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CASE REPORTS

SPECIAL ATTRACTION

Editorial

LET US START A RESEARCH

Manoj Kumar Mohapatra.

Research which is a methodical inquiry into a subject matter may add, revise, or delete the existing information related to that subject. It may bring a solution to a difficult problem. Therefore, apart from teaching and treating, a medical college teacher should encourage and promote research. Everyone knows that medicine is an ever changing science. There is addition of new diseases, new agents causing diseases, new findings of existing diseases, new diagnostic methods, and treatment. Therefore, what we use for a disease at present may become obsolete tomorrow. All these point to one thing i.e. our knowledge is incomplete and this incompleteness gives a scope to everyone to enrich the existing knowledge through research. Hence, research is an unending journey. It is essential for the progress of human civilization. Whatever we are utilizing today may be better than yesterday, but never the best one. We can never achieve the best because better has yet to come. Only through research, one can achieve it.

The changing behavior of a disease and related problems can only be learnt through research and accordingly patient care can be improved. One should not think that research is a luxury and only doctors in cities and good hospitals are privileged to conduct research. Remember, research is not a luxury but a necessity. One can do clinical research at any place and start at any time. It can be performed in small hospitals where the doctor is working. You are dealing with the patients of your locality hence; you should neither think to go outside for doing research nor expect an outsider to come to study the disease of your locality. Therefore, a beginner should start research on common diseases found in his work place. It will help to know the natural history and clinical pattern of a disease and accordingly he can prepare treatment guidelines.

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In clinical medicine, most of the decisions are taken by anecdote and experience. The clinicians cannot ignore their personal experiences while treating patients in the name of evidence based medicine. To make their experiences as evidence they have to put the observations systematically in accordance with a proper study design and convert it to a scientific documentation. Then, one can be a part of thousands of clinicians treating millions of patient worldwide. Many good pieces of research come from small places. One should follow the research guidelines and ignite the power of research within. The later can be manifested by improving the ability to see new, ability to think and ideate, and the ability to transform the idea to reality. During this process one should have also the ability to choose right advisor for guidance and restrain from high ambitions. Lastly, if a doctor understands the basic concept of research methodology and change his attitude accordingly then research will be a pleasure.

I. Ability to see new:

The ability to see with a scientific mind is essential for an investigator. People may argue that everything of a particular disease has been studied and there is nothing to do. It is a wrong notion. Existing knowledge about a disease should not be a bondage for research. An investigator has to edit and audit the knowledge about the topic of interest and try to visualize the blind areas. Always something new is hidden inside the blind area. It is true for everything in the world. Look at the disease as though you are looking at it for the first time. Then you can spot the hidden fact. Everything in the universe is changing so also the behavior of the disease but we cannot see the change. The ability to see the new in a disease brings out good clinical research.

Citation - Mohapatra M. K. : Let us start a research, Orissa Phys. J., 12 (2);2015: 77 - 79

II. Ability tothinkand ideate:

Everyone is a man of research (scientist) unless and otherwise disproved. Ideas are the essential ingredients of research. Ideas do enter the brain of an individual from different sources. It does not know any boundary. It can strike anybody irrespective of his age, gender, educational status, background, and geographical boundary. However, one has to think and live in the world of thoughts to get new ideas. A prepared mind can think in vacuum, visualize something new and able to give a shape to the idea.

Different ways of getting the idea:

A. Spontaneous: Human brain by nature is creative. The ideas come spontaneously, like a flash of light. Many a times ideas come like this, but a prepared mind only can pick it up and utilize it. Many may see the fall of apple from a tree, but only a Newton can observe and derive the law of Gravity out of it. For this one has to live in the world of thoughts.

B. Problem oriented. Mostly ideas come out of some problems faced by the innovator. When one faces some difficulty, he wants to overcome it with application of new ideas.

C. Necessity based. Necessity demands new ideas that can change any thing to a newshape.

D. External sources. The idea does not belong to the person. He may either burrow or steal from others. It may come while discussing, reading, viewing, and listening to others. Therefore, spend some time for discussion with like-minded people, reading various books, viewing nature in any form, and listening to learned persons. These are essential to get good ideas. Once you get it, pick it up, note it down, and try to work on it.

III. Ability to transform:

Few ideas can be transformed into reality. Many ideas get lost in the mind of innumerable individuals. Only a person who works sincerely on his idea in spite of all adverse situations and distractions can succeed in transforming it to reality. Hence, once the idea comes to mind, you should try to transform it to reality.Once you get it, it has become your treasure. Do not swallow it or throw it, but utilize it. Who knows your idea may have the potentiality to change the world. Ideas become powerful only after its execution. Therefore, after ideation one should innovate and improvise different methods to transform it into a good project.

The ability of transformation depends on the scientific temperament of a doctor. Conventional education system only produces professional groups in different fields like medicine, engineering, science etc. The practices are based on tunnel vision of passing examination from established facts, information, theories, and case studies to achieve some feasible action plan i.e. minimum knowledge with a degree to practice the profession. Present world demands a broad vision with innovation in every field of study in general and health science in particular. Therefore, from student career one has to transfer himself to develop interest in research. Like any other professionals, perseverance, intelligence, patience, originality, and curiosity are some of the qualities for an investigator. All doctors have these qualities in different proportions but they utilize it mostly for patient care and service. If they utilize a fraction of these qualities for research then they can achieve wonders.

IV. Ability to choose the right advisor:

Before initiating research, the beginner usually discusses about his idea with others either for a suggestion or for appreciation. One has to choose a right person for this purpose. From my personal experience I know that most of the so called advisors or counselors are distracters. Once you discuss the matter with such persons, they usually discourage you and/or out rightly reject the idea. The result is loss of interest in research. In my opinion, an advisor either accepts or modifies a research proposal, but never rejects it. Rejection and discouragement for any research how small it may be, causes mental upset not only to a beginner but also to an experienced researcher. Therefore, select a person who can really help you to work with or without modification. If you cannot find such a person work with determination with your own idea and subsequently you will learn and rectify accordingly. Of course, it takes a long time, but does not hamper the scientific temperament of a beginner. Therefore, the ability to choose the advisor is essential for a beginner.

V. Ability to restrain:

While doing research never think about the result. I have seen many clinicians who are interested for research but lost interest because of their ambition of immediate publication and grant. True, it is essential for a researcher as recognition of his work, but not at the outset. It usually takes some time. Even publication of a good paper may take years. Same thing may happen for a grant. One may not get. If the objective of clinical research is to learn more about the disease and its application to give benefit to the patient then one will not feel remorse or regret in doing research.

VI. Ability to recognize that research is not difficult:

Patient is most important for a doctor. Doctor devotes his time, knowledge, efficiency, for patient care. In this process he hardly gets time to understand what research is. A doctor never hesitates to examine a patient because the curriculum is meant for that. When he enters to a medical college he has no knowledge about medical science and he is not in a position to examine a patient and diagnose a disease. As time advances he understands the normal functioning of human body, abnormalities detected during a disease, clinical presentations, investigations to reach at a diagnosis and treatment. Then after completion he is confident to deal with the patients. But the medical curriculum does not provide any information about research. As a result he has limited knowledge about research and has a perception that research is difficult to conduct and it is not within the reach of a doctor working in small places. He should develop the ability to recognize that research is not difficult, the research methodology is same as clinical methodology, and it can be done anywhere.

Whenever a patient approaches a clinician with a set of complaints the chain of events begins. The clinician elicits different signs, reaches at a provisional diagnosis. After it he advises various investigations to confirm the diagnosis, gives treatment and assesses the outcome. All doctors are familiar with these steps and a doctor performs these steps effortlessly in every patient. Research method is similar to clinical methods. Once you understand the similarities and the methods to adapt it will become easier to do research like clinical method. Now let us consider clinical methods stepwise and compare with research methods.

Step-1: Patient enters to a clinic or hospital and consult a doctor with a set of complains (symptoms).

Step-2: Doctor listens and then examines the patient to elicit the findings (signs) and advises various investigations if needed for the diagnosis of disease.

Step-3: He collects, analyses, and interprets the data collected from Steps 1 & 2.

Step-4: After analysis he reaches at a conclusion i.e. diagnosis of a disease.

Step-5: The he administers treatment and follow up the patient until the recovery.

During this period, he also observes response to treatment, side effect of the drugs, and development of any complication. Depending on these, he takes further course of action.

In a clinical research, the doctor (investigator) also follows the same steps.

Step-1: The investigator has faced a problem. It is similar to "complains" of the patient.

Step-2: He adopts different methods to collect information related to the problem. It is similar to "clinical" examination and "advising" investigations.

Step-3: Then he collects, analyzes, and interprets data (results).

Step-4: Reach at a conclusion.

Step-5: Preparation of the report and follow-up the subjects if required.

Hence, there is a great similarity between the patient management and clinical research. Thus a clinician is doing a research in every patient. If there is no difficulty in examining and treating a patient then why there will be difficulty in doing research? But when it comes to research one has to modify it slightly. He has to formulate the objective, choose the type of clinical study, make a proper study design, take the permission of ethical committee, collect the data, analyze the data, reach at a conclusion, and publish it.

Chairman's address, 2015

SEPSIS AWARENESS

Laxmi Kanta Dash

Sepsis is one of the oldest and most elusive syndromes in medicine. Hippocrates claimed that sepsis (σήψις) was the process by which flesh rots, swamps generate foul airs, and wounds fester. Galen later considered sepsis a laudable event, necessary for wound healing. With the confirmation of germ theory by Semmelweis, Pasteur, and others, sepsis was recast as a systemic infection, often described as "blood poisoning," and assumed to be the result of the host's invasion by pathogenic organisms that then spread in the bloodstream. However, with the advent of modern antibiotics, germ theory did not fully explain the pathogenesis of sepsis: many patients with sepsis died despite successful eradication of the inciting pathogen. Thus, researchers suggested that it was the host, not the germ, that drove the pathogenesis of sepsis

In 1992, an international consensus panel defined sepsis as a systemic inflammatory response to infection, noting that sepsis could arise in response to multiple infectious causes and that septicemia was neither a necessary condition nor a helpful term. Instead, the panel proposed the term "severe sepsis" to describe instances in which sepsis is complicated by acute organ dysfunction, and they codified "septic shock" as sepsis complicated by either hypotension that is refractory to fluid resuscitation or by hyperlactatemia. In 2003, a second consensus panel endorsed most of these concepts, with the caveat that signs of a systemic inflammatory response, such as tachycardia or an elevated white-cell count, occur in many infectious and noninfectious conditions and therefore are not helpful in distinguishing sepsis from other conditions. Thus, "severe sepsis" and "sepsis" are sometimes used interchangeably to describe the syndrome of infection complicated by acute organ dysfunction.

