are due to folic acid deficiency. Whole liver extract and pentanucleotides have sometimes proved useful in neutropenic states with 'maturation arrest' in the bone marrow. Provided there has been no irreversible damage to the bone marrow, most of the cases recover after a variable period. BAL may be useful in haemodepressive reactions following arsenicals, mercurials and gold salts. During the period of recovery as also in the immediate postrecovery period when the haemopoietic equilibrium has not been firm and stable, especial care should be taken to protect the bone marrow.

Summary

Haematological reactions, often of severe degree, may result from many of the common drugs. Drugs with a 'benzamin' linkage are particularly liable to cause these reactions. These drugs affect the circulating blood cells in the peripheral blood or their precursors in the bone marrow either directly or through the mediation of cellular antibodies developing on an immunologic basis. The peripheral blood shows cytopenias of varying grades and composition. The bone marrow picture is either cellular with maturation arrest or hypocellular. Preventive and curative aspects of drug-induced haematologic reactions are discussed.

From Archive

JIMA, Vol 27, No 3, AUGUST, 1956, P-102

ACKNOWLEDGMENT

Thanks are due to Dr. N. K. Chakravarty of the Department of Pharmacology, School of Tropical Medicine, Calcutta, for his valuable suggestions.

SCHEDULE 1

A. GRANULOCYTOPENIC DRUGS :

Amidopyrine†, Antithistaminics, Arsenicals†, Chloramphenicol†; Chlorpromazine, Dinitrophenol, Diethazine hydrochloride, Isoniazid, Methoin, Pamaquin, Pethidine, Phenylbutazone†, Procaine amide, Salicylates, Streptomycin, Sulphonamide†, Tapazole, Thiosemicarbazone, Thiouracil†, Troxidonum†.

B. THROMBOCYTOPENIC DRUGS :

Arsenicals†, Digitoxin, Gold salts, Hydantoins, Mercurial diuretics, Oestrogen, P-amino salicylic acid, Pertussis vaccine, Phenylbutazone, Procaine, Quinidine†, Quinine, Streptomycin, Sulphonamides, Thiouracil.

C. HAEMOLYTIC DRUGS :

Methoin, Mephanesin, Phenacetin†, Phenylbutazone, Phenylhydrazine†, Plasmochin†, Quinine†, Sulphonamide†.

D. PANCYTOPENIC DRUGS :

Antimitotic drugs†, Arsenicals†, Mepacrine, Chloramphenicol†, Gold salts, Hydantoin, Mercurials, P-aminosalicylic acid, Phenylbutazone, Radioactive isotopes, Streptomycin, Sulphonamides.

SCHEDULE 2

DRUGS LIABLE TO CAUSE HAEMATOLOGIC REACTIONS

(Letters—H, N, P, T, within parenthesis—to the left of the drugs refer respectively to haemolytic, neutropenic, pancytopenic and thrombocytopenic potentialities).

A. ANTIEPILEPTICS :

Oxazolidine—2, 4-diones : (P) Troxidonum (Trimethadione); (P) Paramethadione. *Hydantoin compounds* : (P, H) Methyl-phenyl-ethylhydantoin (methoin); (P) Diphenylhydantoin (phenytoin sodium); (N) 5, 5-phenyl ethyl hydantoin. *Others* : (N) Atrolactamide; (P) Phenacemide.

B. ANTIHISTAMINICS :

(N) Phenothiazine type; (N) Ethylenediamine type (tripelennamine hydrochloride); (H) Diphenhydramine hydrochloride.

C. ANTI-INFECTIVES (Chemotherapeutics and antibiotics) : (P) Arsenobenzols; (P) Chloramphenicol; (H, P) Sulphonamides; (H, P) Thiosemicarbazone; (P) Streptomycin; (N, P) P-aminosalicylic acid; (H, P) Isonicotinic acid hydrazide; (N) Glycobiarsol.

D. ANTIMITOTICS :

(P) Benzene; (P) Urethane; (P) Nitrogen mustard (Methyl bis-β chlor ethyl amine or HN_2); Triethylene melamine—TEM); (P) Folic acid antagonists; (P) Purin antagonists (6-Mercaptopurin); (P) Sulphonic acid ester.

† Reactions more frequent with these drugs.

E. ANTITHYROIDS :

(H) Thiouracil; (N) Methyl thiouracil; (H) Propyl thiouracil; (N) Methimazole.

F. ANTIMALARIALS :

(H, N) Quinine; (T) Quinidine; (H, N) Plasmochin; (N) Mepacrin (Quinacrine); (N) Amodiaquin [4-(3-diethylaminomethyl-4 hydroxyanilino)-7-chloroquinoline].

G. ANALGESICS AND SEDATIVES :

(T) Allylisopropylacetylurea; (N) Aminopyrin; (H) Phenacetin; (N) Chlorpromazine.

H. HORMONES :

(T, N) Oestrogens; (P) Corticotropin.

I. RADIOACTIVE ISOTOPES AND IONISING RADIATIONS :

These may cause pancytopenic and occasionally haemolytic reactions.

J. OTHERS :

(T) Ergot; (N, P) Gold preparations; (P, H) Phenylbutazone; (H) Phenylhydrazine; (T) Iodine and Potassium iodide; (N) Nitrophenols.

REFERENCES

ACKROYD, J. F.—*Clin. Sci.*, **8** : 269, 1949.
AMANO, S.—Communication to Internat. Congress of Haematology, Mar del plata, Argentina, Sept., 1952.
BADENOCH, J.—*Proc. Roy. Soc. Med.*, **42** : 426, 1954.
BARKHAM, P. AND TOCANTINS, L. M.—*Blood*, **9** : 134, 1954.
BIGELOW, F. S. AND DESFORGES, J. F.—*Am. J. M. Sc.*, **224** : 274, 1952.
DAMESHEK, W.—Editorial, *Blood*, **7** : 755, 1952.
DAMESHEK, W.—*Postgrad. Med.*, **16** : 369, 1954.
DAMESHEK, W. AND COLMES, A.—*J. Clin. Invest.*, **15** : 85, 1936.
DAUSSET, J., NENNA, A. AND BRECY, H.—*Blood*, **9** : 696, 1954.
DOBRINER, K. AND RHOADS, C. P.—*Physiol. Rev.*, **20** : 416, 1940.
FERTMAN, M. H. AND FERTMAN, M. B.—*Medicine*, **34** : 131, 1955.
GIRDWOOD, R. H. AND LANEMAN, J. A. R.—*Brit. M. J.*, **1** : 146, 1956.
GRANDJEAN, L. C.—*Acta med. scandinav., Suppl.*, **213** : 165, 1948.
HARRINGTON, W. J., SPRAGUE, C. C., MINNICH, V., MOORE, C. V., AULVIN, R. C. AND DUBACH, R.—*Ann. Int. Med.*, **38** : 433, 1953.
HAWKINS, C. F. AND MEYNELL, M. J.—*Lancet*, **2** : 737, 1954.
ISRAELS, M. C. G. AND SHARP, J.—*Ibid*, **1** : 752, 1950.
KRACKE, R. R. AND PARKER, F. P.—*J. Lab. & Clin. Med.*, **19** : 799, 1934.
LARSON, R. K.—*Blood*, **8** : 16, 1953.
LAW, L. W.—*Cancer Res.*, **1** : 564, 1941.
LIGNAC, G. O. E.—Quoted by Dameshek, W.—*New England J. Med.*, **250** : 131, 1954.
MADISON, F. W. AND SQUIER, T. L.—*J. A. M. A.*, **102** 755, 1934.
MALLORY, T. B., GALL, R. A. AND BRICKLEY, W. J.—*J. Indust. Hygiene & Toxicol.*, **21** : 355, 1939.

From Archive

JIMA, Vol 27, No 3, AUGUST, 1956, P-103

MARCH, H. C.—*Radiology*, **43** : 275, 1944.
Idem—Am. J. M. Sc., **220** : 282, 1950.
MOESCHLIN, S., MEYER, H., ISRAELS, L. G. AND TARO-GLOOR, E.—*Acta haemat.*, **11** : 73, 1954.
MOESCHLIN, S. AND WAGNER, K.—*Ibid*, **8** : 29, 1952.
PLITMAN, G. I. AND STEFANINI, M.—Unpublished data quoted by Stefanini, M. and Dameshek, W., *Lancet*, **2** : 209, 1953.
PLUM, P.—Clinical and Experimental Investigations in Agranulocytosis, H. K. Lewis & Co., Ltd., London, 1937, p. 410.
SCHULTZ, W.—*Deutsche med. Wchrschr.*, **48** : 1495, 1922.
SELLING, L.—*Bull. Johns Hopkins Hosp.*, **21** : 33, 1910.
SHAY, H., GRUENSTEIN, M., HARRIS, C. AND GLAZER, L.—*Blood*, **7** : 613, 1952.
SMADEL, J. E.—*Am. J. Med.*, **7** : 671, 1949.
STEFANINI, M., DAMESHEK, W., CHATTERJEA, J. B., ADELSON, E. AND MEDNICOFF, J.—*Blood*, **8** : 26, 1953.
ULRICH, H.—*New England J. Med.*, **234** : 45, 1946.
YULES, J. H. AND BAKER, H.—*Bull. Tufts. New Eng. Med. Center.*, **1** : 224, 1955.

CASE NOTE

PHENYLBUTAZONE IN HODGKIN'S DISEASE

P. L. DESHMUKH, M.D., D.T.M. & H., F.C.P.S., F.A.C.C., F.C.C.P.,

Hony. Physician, Sassoon Hospital and Hony. Lecturer in Medicine, B. J. Medical College, Poona.

Phenylbutazone was synthesised in 1948. From its toxic action on cells and corticosteroid-like action, we thought that it might be used with advantage in leukaemia, carcinoma, and Hodgkin's disease where there are extensive tissue infiltrations. We were disappointed in the two former conditions but we met with great success, though temporary, in a case of Hodgkin's disease.

CASE REPORT

A male labourer, aged 35, was admitted in the Sassoon Hospitals under our care on the 4-4-54 with the history of fever fluctuating between 100°-102°F, anorexia, and enlargement of the glands in the neck, axilla and groin for 12 days. The liver and the spleen were palpable.

Laboratory examination: Hb. 80 per cent, R.B.C.—4·1 mill. per c.mm. W.B.C.—13,000 per c.mm. with polymorphs 68 per cent, lymphocytes 10 per cent, monocytes 14 per cent and eosinophils 8 per cent. Kahn test was negative. Heterophil antibody test and cold agglutination test were negative. Urine and stools were normal.

Blood examination 15 days later revealed: Hb. 68 per cent, R.B.C. 3·5 mill. per c.mm. W.B.C. 20,000 cells per c.mm., polymorphs 21 per cent, lymphocytes 11 per cent, monocytes 2 per cent and eosinophils 66 per cent.

A gland biopsy and bone marrow examination showed that the clinical condition under consideration was Hodgkin's disease. Before the diagnosis became clear, the patient had received penicillin, streptomycin and chloromycetin. Later on he was given liq. arsenicalis, nitrogen mustard and deep x-ray without much improvement. He went downhill inspite of the treatment, being kept up on repeated blood transfusions.

Cough and breathlessness developed later. A radiological examination showed the enlargement of the mediastinal glands which were perhaps pressing upon the trachea. At this stage he was put on phenylbutazone tablets, 200 mg. three times a day. From the third day of the treatment his temperature came down and remained normal, for the first time since his admission. His cough, breathlessness and glandular enlargement diminished very rapidly. His appetite returned. His colour improved. In three weeks' time he showed marked improvement, so much so that he demanded discharge. He discontinued the drug since his discharge on 7-9-54 and did not report for the next 11 months. Occasional inquiries revealed that he was doing well and earning his livelihood. He was re-admitted on 10-8-55 for breathlessness, swelling of the feet and enlargement of the abdomen, of about two weeks' duration. He was pale and emaciated. Inguinal, axillary, cervical and supraclavicular glands were markedly enlarged. Blood pressure was 105/75 mm. Hg. The spleen and the liver were enlarged 2 fingers below the costal arches.

Blood examination showed: Hb. 65 per cent, R.B.C. 2·91 mill. and W.B.C. 10,300 per c.mm.

This time phenylbutazone could not be procured for him. He was given repeated transfusion but he progressively became worse and died on 21-8-55. Autopsy examination could not be done.

COMMENTS

During the first admission of the patient there was a marked improvement in the clinical condition after the administration of phenylbutazone. The short treatment with the drug during his first stay in the hospital appears to have given him a fairly long remission during which he was able to earn for himself and his family. It is true that spontaneous remissions and intermissions are found during the course of Hodgkin's disease; but in this case the improvement was so dramatic after the use of the drug that it cannot be attributed to just a coincidence. A single case report is in no way conclusive but the experience definitely warrants a more extensive trial of the drug in Hodgkin's disease which has stubbornly eluded successful treatment so far.