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Incidence:

In the United States, severe sepsis is recorded in 2% patients admitted to the hospital. Of these patients, h are treated in the intensive care unit (ICU), represent 10% of all ICU admissions.Studies from other high-inc countries show similar rates of sepsis in the ICU. T incidence of severe sepsis outside modern ICUs, especially in parts of the world in which ICU care is scarce, is largely unknown. Extrapolating from treated incidence rates in the United States, it has been estimated that up to 19 million cases worldwide per year.The true incidence is presumably far higher

Pathogenesis of sepsis

The pathogenesis of sepsis is complex and is believed to be initiated by the interaction between pathogen-associated molecular patterns and pattern recognition receptors on host immune cells. This sets off a series of pro-inûammatory mechanisms including synthesis and release of cytokines and complement, chemotaxis and activation of neutrophils, and initiation of coagulation. These, in turn, have widespread effects on other cells including inûammatory cells, immune response, endocrine and autonomic nervous systems, and vascular endothelium, mainly aimed at limiting spread or eliminating the infecting pathogen. Current opinion suggests that the systemic inûammatory response syndrome (SIRS) that characterizes severe sepsis results from an excessive activation of pro-inûammatory mediators, which have pleiotropic effects that overwhelm the body's anti-inûammatory mechanisms, leading to widespread vascular, endothelial, and organ dysfunction that is often fatal. Many of the intermediaries in the systemic inûammatory processes are serine proteases. These

Citation - Dash. L. K. Sepsis Awareness, Orissa Phys. J., 12 (2);2015: 80-85

include trypsin, thrombin, chymotrypsin, kallikrein, plasmin, neutrophil elastase, cathepsin, neutrophil protease-3, and coagulation factors IXa, Xa, XIa, and XIIa.It is now being recognized that besides their proteolytic activity, these proteases have an important role in regulation of inûammation through inter- and intracellular signaling pathways.

Sepsis is a dysregulation of host defense. It has taken a century to understand that, paradoxically when the host succumbs to the effects of an acute bacterial infection, it is the host himself who sets the fire. Inflammation is meant to preserve health, but it is a double edged sword because of its potential to cause irreversible tissue damage. Like other physiologic systems, the inflammatory response must be turned on and off as required. Cytokine generation and the inflammatory process are normally strongly repressed by a number of homeostatic regulatory mechanisms, some of which are known: (1) Shedding of specific cytokine receptors on host cell (2) Synthesis of endogenously generated cytokine antagonists. (3) Hormonal controls

Septic Shock develops when homeostasis is disrupted, most of the time for unknown reasons. Impairment of host defense mechanisms predisposes to the development of sepsis: Trauma, Neoplasms, DM, Burns, Immunosuppression, Chemotherapeutic agents. Sepsis develops with localized infection tissue invasion, damage to epithelial surface, heavy colonization, passage of bacteria or bacterial products into the blood stream.

Local and systemic activation of host cells: Microbial products activate macrophages and neutrophils inducing cytokines and mediators that recruit additional macrophages and neutrophils.

Systemic spread of what are ordinarily local tissue inflammatory responses is the hallmark of Sepsis.

Instigators of Sepsis:

Gram positive bacterial infection- Exotoxin, Cell wall peptidoglycan

Gram negative bacterial infection= Lipopolysaccharide (LPS) is the major component of outer membrane that causes sepsis. The development of Sepsis is also influenced by virulence of the Infecting agent and immune-competence of the host.A host protein (LPS binding protein) binds to Lipid A. Transfers the LPS to CD14 on the surface of monocytes, macro-phases, neutrophils. LPS is then passed to MD-2 bound to Toll like receptor 4 (TLR 4) to form a molecular complex that transduces the LPS recognized signal to interior of the cell. This triggers the production and release of mediators – TNF –that amplify the LPS signal- transmits to other cells

GENETICS

There is considerable interest in the contribution of host genetic characteristics to the incidence and outcome of sepsis, in part because of strong evidence of inherited risk factors. Many studies have focused on polymorphisms in genes encoding proteins implicated in the pathogenesis of sepsis, including cytokines and other mediators involved in innate immunity, coagulation, and fibrinolysis. However, findings are often inconsistent, owing at least in part to the heterogeneity of the patient populations studied.

Definition:

Conventionally, sepsis has been defined as the systemic host response to an infection. Previously, sepsis was believed to be associated with the presence of bacteria in the blood (bacteraemia), and the terms: "sepsis" and "septicamia" were frequently interchanged in the clinical setting.

In 1989, Bone et al established a simple definition for sepsis syndrome, which was based on specific clinical symptoms and included known source of infection. However, these were frequently seen in the absence of measurable levels of bacteria in the blood, also in non-infectious conditions, like acute pancreatitis and trauma. Consensus conference held by the Society of Critical Care Medicine and the American College of Chest Physicians in 1992 resolved these discrepancies and introduced the term "systemic inflammatory response syndrome" (SIRS), for which no definable presence of bacterial infection was required. Additionally, the terms "severe sepsis" "septic shock" and "multiple organ dysfunction syndrome" were introduced to differentiate between various stages of diseases Population data suggest that severe sepsis is the leading cause of hospitalization.In a study involving a sample of in-patients from eight hospitals during a 16-month period, observed

that sepsis accounted for two percent of all hospitalizations, with 59% of patients with sepsis requiring admissions to the intensive care units (ICUs). In addition, the incidence of sepsis is increasing and projected to grow at a rate of 1.5% per year. Almost every discipline in medicine deals with this entity, though much of the management is rendered by critical care physicians in the ICUs. Care of patients with sepsis is a costly affair resulting in substantial consumption of health care resources.5,6 Sepsis is often lethal, with mortality of 25% to 30% and 40% to 70% in severe sepsis and septic shock, respectively.7 It is the second leading cause of death among patients in non-coronary ICUs. Furthermore, sepsis also substantially reduces the quality of life of those who survive.9 Despite availability of potent antibiotic the mortality with sepsis is very high.There is ongoing effort to find out and try strategies which would improve outcome of this population. An international consensus committee was formed in 2002 and evidence-based guidelines were elaborated to increase overall clinician's awareness and improving outcome in severe sepsis and septic shock.This was termed Surviving Sepsis Campaign (SSC). The SSC aims to achieve a 25% reduction insepsis mortality within five years.11 Over the last few years several strategies, like fluid resuscitation, early antibiotics, tight glycemic control, administration of corticosteroids and rh APC, and lung protective ventilation have been tried with favourable results. However, not all the studies have uniform outcome in terms of beneficial effect on mortality. This is not unexpected, given the fact that patients with sepsis are heterogeneous group with different diseases and co-morbid conditions. It is thought that when all these strategies are combined in the form of "bundle" the outcome will improve

Sepsis is defined as systemic inflammatory response syndrome (SIRS) caused by infection. However, infections can be difficult to confirm. Fever, tachycardia, hypotension, and other vital sign abnormalities found in SIRS are not specific for infection and overlap with noninfectious etiologies presenting with systemic inflammation. There is no gold standard for diagnosing infection, and though blood cultures processed with standard microbiologic techniques are a frequent diagnostic step, their likelihood of returning with the pathogen of interest depends on a variety of factors, including prior antibiotic therapy. Delays in empiric treatment for sepsis and bacteremia increase mortality as well as length of stay and cost, making timely recognition of infection and initiation of appropriate therapy an important goal

Severe sepsis and septic shock are majo healthcare problems, affecting millions of people around the world each year, killing one in four (and often more), and increasing in incidence. Sepsis affects over 26 million people worldwide each year and kills more people thar breast, cancer, and lung cancer combined, yet mo people haven't heard of it. Every year, severe seps strikes more than a million Americans. It's been estimate that between 28 and 50 percent of these people d According to the CDC (2014), anyone can get seps but the risk is higher in: • People with weakened immu systems • Infants and children • Elderly people • Peopie with chronic illnesses, such as diabetes, AIDS, cancer and kidney or liver disease • People suffering from a severe burn or physical trauma.

If the statistics are to be believed, why are rates of sepsis increasing? Undoubtedly the causes are multifactorial, with perhaps greatest culpability resting with shifts in population demographics, modern medical practice and the increasing incidence of common complex diseases. Improvements in life expectancy have resulted in a more elderly population – a trend forecast to continue. Surgical innovations have expanded treatment possibilities and although such invasive procedures may increase infection risk, their development has paralleled improvements in antiseptic techniques.

Sepsis Management Bundles

The sepsis management bundle consists of: (i) administer low dose steroids as standard policy; (ii) administer rhAPC as standard policy; (iii) maintain tight glycemic control; and (iv) lung protective strategy-prevent excessive inspiratory plateau pressure.

RATIONALE BEHIND SEVERE SEPSIS BUNDLES

Sepsis Resuscitation Bundle

Serum lactate levels. Hyperlactataemia in pateints with severe sepsis or septic shock represents anaerobic metabolism secondary to tissue hypoperfusion. It can

be measured easily and results are usually available within minutes. Although its elevation may be multifactorial, values greater than 4 mmol/dL (36 mg/dL) are associated with poor prognosis, particularly if the high levels persist.12-14 Studies have shown association of mortality with gastric mucosal pH measured by gastric tonometry but, interventions designed for correction of regional acidosis did not influence mortality. In addition, blood lactate levels have been shown to have greater prognostic value than oxygen-derived variables.In patients with persistent hyperlactataemia, effort should be made to improve haemodynamic support. Serum lactate measurement is recommended for identifying tissue hypoperfusion in pateints who are not yet hypotensive but are at risk for septic shock. Blood cultures obtained prior to antibiotic therapy. Both timing and volume of blood sample are important while obtaining blood sample for culture. Collecting blood cultures prior to antibiotic administration offers the best hope of identifying the organism that caused severe sepsis in an individual patient. Failure to check blood cultures prior to antibiotic infusion will perhaps affect the growth of any blood-borne bacteria and prevent a culture from becoming positive later. The yield of blood cultures depends on the volume of blood cultured, and recommended that blood cultures for adults should contain at least 10mL per culture, preferably 20 mL. At least two blood cultures should be obtained one of which should be drawn through lumen of intravascular catheter.

Improve time to broad-spectrum antibiotics. Once severe sepsis is identified, appropriate antibiotics must be started without delay.Initiation of broad-spectrum antibiotics is recommended within one hour of observation of sepsis.