Prof. J.B. Chatterjea
(1919-1972)

Dr. Jyoti Bhusan Chatterjea, Professor of Hematology and Director of the Calcutta School of Tropical Medicine was a renowned Indian hematologist, whois well known for his contribution in the field of hematology, notable among which is his research on Hemoglobin E/â-thalassaemia. [1]J. B. Chatterjea was born on 16 February 1919 in Kolkata, completed his graduation from Calcutta Medical College in 1942 and secured the degree of Doctor of Medicine from the same institution in 1949. He started his career as an assistant research officer under the ICMR at Calcutta School of Tropical Medicine and achieved the rank of a professor of hematology in 1956.[2] He was also appointed as the director of the institution in 1966.

Chatterjea's researches and contributions have played a significant role in understanding the hematological aspects of tropical diseases. His work on nutritional and iron deficiency anemia and biophysical, biochemical, genetics of Hemoglobin E in Bengali people established him as a stalwart and an international figure in hematology.[3] He was the honorable president of various medical organizations namely, Indian Society of Hematology, Indian Anthropological Society, Indian Public Health Association and at Indian Association of Pathologists and Microbiologists. His service as a counselor to international organizations such as International Society of Hematology, International Society of Blood Transfusion and the Reticuloendothelial Society has been remarkable.

His research has been acclaimed and applauded globally and he was awarded the Coates Medal of the University of Calcutta in 1958 and the Barclay Medal of the Asiatic Society in 1963.[4]

The ICMR honored him with the Basanti Devi Amir Chand Prize in 1964. He was elected as a fellow by the National Academy of Medical Sciences and received the Minto Medal in 1965.He was awarded Shanti Swarup Bhatnagar Prize by the Council of Scientific and Industrial Researchin 1966. He travelled worldwide to New York, New Jersey, Newcastle, Sydney to deliver lectures on his research.

On 29th February 1972, Prof. J.B. Chatterjea suffered a massive myocardial infarction and succumbed to death. His contributions and legacy in the field of hematology is indelible.

Comments of the Experts

Hematological Reaction to Drugs

Drug-induced hematological disorders may involve the entire spectrum of hematology, affecting red cells, white cells, platelets, and the coagulation system. Adverse effects of these drugs may be attributed to a direct toxic action of the drug or its metabolites on the bone marrow oron the circulating cells.Most drugs may act via an immunological mechanism. The drug may act as a hapten or maylead to the production of antibodies against the drug as well as autoantibodies.[5] Some drugs may act on erythrocytes with enzymatic pathway defects, e.g. glucose-6-phosphate dehydrogenase (G-6-PD) abnormalities, to produce hemolysis. However,in many cases, the mechanism of the adverse drug reaction is unknown.Early diagnosis and prompt treatment of drug-induced hematological dyscrasias are crucial to limit the seriousness of these disorders.

The common hematological reaction to drugs are formulated in Table 1.

Syndrome	Examples of associated drugs
Immunohemolytic anemia	Pencillins, cephaloporins, alpha-methyl-DOPA, oxaliplatin, fludarabine, anti-Rh D antiglobulin
Nonimmune hemolytic anemia	Ribavirin, phenazopyridine, chloroquine,
Methhemoglobinemia	Phenazopyridine, dapsone, benzocaine, prilocaine
Megaloblastic anemia	Rrimethoprim, pyrimethamine, diphenyhydantoin
Sideroblastic anemia	Isoniazid, chloramphenicol, linezolide
Aplastic anemia	Chloramphenical, gold, NSAIDs,
Pure red cell aplasia	Diphenylhydantoin, azathioprine, chlopropamide, isoniazid, erythropoietin
Immune thrombocytopenia	Quinine, quinidine, heparin, vancomycin, sulfas, pencillins, glycoprotein IIb-IIIa inhibitors
Thrombotic microangiopathy	Quinine, quinidine, clopidogrel, ticlopidine, cylosporine A, mitomycin-C, cisplatin
Platelet dysfunction	Pencillins, beta-lactam antibiotics, aspirin, NSAIDs
Hypercoagulability	Estrogens, tamoxifen, asparaginase, heparin, bevacizumab, thalidomide/lenalidomide, COX-2 inhibitors, erythropoietin
Circulating anticoagulants	Isoniazid, hydralazine, procainamide
Hypoprothrombinemia	Cephalosporins, pencillins, sulfas
Neutropenia	Antithyroid drugs, procainamide, sulfas, captopril, phenothiazines, diphenylhydantoin, rituximab
Neutrophilia	Glucocorticoids, lithium, G- and GM-CSF
Eosinophilia	Pencillins, sulfas, allopurinol, diphenylhydantoin
Polycythemia	Erythropoietin, anabolic steroids, diuretics
Acute leukemia/myelodyplasia	Alkylating agents, topoisomerase II inhibitors

Table 1 — Common hematological reaction to drugs.Source: David M. Mintzer, Shira N. Billet, Lauren Chmielewski, "Drug-Induced Hematologic Syndromes", Advances in Hematology, vol. 2009, Article ID 495863, 11 pages, 2009. https://doi.org/10.1155/2009/495863. Advances in Hematology / 2009 / Article / Tab 1

References

1 "Brief Profile of the Awardee". *Shanti Swarup Bhatnagar Prize. 2017.*
2 Blood (1972) 39 (6): 890–891. https://doi.org/10.1182/blood.V39.6.890.890
3 "Deceased fellow". Indian National Science Academy. 2016.
4 A, K, Basu (2017). "Obituary". Calcutta School of Tropical Medicine.
5 Lubran MM. Hematologic side effects of drugs. Ann Clin Lab Sci. 1989 Mar-Apr;19(2):114-21. PMID: 2665627

Uddalak Chakraborty
MBBS, MD (Internal Medicine); Senior Resident, Department of Internal Medicine; COM &SDH, Kolkata.

Atanu Chandra
MD (Internal Medicine), DNB (Medicine), MRCP (UK); Assistant Professor, Department of Internal Medicine, RG Kar Medical College & Hospital, Kolkata

History : Remembering the Stalwarts

Yellapragada Subbarow : The forgotten Indian Physician-Scientist

Dr YellapragadaSubbarow was one of the greatest scientists India has ever produced. In terms of scientific output, he is in the same legion as Satyendranath Bose, HomiBhaba and Jagadish Chandra Bose (or even greater, as later discussions will show). But sadly, he is still an obscure historical figure in India and the current generation of learners are almost unaware of this founding father of modern Indian scientific research. No Indian school text book ever mentions the name of this pioneering scientist.