Commonly used antimicrobial are
Specific examples of commonly used antimicrobial agents
Carbapenems: Imipenem, meropenem, doripenem, ertapenem
Carbapenemase-producing organisms.
-lactams Piperacillin–tazobactam, cephalosporins
Carbapenemase-and ESBLb-producing organisms.
Quinolones Moxifixacin, ciprofixacin, levoûoxacin
Quinolone-resistant organisms, which include many of the carbapenemase- and ESBL-producing organisms.
Aminoglycosides Gentamicin, tobramycin, amikacin
Most Gram-positive organisms, aminoglycoside-resistant organisms, and most of the carbapenemase- and ESBL-producing organisms.
Macrolides: Azithromycin, clarithromycin, erythromycin
Macrolide-resistant organisms including many Gram-positive organisms and most of the carbapenemase- and ESBL-producing organisms.

Anti–Gram-positive Glycopeptides (including vancomycin, oritvancin, televancin), linezolid, daptomycin

Vancomycin-resistant Staphylococcus aureus and enterococcus spp. (for vancomycin). Typically used in combination with one of the above classes of antimicrobial agents.

Treatment of hypotension and/or elevated lactate. All patients with severe sepsis who either have suspected hypovolaemia or serum lactate greater than 4 mmol/dL (36mg/dL) should be given a fluid challenge which consists of 20 mL/kg of fluid over 30 minutes. As a resuscitation bundle, this is minimum amount of fluid, and additional fluid can also be given. Crystalloid and colloid fluids are equally effective as resuscitative fluids. For the selection of fluid, clinicians will need to include cost considerations and specific clinical scenario in their decision making process to select the appropriate type of fluid for resuscitating patients with sepsis. The end-point of fluid resuscitation is to achieve central venous pressure (CVP) of 8-10 mmHg.

Vasopressor therapy is required when an appropriate fluid challenge fails to restore a mean arterial pressure (MAP) to 65 mmHg or more and organ perfusion remains inadequate. In the case of life-threatening hypotension, vasopressor therapy may be required simultaneously with fluid challenge to sustain life and maintain perfusion, even when hypovolaemia has not been resolved. Norepinephrine or dopamine shuold be used as first-line agents to correct hypotension in pateints with sepsis. As other vasopressors have disadvantages like tachycardia and reduced splanchnic blood flow (epinephrine), and decreased stroke volume (phenylnephrine), in patients who do not respond to initialvasopressors, epinephrine and phenylnephrine are recommended. Finally, vasopressin is not recommended as a firstline agent and can be used, as hormone replacement, in cases

refractory to other vasopressor at low doses (0.01-0.04 U/min) 24 hours after the onset of shock. Low dose dopamine is not recommended for the purpose of renal protection. Target is to achieve MAP to 65 mmHg or more. The patients with sepsis-induced tissue hypoperfusion with a haematocrit below 30% despite achieving a CVP above 8 mmHg and a MAP above 65 mmHg, should receive blood transfusion. Blood transfusion may serve dual purposes; first it increases ScvO2 due to increased oxygen delivery to ischaemic tissue beds, and secondly, by increasing CVP that will correct hypovolaemia for longer periods than fluids alone. Blood transfusion was associated with significant improvement in mortality in these pateints. Critical evaluation of outcomes based on different haemoglobin thresholds for transfusion in a general population of critically ill patients have suggested that keeping haemoglobin level above 10 g/dL offered no benefits when compared with a more conservative target of 7g/dL.30 A group of pateints such as those with myocardial ischaemia or severe hypoxaemia may require higher haemoglobin levels, though the effectiveness of transfusion in these pateints is inadequately characterised. Recommended target of haemoglobin is 7-9 g/dL in pateints with sepsis, recognising that some pateints with altered oxygen transport are likely to benefit from blood transfusions targeted at achieving a ScvO2 of 70% or more.

Sepsis Management Bundle

Administer low dose steroids as standard policy. The stress response to infection and the anti- inflammatory effects of steroids in sepsis is the rationale behind use of glucocorticoids in sepsis trials. Use of corticosteroids in sepsis has been a point of controversy for decades. Various doses have been tried with inconsistent results. Randomised controlled trialsusing high-dose glucocorticoids (30 mg/kg methylprednisolone or equivalent) have failed to improve outcome and may even worsen the outcome.However, recent randomised, controlled trials with low doses of hydrocortisone (200-300mg of hydrocortisone or equivalent) administered for five to seven days or longer in septic shock showed improved outcome, in the form of reduced vasopressor requirement and mortality. Some authors argue ACTH stimulation test to identify survivors, i.e., responders of septic shock,44,47 but treatment with corticosteroids was ineffective in

Lung protective strategy: prevent excessive inspiratory plateau pressure. Respiratory failure is a common finding in patients with severe sepsis/ septic shock. About half of these patients develop acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) requiring endotracheal intubation and mechanical ventilation (MV).

Ventilatory strategies are to avoid high tidal volumes and high plateau pressures ALI/ARDS Clinicians should use as a starting point a reduction tidal volumes over oneto two hours to a "low" tidal volume (6 mL/kg lean body weight) as a goal in conjunction with the goal of maintaining end-inspiratory plateau pressure of to 30 cm H2O or less. Various trial with low tidal volume showed mixed results.

The largest trial of a volume and pressure-limited strategy showed a 9% decrease in the all-cause mortality in patients ventilated with tidal volumes of 6 mL/kg of estimated lean body weight (as opposed to 12 mL/kg) while aiming for a plateau pressure of less than 30 cm H2O. Permissive hypercapnea, in conjunction with limiting tidal volume and minute ventilation has been demonstrated to be safe and useful intervention in small studies.82-84 Other strategies like semi-recumbent position ventilation and minimal PEEP to prevent lung collapse at end expiration and to maintain adequate oxygenation, i.e., a pulse oximetric saturation of 90% or more and fraction of inspired oxygen less than 0.60 were also shown to be useful.

Each intervention, thus, seems rational and more or, less efficacious and are recommended by SSC guidelines though, the evidence for individual intervention is not so strong. These interventions are

Severe organ dysfunction, as indicated by mean APACHE II scores, were significantly lower in the patients assigned to early goal-directed therapy than in those assigned to standard therapy (13.0 ± 6.3 vs 15.9 ± 6.4, $p<0.001$). Compliance to the recommendation is variable at present. Gao at al87 found that the compliance with the six-hour sepsis bundle was 52% and with the 24hour sepsis bundle was achieved in only 30% (21/69) of the

eligible candidates. In this study, sources of infection were sought and confirmed in 87 of 101patients. The chest was the most common source (50%), followed by the abdomen (22%). Compared with the compliant group, the non-compliant group had a more than two-fold increase in hospital mortality [49% vs23%; relative risk (RR) 2.12, 95% confidence intervals (CI) 1.20 to 3.76, p=0.01] despite similar age and severity of sepsis. Hospital mortality was increased in the non-compliant group from 29% to 50%, with a 76% increase in risk for death, although the difference did not reach statistical significance (RR 1.76; 95% CI 0.84 to 3.64, p=0.16). The number needed to treat to save one life was approximately four. Despite the fact that individual strategy for the management of sepsis have been used by various workers, the evidence favouring the benefits are not robust.

It is agreed by most workers that when these recommendations are combined, in the form of bundles, will lead to improvement of outcome of severe sepsis, although no large randomised controlled trial is available to favour this.

It is also true that recommendations for the management of sepsis will keep on changing and improving with future research. In India, critical care is advancing at rapid pace, although same is not widely available in all settings due to economic reasons and lack of trained manpower. However, in hospitals where well equipped ICU and emergency room (ER) facilities are available, sepsis bundles can easily be used. The strategies of measurement of pH, blood culture, early antibiotic therapy, fluid resuscitation, administration of steroid and lung protective ventilation are easy to implement.

Conclusion

Sepsis is a serious worldwide healthcare condition that is associated with high mortality ratios despite improvements in the ability to manage infection. This continuing education course reviewed the updated guidelines for the management of sepsis that were recently released that advocate for implementation of care based on evidence-based practice.

Prevention of Sepsis:

There is perhaps no easy answer but prevention would, as always, be the best solution.

Strict adherence to infection-limiting techniques such as hand washing and appropriate indwelling device stewardship, combined with swift identification of early infections, is vital.

BEST PAPERS OF 2015

The following original article & case report are selected as best papers of 2015 by the following refrees.

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Best Original Article

Title: SCRUB TYPHUS: AN UNRECOGNIZED DISEASE IN ODISHA

Authors: Dr Samir Sahu (AMRI), Dr Banambar Ray, Dr S.Sinha, Dr S.Pattanaik, Dr S.Dash, Dr Sunita Sahoo

Best Case report

Title: IDIOPATHIC HYPOPARATHYROIDISM WITH EXTENSIVE INTRACRANIAL CALCIFICATION

Authors: Dr Manoranjan Behera, Dr Jayanta Kumar Panda ,Dr Ramachandra Sethy , Prof. B.L.Parija, Dr Sujit Kumar Tripathy

Original article

PROFILE OF HYPOKALEMIC PERIODIC PARALYSIS- A PROSPECTIVE STUDY

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Prafulla Kumar Bariha*, Dukhia Murmu**, Asutosh Rath**, Seshadev Chhatar**

Abstract:

Background: Hypokalemic periodic paralysis (HypoKPP) is characterized by episodes of flaccid muscle weakness occurring at irregular intervals. It has a high prevalence in Western Orissa.

Objective: To study the clinical profile of patients admitted with HypoKPP to a tertiary care hospital in western Orissa.

Material and Methods: This was a prospective observational study, conducted at VSS Medical College Hospital Burla from 2010 to 2013. All patients with a diagnosis of HypoKPP were included in the study. The diagnosis of HypoKPP was made with history of flaccid paralysis, low serum potassium (< 3.5 mEq/L) and U waves in ECG. After the admission all the routine hematological (CBC) and biochemical (FBS, blood urea, serum creatinine, LFT) investigations were done. Investigations for other common diseases like sickle cell disease / MP were done in all cases. Serum sodium, potassium, calcium and magnesium; and ECG were done in all cases. All the patients were subjected to detailed neurological examination. Patients were treated with oral / injectable KCl. The comorbid conditions like malaria, diabetes mellitus were treated accordingly. The patients were followed up for one year.

Results: During the study period 423 patients were admitted with HypoKPP. Of them, 376 patients (88.89%) presented with quadriparesis, 38(8.9%) presented with paraparesis, 2(0.47%) patients had respiratory paralysis, 2(0.47%) had bulbar palsy, and 3 patients presented with GTCS. 2 patients had bladder involvement. Most patients were in the age group 20 – 39 (54.61% of cases). The male : female ratio is 2.95:1. There was a marked seasonal variation with maximum cases presenting in months of May and June (55.48%, 31.43% and 53.01% of cases in 2005, 2006 and 2007 respectively). The range of serum Potassium observed varied from 1.0 to 3.4 mEq/L (average- 2.2+-0.5 mEq/L). ECG changes (Bradycardia, Flat T waves, U waves, ST segment depression, and arrhythmia) were seen in 76.6% cases. 165 patients had additional electrolyte abnormalities (e.g. hyponatremia). Precipitating factors included heavy meal, vomiting, alcoholism, malaria like renal failure was present in 18(4.2%)of cases.

Conclusion: The occurrence of HypoKPP is very high in this part of the country. Majority have quadriparesis at the time of presentation. All patients responded to oral / parenteral KCl supplementation. Rarely bladder involvement, respiratory muscle paralysis and bulbar palsy are seen.

Introduction:

Hypokalemic periodic paralysis (HypoKPP) constitutes a heterogeneous group of disorders characterized by episodes of flaccid muscle weakness occurring at irregular intervals. When recognized and treated appropriately, patients recover without much clinical sequelae. Although a number of these cases may be associated with ion channel mutations, some are due topotentially reversible causes. The prevalence of hypokalemic periodic paralysis has been estimated to be 1 in 1,00,000 population. There is no official estimate of the prevalence of this disease in India. Moreover there have been very few Indian studies on hypokalemic periodic paralysis. A study from North India (New Delhi) has revealed only forty cases over a period of 23 years[1]. In another series fromSouth India (Vellore) 31 cases within a period of 6 years[2].

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In view of increased incidence of hypokalemic periodic palsy (Hypo KPP)in our Hospital the present study was conducted with an objective to study the clinicoepidemiological profile and outcome of such patients admitted to the Hospital[1].

Maerial and Methods:

This was a prospective observational study, conducted at VSS Medical College Hospital, Burla,Sambalpur,Odisha from 2010 to 2013. VSS Medical College Hospital is a university-associated teaching hospital catering the patients of 10 districts of western part of Odisha,adjacent Chhatisgarh and Jharkhand.All patients with a diagnosis of HypoKPP were included in the study. The diagnosis of HypoKPP was made with history of flaccid paralysis, low serum potassium (< 3.5 mEq/L) and U waves in ECG. All the patients were evaluated for initial symptoms and were subjected to detailed neurological examination. The clinical data collected included age, sex, duration of illness, number of episodes of acute muscular weakness, precipitating factors, comorbid conditions and a family history of HypoKPP. Serum sodium, potassium, calcium and magnesium were done in all cases. Serum potassium was estimated by ion selective electrode method during and after paralysis. Complete blood count, fasting blood sugar, blood urea, serum creatinine, serum bilirubin (total and direct), AST, ALT, ALP, thyroid function tests and investigations for other common diseases like sickle cell disease / MP were done in all cases. Electrocardiographic changes, recovery time from hypokalemia, and duration of hospitalization were also evaluated. Recovery time used in this study is the time between the patient's arrival at the hospital with paralysis and hypokalemia and the time of the first normal or elevated serum K level.Potasium was supplemented either orally or parenterally with Inj.Potassium chloride diluted in Normal saline/ mannitol.Patients were treated with oral / injectable KCl. Patients with mild to moderate hypokalemia (potassium of 2.5-3.5 mEq/L) were given oral potassium replacement with potassium chloride 20 mEq repeated every 3-4 hours. Patients with severe hypokalemia (potassium < 2.5 mEq/ L). The maximum administered dose of potassium over 24 hours was 200mEq.Additional therapies were given for patients presenting with complications like bradycardia, arrhythmias, seizures or respiratory muscle paralysis. The comorbid conditions like malaria, diabetes mellitus were treated accordingly. The patients were followed up for one year. Data analysis was done with SPSS ver. 9.0. Where possible, all values were expressed as means (SD).

Results:

total emergency admissions due to all causes to the Department of Internal Medicine in VSS Medical College Hospital, Burla. Most patients were in the age group 20 – 39 (54.6% of cases). 75.8% cases were in the age group 20 – 49 (Fig 1). Males were more commonly affected. The male:female ratio is 3:1.

Preceding paralysis, 65 patients had attacks of vomiting, 39 patients had abused alcohol, 33 patients had eaten large carbohydrate meals, 19 patients had extensively exerted themselves, and 16 patients had a febrile disorder (e.g. malaria) and one patient had sickle cell disease- vasoocclusive crisis (Table 1). No precipitating factors were found in 250(59%) patients. There was a marked seasonal variation with maximum cases presenting in summer. May and June accounted for 51.1% of total HypoKPP cases from 2005-2007 (fig2).

Out of 423 patients 376(88.9%) patients presented with quadriparesis and 38(8.9 %) present with paraparesis. Among the patients with quadriparesis lower limb was more affected than upper limb. In lower limb proximal muscle was more affected than distal muscles lower limb power was 0/5 in 150 (35%), 1/5 in 200 (47%), 2/5 in 30 (7%), 3/5 in 35 (8.2%), 4/5 in 8 (1.8%). Uppor limb power was 1/5 in 10 (2.3%), 2/5 in 80 (18%), 3/5 in 120 (28%), 4/5 in 200 (47%), 5/5 in 13 (3%) of cases. DTR was normal in 380 (90%) and absent in 43 cases. Plantar was accept 30 (7%) cases in which plantar was extensor. Other uncommon features include GTCS , respiratory paralysis, bulbar palsy, bladder and bowel involvement in 3(0.7%),2(0.47%),2(0.47%),2(0.47%) cases respectively

Initial serum Potassium ranged from 1.0 to 3.4 mEq/L (mean- 2.2+0.45mEq/L).165(39.0%) patients had additional electrolyte abnormalities like hyponatremia, hypernatremia, hypocalcemia. The most common associated electrolyte abnormality was hyponatremia seen in 127 (30.02%) patients. 34(8.03%)patients had hypocalcemia, 22(5.2%)patients had hypomagnesemia, and 21(4.9 %)patients had hypernatremia. Out of 423

tract infection and diabetes mellitus, 4 (0.94%) patients had upper respiratory tract infection, 3 (7%) had gastritis, and 2 (0.47%) patients each had sickle cell disease, upper GI hemorrhage and hypertension. Acute gastroenteritis and ischemic heart diseases were also seen 1 (0.23%) patient each).

Patients received both intravenous and oral potassium chloride as per the requirement. Co morbid conditions and other dyselectrolytemia have been treated accord failure. Multi organingly. The median recovery time was 2 days.Out of 423 patients majorities recovered and 02 patients died.One patient sickle cell disease with vaso occlusive crisis and another of malaria with However there were 3 deaths, 1 death each due to arrhythmias, respiratory paralysis and seizures.

On follow up recurrence of attack was seen in 127 (30%) patients. 2 patients having recurrent attacks of HypoKPP had residual proximal muscle weakness.

Fig 1: Age Distribution:

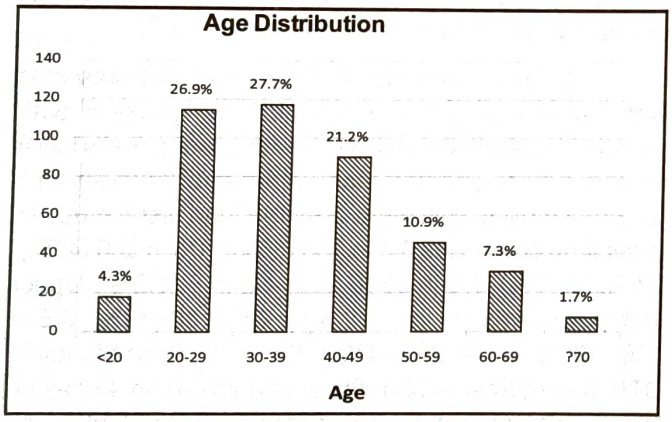

Table 1: Precipitating factors:

	No. of patients	Percentage
Vomiting	65	15.4
Alcohol	39	9.2
Heavy meal	33	7.8
Strenuous Activity	19	4.5
Malaria	16	3.8
Sickle cell disease with vaso-occlusive crisis	1	0.2
None	250	59.1

Fig 2: Monthly distribution of cases:

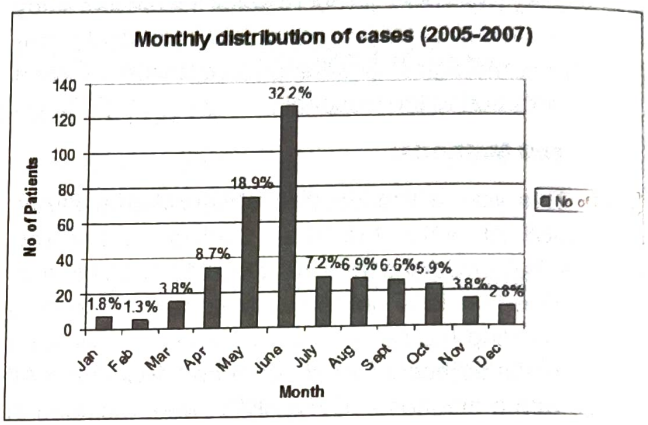

Table 2: Neurologic Features:

Neurologic Feature	No. of patients	%age
Quadriparesis	376	88.9
Paraparesis	38	9.0
GTCS	3	0.7
Quadriparesis; bulbar palsy	2	0.5
Quadriparesis; bladder involvement	2	0.5
Respiratory palsy	2	0.5

DISCUSSION:

Periodic paralysis is a group of disorders with varied etiologies characterized by episodic, short-lived and hyporeflexic skeletal muscle weakness with or without myotonia, but without sensory deficit and without loss of consciousness. HypoKPP is the best-known form of periodic paralysis and is characterized by hypokalemia occurring during the episode of muscle weakness[3]. HypoKPP has been conventionally divided into two forms: primary and secondary. Primary (familial) HypoKPP is a group of disorders associated with single-gene mutations in the ion channels. Secondary HypoKPP is associated with demonstrably known causes such as thyrotoxic periodic paralysis (TPP), renal or gastrointestinal potassium loss, medication effects, or acute barium toxicity[2].

During the study period 423 patients were admitted with HypoKPP. This accounts of approximately 1% of the total admissions due to all causes to the

Department of Internal Medicine in our hospital. Thus this disorder is very common in this part of the country. The present study cites one of the largest numbers of cases of HypoKPP reported in the literature.