This picture is available via National Data Sharing and Accessibility Policy (NDSAP) of Government of India

Dr Rao was born in Bhimavaram of modern Andhra Pradesh in 1895. He hailed from a very poor family and his education at Madras Medical College had to be financially supported by his friends and relatives. After passing with an LMS certificate, he first joined an indigenousAyurvedic medical college as a lecturer in Anatomy. Then, in 1922, he arrived in Boston, USA for further studies after being inspired by a visiting physician from USA, John Fox Kendrick. He enrolled in the Harvard school of Tropical Medicine for a diploma course. After passing, he joined the same institution as a junior faculty member. He started working with another scientist named Cyrus Fiske and together, they developed a method for estimation of phosphorus in body fluids and tissues. This was considered a landmark discovery in the field of biochemistry and YellapragadaSubbarow's name was entered into contemporary biochemistry text books in the western world. His published paper, titled "The colorimetric determination of phosphorus" is one of the most cited publications in the history of biochemistry and has received more than 20000 citations till date.

But Subbarow's research activities were just beginning. Within a very short span of time, he made his most important discovery, describing the function of ATP in human body. This research earned him a PhD degree and a fellowship from the Rockefeller foundation. However, he was still denied a permanent post at Harvard Medical School. Then, he left Harvard and joined the Lederle laboratories at Pearl River, New York as a biochemist. There, he did more spectacular work like artificially synthesizing folic acid, inventing the anti-folate, methotrexate, describing the mechanism of action of diethylcarbamazine (Hetrazan), extracting vitamin B12 from pig liver and discovering the first tetracycline antibiotics. Any one of these achievements should have been enough to guarantee a permanent place in the history of science but sadly, YellapragadaSubbarow remained in obscurity for the next half century. His research on anti-folates paved the way for future targeted chemotherapy and transformed the vista of pediatric oncology. The landmark paper published in NEJM in 1948 by the legendary Sydney Farber acknowledged the support of Dr Subbarow in that path-breaking research.Lederle laboratories also successfully marketed Aminopterin, the precursor to methotrexate for over a decade, till other chemotherapy drugs came to the market.

Dr Subbarow was also involved in some biochemical research for the US military during the 2nd world war. But naturally, the details of that research are classified. However, his discovery of Hetrazan was one of the results of that military-centred project. This drug has saved the lives of millions all over the world over the next six decades.

Dr Subbarow had authored over 100 brilliant research papers. Some of his early research was destroyed out of jealousy by an American colleague. Thus, some nucleotides discovered by him had to be rediscovered by other western scientists years later (according to Dr George Hitchings). Surprisingly, he never filed patent claims for any of his discoveries. Thus, he shunned the commercial side of science and only concentrated on tireless work to relieve human

suffering. His scientific research is saving millions of lives with cancer, nutritional deficiency or infections every year.

Dr Subbarow had another fascination: he wanted to delve into the scriptures of ancient Indian system of medicine and bring out forgotten cures for contemporary diseases. As discussed earlier, he started his life in an Ayurvedic college. During that short tenure, he published some articles on Ayurvedic system. He had also written a manuscript titled, "Hindu Pharmacology" which was never published.

Dr Subbarow himself was an introvert person and avoided publicity. Compared to other flamboyant scientists of his generation like Einstein, Linus Pauling or Ronald Ross, who were media savvy, Subbarow liked to work quietly in the background. It was only in 1995 that the India government first recognized his contribution to science with a commemorative postage stamp (picture in this article). However, although forgotten in his country of birth, he did get some recognition abroad. After his death, one newspaper of New York described him as "one of the most eminent medical minds of the century". He was revered by the academics in USA. For example, in 1953, in the USA, a newly discovered species of fungus was named after him: Subbaromycessplendens. It was only when a book "In Quest of Panacea" was published in 1987, that Indians woke up to the achievements of this great scientist. Due to his untimely death at the age of 53, he did not get any opportunity to publish an autobiography. Thus, we can only know about his life from his colleagues and friends. Recently, after publication of the Pulitzer-winning book, "The Emperor of all Maladies" in 2010, the name of Subbarow has become somewhat familiar to the educated section of Indian society. However, still there are very few books or documents about this great scientist which are available in India. There are a few books like: -

- Wizard of Wonder Drugs: National Institute of Nutrition, Hyderabad
- In Quest of Panacea: SPK Gupta

But the author of this article (Rudrajit Paul) found that both the books are notoriously difficult to procure. However, there is a wonderful online resource (https://www.ysubbarow.info/index.html) which can be used by those interested in medical history. Some papers and documents of his life are archived at the Nehru Museum and Library, New Delhi.

BOOKS EVERY DOCTOR SHOULD READ : 1

Aequinimitas : With other addresses to Medical Students, Nurses and Practitioners of Medicine.

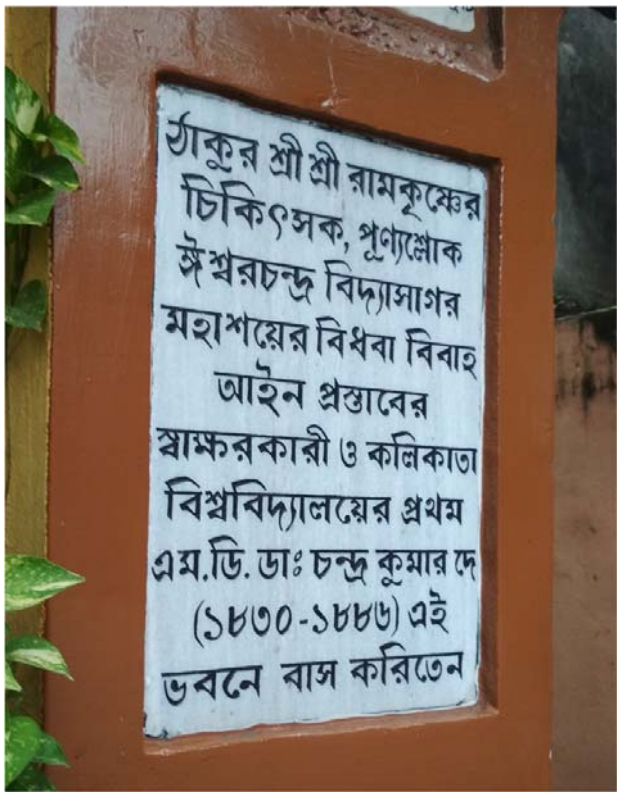
— Sir William Osler,
New York : The Blakiston Company

Medical History

A Glimpse of the Medical History of Kolkata

Rudrajit Paul

If one walks down the Amherst street of Kolkata, just opposite the famous Lady Dufferin Hospital (where Dr KadambiniGanguly once worked), one can see this plaque on the sidewalk.