The disease is clinically clinically apparent in young patients with most of the patient presenting before 25 years of age. However, in sharp contrast, only 18 patients (4.3%) in our study were <20 years of age. Most of the patients in our study were in the age group 30–39 (27.7% of cases) followed by 26.9% and 21.2% of patients aged between 20-29 and 40-49 respectively. 19.9% of patients were of age >50 years. 69% of these patients have never had a previous attack of muscle weakness. Sex uppression of our patients was similar to that reported in the literature[3-6] where there was a predominance of males affected. The male: female ratio was 3:1.

Vomiting, alcohol abuse, heavy meals high in carbohydrate / salt, rest after strenuous activity, and febrile disorders were found to precipitate an attack of hypokalemic paralysis. Vomiting can precipitate an attack by causing potassium loss[7]. An important factor in the transport of potassium into the cells is the sodium pump. The Na-K-ATPase pump is activated by insulin which may explain the relationship of paralytic attacks to alcohol consumption or carbohydrate loads[8, 9]. Another striking observation was a marked seasonal variation with maximum cases presenting in summer. May and June accounted for 51.1% of total HypoKPP cases from 2005 – 2007. Thus, dry hot weather may precipitate attacks of HypoKPP. The cause of the relation of attacks of hypokalemic palsy to hot and dry environment needs further evaluation although it may be related to increased potassium loss via sweat (the sweat potassium content is 150-200 mg/L) and local feeding habits.

Clinical presentation of our patients was similar to that reported in the literature[3-6]. 376 patients (88.89%) presented with quadriparesis with one having associated facial spasms. 38 patients presented with paraparesis. Patients typically had an acute episode of paralysis involving the muscles of the extremities and limb girdles and occasionally trunk muscles. Muscles of the lower extremities were more frequently and severely involved than those of the upper extremities. Proximal muscle strength was more severely impaired than was distal strength. Patients noted prodromal muscle pains, stiffness, or cramps associated with paralysis. Episodes of paralysis occurred during the night in more than 80% of our patients. However atypical presentations were seen in a few patients. 3 patients presented with GTCS which were attributed to associated electrolyte abnormalities (2 of these patients had associated hypocalcemia while one had severe hyponatremia), 2 patients had respiratory paralysis, 2 had bulbar palsy, and 2 patients had bladder involvement.

All patients in our study had mild to severe hypokalemia (1.0-3.4 mEq/L) when first seen (mean- 2.2 mEq/L; Standard deviation- 0.45). It has been demonstrated that hypokalemia is a result of a K shift into cells and that it is not caused by total-body K depletion. An interesting observation was a high frequency of associated electrolyte abnormalities seen in 165 patients. The most common associated electrolyte abnormality was hyponatremia seen in 127 (30.02%) patients. 34 patients had hypocalcemia, 22 patients had hypomagnesemia, and 21 patients had hypernatremia. A number of patients had multiple electrolyte abnormalities. Hyponatremia has not been previously reported in cases of HypoKPP. The causes of hyponatremia were due to integumentary loss (sweating), gastrointestinal loss (vomiting), fever etc. ECG changes (Flat T waves, U waves, ST segment depression, prolonged QU interval, prolonged PR interval, and arrhythmia) were seen in 76.6% cases.

The patients were treated with oral potassium chloride 20mEq 3-4 hourly and/or intravenous KCl added to normal saline at a concentration of 40mEq/L and infused at a rate of 5 mEq/hr. The maximum administered dose of potassium over 24 hours was 200mEq. The total dose of potassium chloride required varied from 100 to 600 mEq (mean, 400mEq). Most patients responded to oral/ parenteral KCl supplementation. The median recovery time was 2 days. However there were 3 deaths, 1 death each due to ventricular fibrillation, respiratory paralysis and seizures. On follow up recurrence of attack was seen in 127 (30%) patients. 2 patients having recurrent attacks of HypoKPP had residual proximal muscle weakness. This is consistent with published literature[5].

Primary (familial) HypoKPP is caused by mutations in either of two genes. HypoKPP type 1, the most common form, is inherited as an autosomal dominant disorder with incomplete penetrance. These patients have mutations in the voltage-sensitive, skeletal muscle calcium channel gene, *CALCL1A3*. Approximately 10% of cases are HypoKPP type 2, arising from mutations in the voltage-sensitive sodium channel gene (*SCN4A*). Total body potassium stores remains adequate, but serum potassium decreases due to potassium migration into muscle cells

which causes the muscles to become electrically inexcitable[4].

K replacement has been advocated for the treatment of paralysis and prevention of fatal arrhythmias. K replacement therapy should be cautious and should not exceed 100 mEq of potassium chloride per 24 hours. Spontaneous recovery from paralysis attacks with subsequent normalization of serum K levels occurs in many patients, which demonstrates that these electrolytes can shift from the intracellular space back to the extracellular space without replacement therapy[10].

Prophylaxis against recurrent periodic attacks has been successful with a wide variety of treatment modalities including 100–200 mg/day of spironolactone, and 250–750 mg/day acetazolamide. Acetazolamide abolishes attacks in the majority of cases. The mechanism of action of acetazolamide is not fully understood, but it may block the flux of potassium from blood into the muscle[11]. The metabolic acidosis that it produces may underlie its beneficial effects. Chronic acetazolamide therapy may be associated with renal calculus and patients should be monitored for this complication. In some patients, attacks may not respond to acetazolamide or may even be exacerbated by it; in such patients, triamterene or spironolactone may be effective. In some patients it may be necessary to supplement potassium and to avoid high carbohydrate meals[4].

In summary, we described clinical and metabolic features seen in 423 patients with HypoKPP that is encountered with high frequency in this part of the country. Clinical features, biochemical abnormalities, pathophysiological effects, treatment, and the complications of treatment were addressed. Majority have quadriparesis at the time of presentation. Rarely bladder involvement, respiratory muscle paralysis and bulbar palsy are seen. Most patients responded to oral / parenteral KCl supplementation.

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Original article

A STUDY ON TOTAL LYMPHOCYTE COUNT AS A SURROGATE MARKER OF CD_4 CELL COUNT IN HIV POSITIVE PATIENT

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ABSTRACT

Introduction: The high cost of CD_4 count estimation in resource limited countries like India is a major challenge in initiating patient on highly active anti retroviral therapy (HAART). Therefore assessment of simple and inexpensive laboratory diagnostic maker like Total lymphocyte count is mandatory to diagnose immunosuppression.

Objectives: To study the correlation of Total lymphocyte count with CD_4 count in HIV positive patients who are on ART and without ART.

Materials and methods: Hundred patients admitted in MKCG Medical College, Berhampur, Odisha from November 2012 to April 2014 were selected for the study. Total lymphocyte count and CD_4 count were estimated at the time of admission and after 6 month follow up. Statistical analysis was done by using Pearson correlation coefficient, receiver operating characteristic (ROC) area under the ROC (AUC).

Results: Among 100 patients selected 59 were males, 41 were females. The mean age was 38.6 yrs. 36 were categorized not on ART and 64 were regularly taking ART. Main mode of transmission was heterosexual. Most of the patients were started with ZDV+LMV+NVP combination. The value of total lymphocyte count 1800 cell/mm^3 showed sensitivity of 83% and specificity 63% in predicting CD_4 count < 200.Total lymphocyte count $\leq$ 1950 cell/mm^3 was found to have maximal sensitivity (83.7%) specificity (60.8%) positive predictive value (78.5%) negative predictive value (67.2%) predicting CD_4 count < 350 cell/mm^3. The value of 2247 cell/mm^3 had a predictive value of CD_4 count < 500.

Conclusion: The study shows total lymphocyte count can therefore adequately serve as surrogate marker for CD_4 count in HIV Positive Patients who are naive for anti retroviral therapy in resource limited areas.

INTRODUCTION

HIV infection/AIDS is a global pandemic, with cases reported from virtually every country. At the end of 2012, an estimated 35.3 million individuals were living with HIV infection according to the Joint United Nations Programme on HIV/AIDS (UNAIDS).

Globally, the number of new HIV infections continues to fall. There were 2.3 million new HIV infections [1.9 million–2.7 million] in 2012. The number of HIV infections declined by more than 50% in 26 countries between 2001 and 2012 and between 25% and 49% in an additional 17 countries. From 2001 to 2012 the number of children newly infected with HIV dropped by 52%—from 550000 [500000–620000] in 2001 to 260000 [230000–320000] in 2012. Therapy at the end of 2012.[1]

India is estimated to have around 1.16 lakhs annual new HIV infections among adults and around 14,500 new HIV infections among children in 2011. Of the 1.16 lakhs, estimated new infections in 2011 are among adults. The six high prevalence states account for only 31% of new infections, while the ten low prevalence states of Odisha, Jharkhand, Bihar, Uttar Pradesh, West Bengal, Gujarat, Chhattisgarh, Rajasthan, Punjab & Uttarakhand together account for 57% of new infections. The greater vulnerabilities in these states are being given higher focus in the AIDS control programme.[2,3]

Post Graduate*, Professor**, Asst. Professor***, Senior Resident****, MKCG Medical College, Berhampur.

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In industrialized nations, changes in CD4 count and plasma viral load enumeration require highly trained personnel and tens or thousands of dollars of initial investment in laboratory instrumentation[4]. In the few resource limited countries where such laboratory facilities exist, they are often concentrated in major cities and the assays are too expensive for the majority of patients to use for routine monitoring of HAART[5].

Cognizant of this problem, the 2003 guidelines from World Health Organization (WHO) acknowledge that total lymphocyte count (TLC) may be used to make treatment decision in resource poor settings when CD4 count is not available and patients are mildly symptomatic[6].

TLC is an inexpensive and widely available laboratory parameter. The rationale for the WHO's recommendation is that most studies concluded a decline in TLC was strongly correlated with a decline in CD4 count, though there were some discrepancies[7-10].

TLC has already been a useful tool in low-income countries for predicting immunosuppression[15] and triggering opportunistic infection prophylaxis[11, 12] due to its low cost & widespread availability.Recent studies have also demonstrated that TLC alone and in combination with hemoglobin may be useful in determining when to initiate antiretroviral therapy[13, 14].

In this discussion capability and clinical utility of TLC as a surrogate marker for CD4 count in monitoring patients who are HIV positive is assessed, which has important implications in resource limited settings.

MATERIALS AND METHODS

A total of 115 patients who attened out door or admitted to Indoor of Dept. of Medicine, M.K.C.G. Medical College, Berhampur during the period from November 2012 to April 2014 were included in this study of them 65 patients were on ART and 50 patients were not eligible for ART as per the NACO guidelines of India. Out of this 100 patients were followed up for 6 months (64 patients on ART and 36 patients not on ART).