Dr Chandra Kumar De is a forgotten figure in the medical history of Bengal. Most people have not even heard about him. The author (Rudrajit Paul) noted this plaque only accidentally in between the hovels and illegal street-side shops. A brief enquiry in the area revealed that the local people were completely unaware of the history of this illustrious doctor from nineteenth century. For the readers who are not Bengali speaking, this plaque reads as: -

"Dr Chandra Kumar De (1830-1886), the physician to the sage Sri Ramakrishna, one of the signatories of the landmark Hindu widow remarriage proposal and the first MD from the Calcutta University, lived here."

Dr Chandra Kumar De got his MD degree in 1862. IswarchandraVidyasagar was fighting for the rights of Hindu widows in 1856. Thus, Dr De participated in this landmark social movement during his student days only, even before he got his MD. He went on to become a successful practitioner in Kolkata. He was one of the doctors treating Sri Ramakrishna although during the final days of the sage, the responsibility of treatment fell mainly on the shoulders of Dr MahendralalSarkar (second MD from Calcutta University).

The highest powers in our nature are our sense of moral excellence, the principple of reason and reflection, benevolence to our creatures and our love of the Divine Being.

— Edward Jenner

Perspective

Public non-compliance to scientific medical advice : A stumbling block in health service delivery

Rudrajit Paul, Jyotirmoy Pal

The recent Covid-19 pandemic has exposed the relation between the medical profession and the common public in a glaring manner. And one significant observation has been the stiff public resistance to evidence-based public health measures in countries like the USA and India. In the USA, there has been vocal resistance to mask-wearing and protests against the ban on public gathering. In places like Ohio and Michigan, there were high levels of public anger against the order requiring mandatory mask wearing in public. In these places, government officials even had to rescind orders regarding mask wearing. This public response occurred even after a coterie of trusted scientists repeatedly issued advisory explaining the benefit of face covering. In India, at the height of the first wave of the pandemic, in several places religious gatherings were organized. This occurred even after there were numerous messages in the media that going to crowded places was the strongest risk factor for getting Covid.

Ratner et al have nicely discussed this public reaction in an article in the ***Lancet*** on October 19, 2020. The authors of this article have expressed surprise at the fact that the public chose to deny medical evidence in spite of having such a wealth of information at their fingertips. Compared to all the previous pandemics, the society in 2020 has access to much more reliable and up-to-date health information. However, while much of the society followed those guidelines, there was a sizeable portion that chose to neglect them. This is not something new; science always had to struggle with the dark forces of superstition and incredulity. Even in the face of overwhelming evidence for climate change, a large section of policy makers around the world still deny its very existence.

The authors propose that mass psychoanalysis should be included in public health planning in future. Psychoanalysis is mainly concerned with dealing with the psyche of individual patients. But when mass hysteria and rumours take the centre-stage and thwart meaningful public health response, then the thoughts and reactions of the public can't be neglected. It is true that anxiety and fear can obliterate rational thought and looming disaster can paradoxically push people into a denial mode. This is where public health professionals can collaborate with psychoanalysts. The latter can suggest some ways to improve the public health messages and remove anxiety from public psyche. Thus, the authors propose adding psychoanalysts in the team dealing with public health crises in the future.

Non-adherence to medical therapy is a common setback in the health sector at all times. A recent study in the USA found that even after repeated counselling, patients with conditions like diabetes, asthma or depression regularly default in the treatment. To be fair, there are a lot of reasons for this behaviour, starting from mistrust in the medical system to cost factor and regimen complexity. Regarding the current Covid pandemic, while preventive therapy like mask-wearing and hand washing are not costly, there are other issues in countries like India like access to clean water. Also, in a country like India with large number of daily labourers, the feasibility of complete lockdown as a sustainable measure is also doubtful. For many Indians, it is a choice between dying from the virus (which has a mortality of around 2%) and dying from hunger (which is a more palpable threat with higher mortality). Naturally for these people, for whom struggle with infections and malnutrition is a part of life, a complete cessation of economic activities for another infection is a bridge too far. This is the point where public health professionals have to factor in the economic and psychological factors. For USA and Europe, ban on religious functions is a feasible step. But many people in India consider religious rituals to be an essential part of their lives and they would like to, rather, increase the rituals during this pandemic to seek deliverance from this danger. How do we counter this attitude?

Thus, this current pandemic has shown that service delivery in public health is not just dependent on evidence based medicine. There are other factors like mass anxiety and denial which can be significant forces hindering effective health measures. Delivering proper information to the public is not enough; we also need to address the natural human instincts of anxiety, denial and fear. This is where there needs to be an urgent cross-talk between public health and psychology professionals.

Further reading :

Ratner A, Gandhi N — Psychoanalysis in combatting mass non-adherence to medical advice. *Lancet* 2020; [Online First, correspondence]

Ads from the Past

Soil Extract for Wound Healing

Rudrajit Paul, Jyotirmoy Pal

This advertisement, published in July, 1945 shows the promotion of a solution for wound anti-sepsis. It was the culture extract of a bacillus, isolated from soil samples. Probably, this culture extract had some exotoxins secreted by the bacteria. Very cleverly, the advertisement emphasises an "earth-derived" panacea and thus, "natural". This was supposed to increase its acceptability.

In 1939, Rene J. Dubos published an article in which he described a bacterium he had isolated from pooled soil samples. Addition of this bacterium concentrate to staphylococcal culture led to cell lysis in vitro. Thus, he deduced that this soil bacillus had anti-bacterial properties against gram-positive pathogenic bacteria. In USA, some Pharma companies (one of which is shown in this picture) seized on the commercial opportunities of this discovery and started selling the bacterial culture extract (mentioned here as Dubos' bacillus) for wound dressing.

Later experiments revealed the active antibiotics in these concentrates (synthesized by the soil bacilli): Tyrothricin and Gramicidin. Tyrothricin, shown in this image, was found to be very toxic and abandoned. Gramicidin is sometimes used still now. Although this was a very crude method of wound antibiosis, it was an important step in anti-sepsis in that era, when antibiotics were still elusive.

References

1 Dubos RJ — Studies on a bactericidal agent extracted from a soil bacillus. I. Preparation of the agent. Its activity in vitro. *J Exp Med* 1939; **70(1):** 1-10

2 Dubos RJ — Studies on a bactericidal agent extracted from a soil bacillus: II. Protective effect of the bactericidal agent against experimental pneumococcus infections in mice. *J Exp Med* 1939; **70:** 11-7.

Science knows no country, because knowledge belongs to humanity, and is the torch which illuminates the world.

— Louis Pasteur

Drug Corner

Remdesivir — First USFDA Approved On-Label Anti COVID-19 Viral Agent

Shambo Samrat Samajdar[1], Shatavisa Mukherjee[2], Santanu Kumar Tripathi[3]

On 1st May, 2020 USFDA had authorized to use remdesivir under an Emergency Use Authorization (EUA) for entire population of USA for COVID 19 management. But very recently on 22nd October, 2020 USFDA approved remdesivir for use in hospitalized adult and pediatric patients (≥12 years of age and weighing at least 40 Kg) for the treatment of COVID-19. Remdesivir is the first USFDA approved treatment for COVID-19 management.

Clinical studies showing benefits with remdesivir:

1. NIAID ACTT-1 Study in Subjects with Mild/ Moderate and Severe COVID-19[1]: Among 1062 randomized patients (541 receiving remdesivir and 521 on placebo), remdesivir arm had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11), and placebo arm had median recovery time of 15 days (95% CI, 13 to 18). Rate ratio for recovery was 1.29 (95% CI, 1.12 to 1.49; P<0.001). Mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).This study had shown that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection.

2. Study GS-US-540-5773 in Subjects with Severe COVID-19[2] : This study had showed that there were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups. All-cause mortality at Day 28 was 12% vs 14% in the 5-day and 10-day treatment groups, respectively.

3. Study GS-US-540-5774 in Subjects with Moderate COVID-19[3] : This study showed that the odds of improvement in the ordinal scale were higher in the 5-day remdesivir group at Day 11 when compared to those receiving only standard of care (odds ratio 1.65 [95% CI 1.09 to 2.48], p=0.017).

Editor's Comment :

- **On 22nd October, 2020 USFDA approved remdesivir for use in hospitalized adult and pediatric patients (≥12 years of age and weighing at least 40 Kg) for the treatment of COVID-19.**
- **Use of remdesivir in India is still under Emergency Use Authorization.**

SOLIDARITY Trials: No Benefit with remdesivir :

From the recently published interim results of the Solidarity Trial[4], we came to know that all 4 treatments evaluated (remdesivir, hydroxychloroquine, lopinavir/ ritonavir and interferon) had little or no effect on overall mortality, initiation of ventilation and duration of hospital stay in hospitalized patients. Though there is no data on baseline status of the patients who were included in the study. Lag time between symptoms initiation and treatment initiation is a very critical issue regarding outcome assessment. Late initiation of antiviral may have reduced response compared to early start.

Relationship between day of illness and morbidity due to virus and immune triggering :

Initial seven to ten days are generally responsible for virus related morbidity whereas after five to seven days of symptoms onset, immune triggering is responsible for morbidity. Between 5th and 10th day of symptoms onset, generally there is some overlap between virus and immune triggering mediated morbidity. After 10th day when generally virus associated morbidity is reduced as viral replication ends; there is very less role of any antiviral therapeutics. It is important to initiate antiviral drugs timely to get optimum benefits.

Indication of remdesivir[5] :

As per USFDA SARS-CoV-2 nucleotide analog RNA polymerase inhibitor, remdesivir is indicated for adults and pediatric patients (12 years of age and older, and weighing at least 40 kg) for the treatment of hospitalized COVID-19 patients. Use of remdesivir in India is still under Emergency Use Authorization. Remdesivir may be considered in moderate COVID 19 patients on oxygen therapy. There should not be any contraindications like a) AST/ALT > 5 times Upper limit of normal (ULN) b) Severe renal impairment (ie, eGFR < 30ml/min/m2 or

[1]MBBS MD DM (Clinical Pharmacology), Consultant Clinical Pharmacologist at Diabetes – Allergy Asthma Specialty Therapeutics Clinic, Kolkata
[2]PhD Scholar, Department of Clinical & Experimental Pharmacology, School of Tropical Medicine, Kolkata 700073
[3]MBBS MD DM (Clinical Pharmacology), Professor & Head, Department of Clinical Pharmacology, School of Tropical Medicine, Kolkata 700073
Received on : 13/11/2020
Accepted on : 17/11/2020

need for hemodialysis) c) Pregnancy or lactating females and d) Children (< 12 years of age) as per updated Clinical Management Protocol for COVID-19 by Government of India[6]. It needs immense discussion to understand the timing of initiation of remdesivir. Delayed initiation of remdesivir due to wait for need of oxygenation may be less beneficial for the patient because initial few days for viral replication may pass out. In adults and pediatric patients 12 years of age and older and weighing at least 40 kg, recommended dosage is as following – A single loading dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg from Day 2 infused over 30 to 120 minutes. The recommended duration of treatment for patients not requiring invasive mechanical ventilation and/or ECMO is 5 days as per USFDA. If a patient does not show improvement in clinical parameters, treatment may be extended for up to 10 days. For patients on invasive mechanical ventilation and/or ECMO, the USFDA has recommended for 10 days remdesivir therapy.

Warning and Precautions :

Hypersensitivity reactions have been seen during and following administration of remdesivir. Slowing down the rate of infusion with a maximum infusion time of up to 120 minutes, can be considered to prevent signs and symptoms of hypersensitivity. Need to be vigilant for signs and symptoms of a clinically significant hypersensitivity reaction and immediately discontinue remdesivir infusion and initiate appropriate management. If ALT increased by 10 times of baseline value after initiation of remdesivir therapy it is important to discontinue it. Stop remdesivir infusion if ALT elevation is associated with signs or symptoms of liver inflammation. There is a chance of decreased antiviral activity when co-administered with chloroquine phosphate or hydroxychloroquine sulfate. In-vitro drug-drug interaction between remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is seen. A cell culture data had demonstrated an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.

Remdesivir in Special Populations :

1. Pregnancy – Data from published case reports regarding compassionate use of remdesivir in pregnant females are available but are relatively insufficient to evaluate for adverse maternal or fetal outcomes. Remdesivir demonstrated no adverse effect on embryo-fetal development in nonclinical reproductive toxicity studies. Pregnant women hospitalized with COVID-19 are at risk for serious morbidity and mortality due to disease. It is important to weigh the risk of giving remdesivir and risk of not giving remdesivir to those patients. Informed prescribing, necessary consents and compassionate risk benefit explanation are extremely important in this regard.

2. Lactation – It is important to consider developmental and health benefits of breastfeeding along with the mother's clinical need for remdesivir. It is also necessary to stress upon the potential adverse effects on the breastfed child from remdesivir or from the underlying maternal COVID 19 infection related condition.