Inclusion Criteria

HIV positive patients undergoing and not undergoing ART enrolled in ART clinic of MKCG Medical College Hospital.

Exclusion criteria

Pediatric HIV positive patients, patients on immunosuppressant therapy, patients with acute retroviral syndrome, patients who are critically ill or having proven malignancies and patients with opportunistic infections were excluded from the study.

Patients who were newly diagnosed of HIV, the diagnosis was made in these patients by detailed clinical history and physical examination. Routine laboratory investigations including Elisa & Western Blot(2 ELISA or 1 ELISA & 1 Western Blot) were done.Those patients already on treatment with ART were thoroughly examined for opportunistic infections as well as adverse reactions of ART drugs. Patients who were not started on ART were also followed up as to look for any new indications for starting ART.

Venous samples were sent for evaluation of CD4 count. At the same time samples were sent for evaluation of TLC. The following parameters are obtained at the time of recruitment from all patients—Hemoglobin, total leucocyte count, and differential count using automated analyzer **Sysmex XT-2000*i*™.** TLC is calculated from absolute leucocyte count and differential leucocyte count.

TLC=Total leucocyte count x Differential lymphocyte count/100.

CD4 count is obtained by flow cytometry by using BD **FACSCalibur** CD4 counter.

These patients are evaluated after 6 months of recruitment & the same parameters are reassessed.CD4 counts were only done on patients who are not acutely ill. In patients who were ill it was deferred until at least 2 weeks of recovery from acute illness.

Statistical Analysis

SPSS™ 15 was used to analyze the data. Linear regression was carried out. Pearson correlation coefficient was also reported. Receiver Operating Characteristic (ROC) was used to determine the cut-off points with best sensitivity and specificity combination. Area under the ROC curve (AUC) was also used to compare the combined sensitivity and specificity among different categories of the study subjects.

The results are presented in numbers and percentages for categorical data and average and SD for continuous data in Tables and Figures.

P value less than 0.05 were taken to be statistically significant.

OBSERVATIONS

Maximum number of patients (36%) is within the age group of 35 to 44 years whereas minimum number of patients (6%) is within the age group of 15 to 24 years of age.

Maximum number of persons in the study group are married (72%), followed by unmarried (13%), widow/ widower (12%) and divorced (3%).Patients staying away from family have increased incidence of infection (60%).

Out of the total 100 patients in the study 87 are married and 13 are unmarried.Of the married persons 50 were found to have extramarital contact and 37 were not having any extramarital contact.

Majority of the patients in the study were construction workers (23%) followed bydrivers (15%). Fishermen (5%) and Ex-military persons (5%) constitute only 10% of the total male patients.

Main mode of HIV transmission in the study group is heterosexual (70%) followed by mode of transmission unknown (9%), then blood transfusion (7%), injectable drug users (IDU-5%), probable unsafe injections (5%), men having sex with men (MSM-3%) and mother to child transmission (1%).

Most of the patients in the study are asymptomatic (28%) followed by Pyrexia of unknown origin (20%), generalized lymphadenopathy (18%), Chronic diarrhea (16%), Unexplained weight loss (14%) and Persistent oral candidiasis (4%).

No. of patients taking ZDV+LMV+NVP is 37, no. of patients taking STV+LMV+NVP is 14, no. of patients taking ZDV+LMV+EFV is 9, no. of patients taking STV+LMV+EFV is 4 and 36 patients were not taking any drugs.

Fig-1. DISTRIBUTION OF CD4 COUNTS AT VARIOUS STAGES

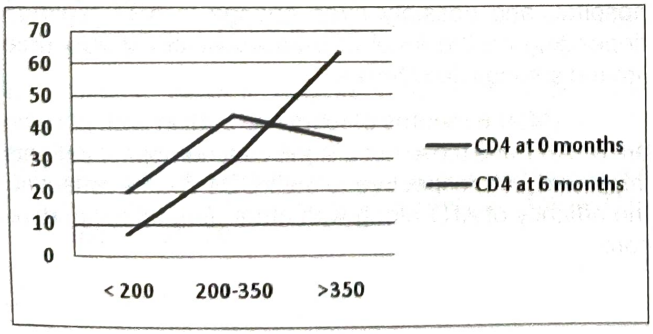
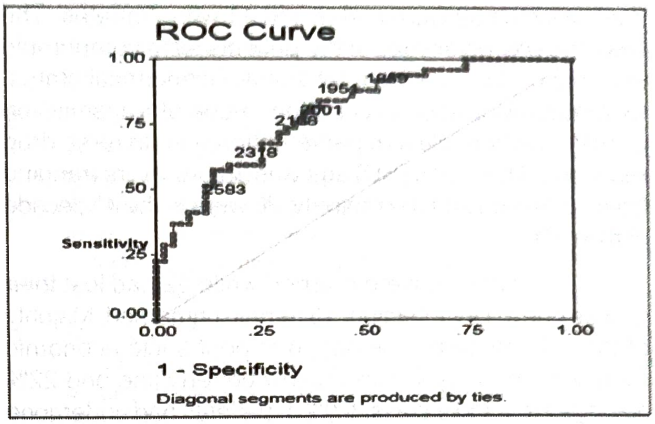
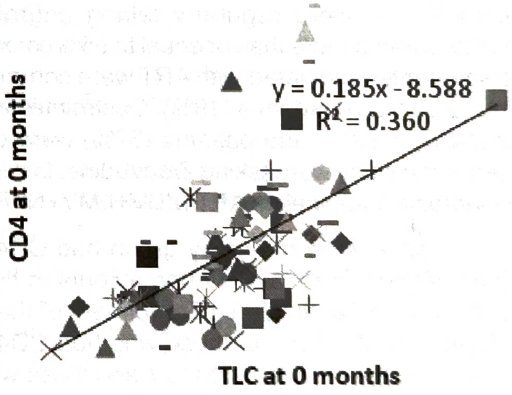


Fig.2 ROC CURVE FOR TLC AND CD4 AT 0 MONTHS



Considering the ROC curve with area under curve 0.797 showed best cut-off values of TLC, that are with the highest sensitivity and specificity combinations, a TLC of 1950 cells/mm^3 was found to have maximal sensitivity (83.7%) and specificity (60.8%) for predicting a CD4 cell count of < 350 cells/mm^3. Results were similar at 6 month follow up.

Fig.3 SCATTER PLOT SHOWING CORRELATION BETWEEN CD4 AND TLC AT 0 MONTHS



The correlation coefficient R for CD4 and TLC was 0.600 ($p < .001$).The linear regression coefficient (β) was 0.185; that is for each 1% increase in TLC there was 0.18% increase in CD4 count. The model was capable of explaining 35.4% (coefficient of determination- adjusted R^2) of the variation.

DISCUSSION

A total of 100 subjects were included in the study, among which 59 were males and 41 were females. The baseline characteristics of the patients were comparable in terms of age, sex, marital status, economical status, extramarital contact, occupation, mode of transmission of HIV infection, clinical presentation and adverse drug reactions. The mean (SD) age was 38.6(9.3) yrs (ranging from 15-64 yrs) and the majority, 36 were in the 4th decade of their life.

72 patients were married while 12 had lost their spouse due to HIV infection. 13 remain unmarried. Majority of the patients (64%) belonged to poor socio economic class with monthly income below poverty line and 22% belonged to middle class. 57% of patients had undergone only primary education compared to 43% who had matriculated. About 40% were staying with their family, 60% were not staying with their family and majority of the people were working in Surat.In the study group most of the enrolled women were housewife (72%) indicating silent epidemic. Most of the men were either construction workers (23%) or drivers (15%).The possible mode of transmission of infection was chiefly heterosexual contact (70%) followed by blood transfusion (7%) and intravenous drug abuse (5%)

Of those 100 patients 36 were categorized as not on ART, 64 were regularly taking antiretroviral medications with a more than or equal to 95% compliance. Adverse events associated with ART were common with Anemia (22%), Dyslipidemia (19%), Gastrointestinal side effect (14%). Most of the patients (37%) were on ART enrolled in the study were taking Zidovudine, Lamivudine and nevirapine combination ART (ZDV+LMV+NVP).

20 patients in the study group had CD4 count less than 200cells/mm^3 and 44 had a count in between 200-350cells/mm^3 at the time of enrolment of the study. After 6 months of follow up those who had CD4 count less than 200cells/mm^3 reduced to 7 and those who had a CD4 count in between 200-350cells/mm^3 were reduced to 30. About 64 patients had TLC count less than 1950 cells/mm^3 at the enrolment of the study. After 6 months of follow up those who had TLC count less than 1950cells/ mm^3 reduced to 36. This shows the effectiveness of ART therapy and supportive care which was comparable to global standards.

In our study, comprising of 100 patients, the value of total lymphocyte count 1800 cells/mm^3 showed sensitivity of 83% and specificity 63% in predicting CD_4 count < 200. Total lymphocyte count ≤ 1950 cell/mm^3 was found to have maximal sensitivity (83.7%), specificity (60.8%), positive predictive value (78.5%) and negative predictive value (67.2%) in predicting CD_4 count < 350 cell/mm^3. The total lymphocyte count 2247 cell/mm^3 showed a sensitivity of 79.2% and specificity of 65.8% in predicting CD_4 count <500. The results obtained were comparable with above studies.

Only few studies have examined the utility of TLC in predicting CD4 measures during HAART

A study in 176 patients demonstrated TLC < 1,80 cells/mm3 could predict CD4+ count < 200 cells/mm3 with 78.26% sensitivity, 73.77% specificity, 84.91% PPV and 64.29% NPV.[16]

In a recently published study in 2011 including 182 patients showed taking ALC of d"1200/µL as a predictor of CD4 cell count d" 200/µL, the sensitivity of the test was 64.4% and specificity was 91.1%. The positive predictive value was 77.6%, negative predictive value was 84.2%, and accuracy was 82.4%.[17]

Correlation of TLC & Hb% to predict CD4<200 before initiation of ART was analyzed by a study conducted in John Hopkins University which included 1451 patients and showed 78% sensitivity and 37.3% specificity.

Including the additional factors improves performance. TLC is simple and inexpensive and can be used in many ways to develop clinical decision-making tools in underserved resource-poor settings during HAART therapy[15].

This study suggests physicians and auxiliary health care workers may readily be able to monitor patient after initiating ART without having concerns that ART use may affect the utility of TLC. The current study also provides new evidence that for patients on ART, TLC and other simple measures may be used in making clinical decisions, such as commencing prophylaxis for opportunistic infections, referral to a physician at a district hospital, and possibly even change in ART regimen depending on the level of care especially in resource limited settings like Odisha.