3. Pediatric Use – As per USFDA safety and effectiveness of remdesivir for the treatment of COVID-19 have been established in pediatric patients 12 years and older and weighing at least 40 kg.

4. Geriatric Use – No dose adjustment is required for geriatric population whose age is more than 65 years. Need to be cautious regarding renal, hepatic condition of the patient.

5. Renal Impairment – Though there is no clinical pharmacokinetics data available for renal compromised patients, it is important to consider that patients having eGFR greater than or equal to 30 mL per minute can continue remdesivir for treatment of COVID-19 with no dose adjustment.

Adverse Drug Reaction of Remdesivir :

Need to be vigilant about following adverse drug reactions which has a incidence greater than or equal to 5% like nausea, ALT increased, and AST increased. There is also a chance of development of rash, local site erythema, seizure, anaphylaxis and angioedema following remdesivir infusion. It is important to identify early and de-challenge remdesivir if any adverse drug reaction appears.

Conclusion :

Remdesivir is shown to be efficacious in three well conducted RCT and therefore approved by USFDA to use it in COVID 19 treatment SOLIDARITY trial conducted by WHO contradicts these RCT results. We need to conduct more RCTs and prospective observational studies considering the timely initiation of remdesivir. Time will say whether Indian drug regulators will be convinced enough to approve remdesivir as first anti-COVID 19 viral agent.

References

1 John H Beigel, Kay M — Remdesivir for the Treatment of Covid-19 — Final Report. *N Engl J Med* 2020; **383:** 1813-26.

2 Jason D Goldman JD,Lye DCB — Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. *N Engl J Med* 2020; **383:** 1827-37.

3 Spinner CD, Gottlieb RL, Criner GJ, *et al* — Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients WithModerate COVID-19-A Randomized Clinical Trial. *JAMA* 2020; **324(11):** 1048-57.

4 Beigel J, Tomashek K, Dodd LE, *et al* — Remdesivir for the treatment of covid-19—final report. N Engl J Med 2020 Oct 8. https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764

5 PRESCRIBING INFORMATION: VEKLURY® (remdesivir) for injection, for intravenous use VEKLURY® (remdesivir) injection, for intravenous use Initial U.S. Approval: 2020

6 MOHFW – GOI, Updated Clinical Management Protocol for COVID-19à03.07.2020.

Mediquiz

Series - 10

Traumatic Brain Injury

Rudrajit Paul
Quiz Master

Look at the following statements and mark which of them are true and which are false : —

1. Secondary decompressivecraniectomy (DC) for late rise of intracranial pressure (ICP) after traumatic brain injury (TBI) is recommended to improve outcome.

2. Therapeutic hypothermia is recommended in diffuse brain injury.

3. High dose methylprednisolone may improve outcomes in raised ICP after TBI.

4. Hyperventilation early after TBI may help in improving mortality.

5. LMW heparin for DVT prophylaxis is absolutely contraindicated after TBI with some evidence of contusions in CT scan.

6. Phenytoin is recommended early after TBI to prevent seizures.

7. Early initiation of feeding is one of the effective means of reducing mortality after TBI.

8. ICP monitoring and management based on ICP levels is beneficial after TBI.

Match the parameters in 1st column with the values in second column : —

9. ICP level (in mm of Hg) for treatment target	**A. 40**
10. Optimum jugular venous saturation (in %)	**B. 22**
11. Age of patient above which ICP monitoring is recommended	**C. 70**
12. Optimum cerebral perfusion pressure after TBI	**D. 50**

13. Antimicrobial impregnated catheters are now used for external ventricular drainage (done to reduce ICP) to reduce chance of infection. Different companies have come up with different types of catheters. What is/are the antibiotics which are impregnated in such catheters?

a. Rifampicin
b. Minocycline
c. Linezolid
d. Triclosan
e. Clindamycin
f. Gramicidin

14. Mannitol is an effective drug to reduce raised ICP. However, different clinicians use different doses. What is the recommended dose of Mannitol to reduce ICP?

a. 0.5-1 g/Kg/day
b. 1.5-2 g/Kg/day
c. 1.5—2 g/Kg over a short period
d. 0.5-0.75 g/kg over a short period

(Answer : next page)

Answer : Mediquiz

1. True.

After publication of results of the **RESCUEicp** trial, it is now recommended that late rise of ICP (after 3 days) after brain injury may also be treated with DC. In this trial, it was seen that the benefits of late DC were evident at 6 and 12 months post surgery.

2. False.

Therapeutic hypothermia did not improve outcomes after TBI.

3. False.

High dose steroids have no role in lowering ICP after TBI and rather, it increases mortality. The CRASH trial tried to study methylprednisolone use early after TBI. But halfway through the study, it was found that mortality in the steroid arm was higher compared to placebo (21.1% vs 17.9%, P = 0.0001).

4. False.

Early after TBI, cerebral blood flow may be reduced. At this juncture, hyperventilation may further jeopardize this blood flow.

5. False.

LMW heparin may be used if the benefit is found to outweigh the risks. There is definitely a risk of cerebral haemorrhage expansion but in stable patients LMWH may be given if the risk of DVT is very high (E.g. malignancy, prior history of DVT)

6. True.

Studies have shown that phenytoin used prophylactically can prevent early (first 7 days) post-traumatic seizures. However, after 7 days, the prophylactic use of anti-epileptics is of doubtful benefit.

7. True.

Feeding, especially enteral feeding, is important to prevent death.

8. True.

ICP monitoring can be a useful tool to guide treatment decisions. ICP values and CT imaging findings are to be used together.

9. B

10. D

11. A

12. C

13. A, B, D, E.

These are some of the antibiotics which have been used to coat catheters in different trials. So far, all have been found to be useful.

14. C

Mannitol boluses are preferred over continuous infusion or prefixed dosing. This method will have less chance of osmotic damage. The peak effect of mannitol on ICP occurs by 30-45 minutes and lasts up to 6 hours. There is some controversy regarding the dose of mannitol after TBI. A 2005 Cochrane review concluded that high dose mannitol reduced mortality more than the conventional dose (0.5—1 g/Kg). However, it must be remembered that mannitol is preferred only for short term management of raised ICP. It is not useful for long term treatment and may rather cause harm.

Letters to the Editor

[The Editor is not responsible for the views expressed by the correspondents]

Tuberculin Therapy – Hope for a Cure

Sir, — Robert Koch, a renowned German Scientist and physician of his time has been credited with making the historical discovery of tubercle bacilli in the year 1882. This was followed by an equally momentous and historical invention of tuberculin in the year 1890.