After 6 months of follow up both in patients who are on ART and those not a significant number of patients improved with respective to their CD4 counts reflecting the efficacy of ART along with other general supportive care.

Limitations of this study include the modest sample size and though the two groups—on ART and not on ART were comparable, were not exactly the same to correlate between pre-ART and post-ART status.These findings suggest that rather than shelve the use of TLC due to concerns of diagnostic utility, further research is needed to define optimum cut off values and should preferably be longitudinal with a much larger sample size.

Summarizing, this study shows a definite correlation between TLC and CD4 count in HIV positive patients. CD4 counts of less than 200cells/mm^3 showed a statistically significant correlation with TLC of less than 1800cells/mm^3 and CD4 count of 350cells/mm^3 correlated well with TLC of 1950 cells/mm^3. This cut off value was 2247 cells/mm^3 for CD4 counts less than 500.

TLC can be substituted for the CD4 count when the latter is unavailable and HIV related symptoms exist.TLC could be used as a low cost tool and as a surrogate marker for monitoring HIV disease and its progression.TLC can serve as a cost effective, affordable index to start HAART treatment and also to monitor HAART treatment.

Though in our study TLC is found out to be a surrogate marker of CD4 count, yet a large sample size study is required for the confirmation of this observation.

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Review article

TUMOR INDUCED OSTEOMALACIA –A BRIEF REVIEW

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Introduction:

Tumor-induced osteomalacia (TIO) is a rare metabolic bone disorder caused by excessive secretion of fibroblast growth factor-23 (FGF-23) from tumors of mesenchymal origin. Its radiological and clinical manifestations simulate features of osteomalacia due to other causes. These tumors are usually small and often missed even with advanced imaging studies making their diagnosis a clinical challenge.

In 1947, Robert McCance first reported a case of TIO in a patient with manifestations of pain, weakness, gait abnormalities and low phosphorus levels with a tumor in her femur. Subsequently, Andrea Prader in 1959 described symptomatic rickets associated with hypophosphatemia in an 11year-old girl who had a large giant cell granuloma on a rib over her left chest. With resection of the tumor rickets resolved with normalization of serum phosphate level and it was postulated that the biochemical derangement was due to a putative "rachitogenic substance" produced by this tumor.[1] Subsequently FGF23 was identified as the most important rachitogenic factor among many having prominent phosphaturic action. Other compounds such as frizzled related protein-4, matrix extracellular phosphoglycoprotein, and FGF7 have also been suggested to be phosphatonins.[2]

The most commonly encountered mesenchymal tumors causing TIO are hemangiopericytoma, hemangioma, sarcomas, ossifying fibromas, granulomas, giant cell tumors and osteoblastomas. About 350 cases of primary TIO have been reported in the literature and the number is growing with advent of newer dedicated investigation modalities.

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FGF23 is secreted by osteocytes and is a phosphatonin that has regulatory effect on phosphate and vitamin D metabolism. It is a poly- peptide of 251 amino acids, the first 24 of which comprise a signal peptide. The full-length mature peptide is required for its biologic activity. FGF23 acts by binding to target cells via an FGF receptor (probably FGFR1), but signaling requires the co-receptor Klotho.[3] FGF23 impairs Na^+- dependent phosphate transport in both intestinal and renal brush border membrane vesi-cles by decreasing the levels of type 2a, 2b, and 2c NaPi transporters and thereby regulating both intestinal and renal phosphate transport. FGF23 is also a regulatory hormone for 1, 25-vitamin D as it down regulates 1α-hydroxylase and up regulates 24 hydroxylase causing a decrease in 1, 25-dihydroxy vitamin D. [4]

Phosphate plays an important role in intracellular signaling, membrane function, energy metabolism, and bone mineralization. Majority of phosphate reabsorption (85–95%) takes place in the proximal renal tubule through type 2a and 2c Na^+-dependent phosphate co-transporters (NaPi-2a and NaPi-2c). [5] Renal phosphate excretion is the primary mode of phosphate clearance and regulation of phosphate balance which is mediated through the combined action of parathyroid hormone (PTH), 1, 25-vitamin D and the so-called "phosphatonins" most important of which is FGF23.FGF23 levels are regulated by dietary phospho-rus, serum phosphorus and calcitriol.

Histopathology:

Histological features of phosphaturic mesenchymal tumor mixed connective tissue (PMTMCT) includes low cellularity with low nuclear and mitotic activity, myxochondroid matrix, bland spindled/stellate cells, distinctive grungy calcification, fat, hemangiopericytoma-like vessels, hemorrhage, osteoclasts like giant cells and an incomplete rim of membranous ossification. FGF23

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staining is positive and appears in the cytoplasm of the tumor cells.

Clinical features:

The symptoms are non-specific and progressive. Patients frequently present with bone pain, muscle weakness, multiple fractures, height loss, and generalized debility. Children usually present with rickets and growth retardation. The diagnosis is often delayed due to a lack of knowledge about the possible existence of the disease. These tumors are usually benign but rarely can have malignant behavior with distant metastases. A TIO-like syndrome with an obvious primary disease can also be seen in conditions like prostate cancer, oat cell cancer, hematologic malignancies, neurofibromatosis, epidermal nevus syndrome and polyostotic fibrous dysplasia of bone.

Diagnosis:

TIO should be suspected in patients who present with consistent symptoms along with hypophosphatemia which is the biochemical hallmark of the disease. Presence of renal phosphate wasting should be confirmed by calculation of percent tubular reabsorption. There are two ways to calculate it: 1) Percent tubular reabsorption of phosphate (%TRP) and 2) Tubular maximum for phosphate corrected for glomerular filtration rate (GFR) (TmP/GFR). TmP/GFR can be calculated only in the fasting state, but %TRP can be calculated at any time using the following formula: 100 x (1-((urine phosphate/urine creatinine) x (serum creatinine/serum phosphate)). [6] A phosphorus tubular reabsorption rate less than 85% is indicative of hyperphosphaturia. 1,25-vitamin D can be low or inappropriately normal. Calcium and PTH are usually normal, but PTH can be high reflecting secondary hyperparathyroidism, which is the normal response to low 1, 25-vitamin D caused by elevated FGF23. Measurement of blood FGF23 is central to the diagnosis. Genetic testing can also be helpful. Localization of these small tumors which can arise in bone or soft tissue from head to toe is done by F-18 fluoro deoxyglucose positron emission tomography, with computed tomography (FDG-PET/ CT) which is most sensitive but is less specific.

Other modalities that help in localization of tumor are ^{111}Indium octreotide scintigraphy combined with single photon emission CT, ^{68}Ga-DOTANOC PET/CT, ^{201}Thallium and ^{99}Technetium MIBI scintigraphy, ^{99}Tc-MDP bone scintigraphy etc. Anatomical imaging to confirm the location of the tumor is done by X-rays, CT and/or magnetic resonance imaging (MRI) scans. Selective venous sampling with measurement of FGF23 is useful in localization of the tumor. Elevated FGF23 level in the aspirate from a suspicious lesion (amenable to needle aspiration) is diagnostic. Despite the tremendous advance in diagnostic imaging studies, tumor detection is still difficult in some cases and periodic imaging studies are indicated every 1–2 years in such subsets.

Differential diagnosis:

Genetic causes include X-linked hypophosphatemic rickets (XLH); autosomal-dominant hypophosphatemic rickets (ADHR); autosomal-recessive hypophosphatemic rickets (ARHR) in which there is hypophosphatemia along with inappropriately normal or elevated plasma FGF23 level. Other genetic causes include hereditary hypophosphatemic rickets with hypercalciuria (HHRH); X-linked recessive hypophosphatemia (XLRH)/Dent's disease; inherited renal Fanconi syndrome. XLH is almost invariably present in early childhood and usually associated with enamel hypoplasia, dental abscess and caries. ADHR can present in either childhood or adulthood. [7] However, the most important fact that distinguishes these genetic syndromes of hypophosphatemia from TIO is that plasma FGF23 is high in TIO, but low in HHRH and Fanconi syndrome. Most of the acquired forms of hypophosphatemia are the result of direct renal tubulardamage by a drug or a toxin. Tubular damage usually results in a generalized tubulopathy,seen as a result of burns, heavy metal exposure (cadmium, lead and arsenic), aminoglycoside antibiotics, certain chemotherapeuticagents, especially cisplatin, and the anti-retroviral drug, tenofovir. It can also occur in association with multiple myeloma and other dysproteinemias.

Management:-

Surgical treatment:

Complete resection of the tumor with a wide margin to prevent recurrence is the gold standard. When the resection of the tumor is complete, there is rapid normalization of FGF23 due to a short half life of around 45 mins. [8] Bone healing starts immediately but serum

phosphate normalizes by second to tenth post-operative day. Late recurrence occurs in less than 5% of the patients with TIO and is often attributed to metastasis. [9] The usual site for metastasis is lungs. There is no role of chemotherapeutic regimen in treating metastatic TIO whereas radiofrequency ablation (RFA) has some role.

Medical treatment:

When the tumor cannot be localized or is not surgically resectable, medical therapy with phosphate supplementation and calcitriol is used. Phosphorus supplementation is the mainstay of treatment and is given orally in a dose of 15–60 mg/kg per day of elemental phosphorus (typically 1–3 g/day) divided into 4–6 doses to keep serum phosphorus level in the lower range of the age appropriate cutoff. Calcium-rich foods should not be provided while on phosphate supplementation. The main side effect is GI upset and diarrhea. Active vitamin D (calcitriol) at a dose of 15–60 ng/kg per day, with a typical starting dose of 1.5 µg/day in an adult is used to prevent or treat secondary hyperparathyroidism that may arise de novo or secondary to phosphate supplementation .Calcium may be necessary to provide mineral ion substrate to heal the bone. Over-treatment with active vitamin D can cause hypercalciuria and nephrocalcinosis/ nephrolithiasis.

Cinacalcet, an agonist of the calcium-sensing receptor lowers blood PTH levels causing medically induced hypoparathyroidism. This may be a potential treatment for TIO because FGF23 action is PTH-dependent. [10] Somatostatin analogue (Octreotide) has some role as somatostatin receptors are present on the cell surface of TIO tumors. [11] The role of external beam radiation or chemotherapy in the treatment of these patients is not clear at present. Calcitonin suppresses FGF23 level. A single s.c. injection of calcitonin was able to suppress FGF23 levels by 44.6% at 9 hrs post-injection. [12]

Monitoring of medical therapy is crucial and is usually done every three monthly by estimation of calcium/ creatinine ratio in morning second void urine. If the calcium/ creatinine is < 0.2, while the serum phosphorus and PTH are within targets, the current regimen can be maintained. If the calcium/creatinine is e" 0.2, urine analysis should be done to check for the presence of blood in the urine. If this is present, calcitriol should be decreased and a 24 h urine calcium and creatinine should be checked with a goal of obtaining normal urinary calcium/creatinine ratio.