Kochs original tuberculin (TO) was a glycerine extract of the tubercle bacilli. It was intended to be a remedy for tuberculosis. However the treatment of patients with original tuberculin did not result in any significant reduction of morbidity or death.

During the era of Robert Koch, tuberculosis had a high mortality and almost one in seven Germans died of tuberculosis. The discovery of causative pathogen and subsequently tuberculin raised hopes for cure and people reacted euphorically. This led to inappropriate and excessive use of tuberculin in large doses in patients with advanced disease resulting in severe reactions.

The review article from Dr M S Valiathan elucidates the wonderful work done by Dr V S Valiathan in the year 1915. It gives an interesting insight into the research work done in Europe and Travancore, India. Today we are blessed to have an armamentarium of diagnostic tools and research methods at our disposal. But still we have limited choice of anti tubercular drugs at our disposal. Perhaps it is time for introspection and to reflect and look at the tuberculin therapy with a fresh perspective.

Professor of Respiratory Medicine, **Prof Dr. D P Singh**
JLNMCH, Bhagalpur, Bihar

==========

Sir, — Medical education in India has been evolved traditionally from the colonial style & culture with regards, to its teaching training & practice. Over the period of last two centuries, the face & corpus of medical education have changed time and again keeping pace with gathered knowledge and meticulous observation and ongoing research. In spite of its inevitable change of system, the basic fabric remained same where curative treatment has been put on the top of the preventive treatment and individualized therapy has attracted more attention than community based service.

Before the advent of globalization & market economy the curative treatment & customized medical therapy were the style of medical service. With the wane of communicable diseases in developed country post 2nd world war by implementing vaccination & other preventive measures. Non communicable diseases prevalent which has drawn attention to the politician and business communities. Gradually the pendulum of medical practice started swinging to the development of more numbers of specialists rather than production of basic medical graduates who are equally competent of providing both curative & preventive service and individualized as well as community based treatment.

Till today, community medicine is being considered as a dearth subject and experts of community medicine are being considered as second class doctors by the general public because, they are not direct care giver to the beneficiaries. This the very unfortunate part of the Indian medical education system where doctors engaged in curative treatment are getting more importance than the experts of prevention services.

Covid pandemic has shamefully opened our eyes and windows as we have felt the importance of experts of community medicine, tropical medicine, microbiologist and expert of infection diseases and also general practioners

Teaching and training of community medicine should not be practiced in the closed walled, classrooms; rather it should be taught at the grass root level where the flavor of community prevails.

I personally feel that the fabric of medical education of post independence, post covid India should be reframed with better & meaningful participation of community based medical practice rather than hyping the only curative treatment. Looking forward to watch that golden horizon.

Siliguri **Dr Sekhar Chakraborty**

==========

Sir, — Firstly I want to convey my sincere thanks for your case based editorial during this covid19 pandemic.From your journal we came to know different case reports of Covid which is useful during this epidemic. Recently we got 2 case presented with bradycardia and heart block due to viral myocarditis.Usually as we know febrile patient presents with tachycardia except typhoid fever.Here during this pandemic these case presented with bradycardia which may be due to temporary AV block and bundle branch conduction abnormalities. Further case studies and review article may give further information regarding this bradycardia in covid patients.

MJN Medical College, Coochbehar **Dr Apu Adhikary**

==========

Once weekly insulin : Is the panacea here?

Sir, — Insulin is used by a large share of patients with diabetes (All types). However, despite repeated counselling and training, the fear of daily injections is still a deterrent to patient acceptance of this life saving medicine. In countries like India, there are also other issues like cost, availability of proper needles and availability of cold chain. In such a scenario, any technology which can decrease the frequency of insulin dosage would be welcome.

On September 22, 2020 Rosenstock et al published the results of a Phase II trial with Icodec, the once weekly insulin (NEJM). In this, they found that the glucose lowering efficacy of Icodec was similar to daily basal insulin regimen. Side effect profile was also similar.

If subsequent phase III trials are successful, we can hope to have a wonderful therapeutic option.

Kolkata **Dr Rudrajit Paul**

How to manage a Dog-bite?

Rudrajit Paul & Jyotirmoy Pal

World Rabies day: 28 September

Rabies is mainly transmitted by dogs;
Children below 15 years : main victims
India annual dog bite: 18 million+

Wash the wound

- Wash with soap and running water: 15 minutes or more
- As soon as possible
- Wash thoroughly even if presented late
- Betadine, alcohol etc. can be applied later

Categorize the wound

CATEGORY	DESCRIPTION	ACTION
I	Touch/lick of intact skin	None
II	Minor nibbling or scratches without bleeding	Vaccine
III	Contamination of mucosa; skin wounds with bleeding	Immunoglobulin (IG)+ Vaccine

IG dose: single dose
Equine: 40 IU/Kg
Human: 20 IU/Kg
Within 7 days of bite
Infiltrate around wound (s)+i.m.

Vaccine:
ID schedule: Days 0, 3, 7, 28 (two doses each time): 0.1 ml each
IM schedule:1 ml each
Days 0,3,7,14,28

Theoretical risk of anaphylaxis

DON'T FORGET
Tetanus vaccine, antibiotics

Rabies is 100% fatal
Don't neglect

Re-exposure: IG not needed; IM vaccine on days 0, 3

The same protocol applies for all types of animal bite except rodents

JOURNAL OF THE INDIAN MEDICAL ASSOCIATION :
Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata - 700 014
Phone : (033) 2237- 8092, Mobile : +919477493027; E-mail : jima1930@rediffmail.com
Website : https://onlinejima.com ; www.ima-india.org/ejima
Head office : Indian Medical Association, IMA House, Indraprastha Marg, New Delhi - 110 002
Telephones : +91-11-2337 0009, 2337 8680, Email : hsg@ima-india.org : Website : www.ima-india.org

Registration No. KOL RMS / 476 / 2020 - 2022

RNI Regd. No. 2557/1957
Vol. 64, No, 11, November 2020, Kolkata

Date of Publication : 15th November 2020

If not delivered please return to
Journal of the IMA (JIMA)
53, Sir Nilratan Sarkar Sarani,
(Creek Row), Kolkata - 700014

Printed and Published by **Dr Sanjoy Banerjee** on behalf of Indian Medical Association and printed at Prabaha, 45, Raja Rammohan Sarani, Kolkata - 700009 and Published from Sir Nilratan Sircar IMA House, 53, Sir Nilratan Sarkar Sarani (Creek Row), Kolkata 700014, Editor : **Dr Jyotirmoy Pal**