Conclusion:

TIO is a puzzling paraneoplastic syndrome of abnormal phosphate and vitamin D metabolism caused by small tumors that secrete phosphaturic hormone FGF23. These tumors are a pathological enigma as differentiation between a benign and malignant tumor merely basing on histopathological features is seldom achieved. It has been clearly shown that metastatic lesion can have an entirely benign cellular characteristic. As the tumors are difficult to locate, a stepwise approach involving functional imaging, anatomical imaging and if necessary selective venous sampling or aspiration for confirmation is usually necessary. It is a debilitating disease and the treatment of choice is excision of the tumors with wide margins to avoid possible late recurrence. When tumors cannot be identified, medical treatment can be successful though periodic surveillance is necessary.

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Review article

THROMBOCYTOPENIA AND PSEUDOTHROMBOCYTOPENIA – CURRENT APPROACH TO DIAGNOSIS AND MANAGEMENT

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ABSTRACT:

With the widespread use of automated cell counters, clinicians in any field of medicine may encounter thrombocytopenia.The symptomatology may vary greatly and the underlying cause may be either inconsequential (pseudothrombocytopenia) or life threatening. It is important to be aware of common conditions leading to thrombocytopenia and have a systematic approach to evaluation and management of these patients. In this review we highlight common etiologies seen in adult patients with thrombocytopenia. A brief description and management approach to common conditions, as well as to conditions that may be less frequent but require emergent intervention, is provided. Often the clinician is called upon to make a decision about platelet transfusions. The review also discusses the various types of platelet products available for transfusion and gives guidance regarding selection of the appropriate product, indications and contraindications, and suggested target platelet counts for various clinical situations. Pseudothrombocytopenia is the result of a spuriously low platelet count induced by agglutinating antibodies that cause in vitro platelet clumping.It is diagnosed by reduction in platelet count to less then one lakh depending on anticoagulant used, presence of platelet aggregates EDTA added sample ,normal bleeding time inspite of thrombocytopenia , clumped platelet on blood smear , platelet satellitism stucked to WBC ,count varies with different anticoagulant

Key Words: thrombocytopenia, platelets, primary care, platelet

INTRODUCTION:

Thrombocytopenia is defined as a reduction in the peripheral blood platelet count below the lower normal limit i.e 1.5 lakh/µl[1].Pseudothrombocytopenia is the result of a spuriously low platelet count induced by agglutinating antibodies that cause in vitro platelet clumping[2,3].Thrombocytosis is defined as an increase above normal values,that is greater than 4.5 lakh/ µl,in the no of platelets in peripheral blood[4] . Thrombocythaemia is a chronic myeloproliferative neoplasm that involves mainly the megakaryocytic lineage,the hallmark is sustained thrombocytosis greater than 4.5 lakh/ µl[5] .Thrombasthenia is the dysfunction of platelets,the numbers remaining normal[4].

GENERAL ASPECTS OF PLATELETS: Platelets are the cellular effectors of primary hemostasis, as they contribute to thrombus formation at sites of vascular injury. Platelets are anucleated circulating cells in mammals approximately 2 µm in diameter and are derived from megakaryocytes within the bone marrow. There are approximately 10^{12} platelets circulating in the blood of an adult human. The lifespan of an individual platelet is only 8–10 days, hence 10^{11} new platelets must be produced daily from bone marrow megakaryocytes to maintain normal platelet counts (150–400 × 10^9 platelets per liter of blood)[6]. Several biologically active molecules stored in intracellular granules can be released into circulation or translocated to the platelet surface to mediate other nonhemostatic functions. Platelets have three major types of storage granules: á-granules, dense granules, and lysosomes. A-granules are the most abundant type of granule, with 40–80 per platelet, and they derive their protein content by a combination of endocytosis and biosynthesis. The proteins housed in á-granules include coagulation factors, chemokines, adhesive proteins, mitogenic factors, and angiogenic regulators. Studies have shown that platelets contain heterogeneous populations of á-granules that undergo differential patterns of release during platelet activation.Two classes of á-granules have been identified one that contains fibrinogen and another that contains von Willebrand factor (Vwf) .Therefore, it is likely that there

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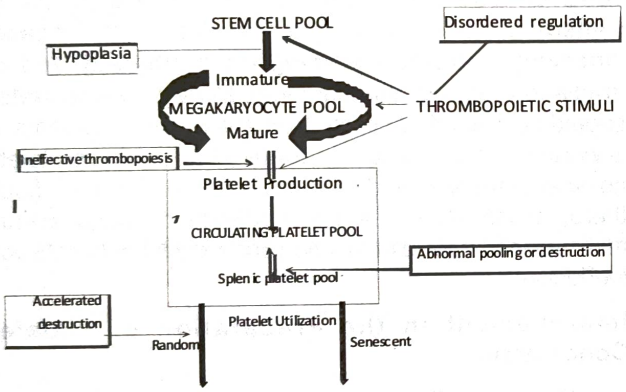
are distinct granule subpopulations with differentially packaged immunomodulatory substances in a specific manner to respond to different types of tissue damage[7,8].

Platelets contain several preformed molecules necessary to mediate hemostasis.Platelets also contain large amounts of mRNA, and the translational machinery packaged during platelet formation can synthesize proteins during hemostatic and inflammatory events. Following thrombin activation, proteomic analyses have demonstrated that platelets secrete more than 300 different proteins, such as interleukin-1 (IL-1), Toll-like receptors (TLRs), and CD154, which are also involved in host defense[6]

Pathophysiology of Thrombocytopenia



Mechanism of thrombocytopenia is due to (A)Artificial thrombocytopenia / pseudothrombo-cytopenia (B)Decreased platelet production (C)Increased platelet destruction (D) Abnormal platelet distribution or pooling (E) Drug induced.

Artificial thrombocytopenia/pseudothrombo-cytopenia[2,3] : Artificialy low platelet count due to clumping of platelets. Causes are (1)Antibody induced platelet agglutination (2)Platelet satellitism (3) Antiphospolipid antibody (4)Glycoprotein 2b-3a antagonist (5)Autoimmune disease (6)Liver disease (7)Sepsis

Diagnostic criteria for pseudothrombocytopenia[3] :

(a)Reduction in platelet count to less then one lakh depending on anticoagulant used (b) Presence of platelet aggregates EDTA added sample (c) Normal bleeding time inspite of thrombocytopenia (d) Clumped platelet on blood smear (e) Platelet satellitism stucked to WBC (f) Count varies with different anticoagulant

Causes of decreased platelet production: There are so many causes but the most commoncauses are,Aplastic anaemia, Post radio/chemo therapy, Human immune deficiency virus infection, Hepatitits C virus infection,Acute leukaemia Megaloblastic anaemia, Drug induced (Heparin, Linezolid, Valproic acid)

Causes of platelet destruction: It may be immune mediated due to primary ITP, neonatal alloimmune thrombocytopenia, post transfusion purpura, heparin induced thrombocytopenia OR non-immune mediated like infection, sepsis, giant haemangioma, disseminated intravascular coagulation, thrombotic thrombocytopenia.

Peripheral uppressione/pooling: It may be due to (1)Massive splenomegaly (2) Hyper-splenism (3) Massive transfusion (4) Pregnancy.

Drugs responsible for thrombocytopenia: There are large number of drugs causing thrombocytopenia. Few of them which are most commonly used drugs mentioned here e.g-Heparin, Valprpoic acid, Carbamazepine, Gold salt, Bactrim, Penicillin, Linezolid, Digoxin, Ranitidine, Clopidogril, Vancomycin, Phenytoin, Amiodarone, Amphotericin B.

Diagnostic approach to thrombocytopenia[1,9,17] : **(A)**First rule out pseudothrombocytopenia by (1) Examine the smear (2) Repeat with heparinized/citrated tube (3) Repeat with fingerstick directly applied to slide(Note: pseudothrombocytopenia often accompanied by falsely high WBC (machine counts platelet clumps as WBCs). **(B)** Enquired any medication history, alcohol consumption, inadequate nutrition intake, bleeding history, family history. (c) Physical examination for finding out splenomegaly, Searcing for any palpable lymph node, detail skin examination to look for petechiae , purpura, ecchymoses.

Peripheral blood smear: On examination of peripheral smear search for (1) large platelets (hign MPV on CBC) imply increased destructionàearly release from marrow (ITP) (2)Normal/small platelets suggest reduced BM response (3)Schistocytes (fragmented RBCs): MAHA (4)Can reveal blasts, (5) Treardrop RBC, nucleated RBCs can suggest marrow invasion (tumor/ fibrosis/granuloma) (6) Marcrocytosis with hypersegmented polys can suggest Vitamin B/folate deficiency

Bone marrow biopsy? More definitively answers the "production vs. destruction" question, generally indicated

in unexplained uppressionenia if platelet count low enough (5-10K) to be at risk for major bleeding.

Laboratory tests for drug induced thrombocytopenia: These are (1)The demonstration of immuneglobulin binding to platelet in presence of offending drug(2)Complement fixation test (3)Platelet serotonin release assay (4) Platelet factor 3 release test (5) Clot retraction inhibition test

Management of Thrombocytopenia:

Platelet transfusion:

Appropriate use of platelet concentrate

The decision to transfuse platelets depends upon the clinical condition of the patient, the etiology of thrombocytopenia, the platelet count and the functional ability of patients' platelets. The strategies vary from hospital to hospital and also between doctors. It has been reported in the past from Western Ontario that the cardiovascular service used the largest proportion of platelet units (28%), aorta coronary bypass grafting being the most common procedure. Current medical literature supports the appropriate use of platelet concentrate in patients with thrombocytopenia due to chemotherapy but prophylactic use of platelet transfusion for patients undergoing cardiovascular bypass procedures is be questioned. Therefore, continued surveillance of use of these reproduces and re-evaluation of the aims of platelet transfusion is essential. Evidence has accumulated to show that serious bleeding usually occurs only when the platelet count is below 10,000 / il and blood loss increased only when the platelet count reached 5000 / il. So, now many hospitals and physicians use platelet counts of 10,000 or 5,000 / il as the indication for transfusion to uncomplicated patients. However, if the patient is febrile or septic, the old trigger of 20,000 / il should be used. Active bleeding does not occur with a platelet count above 50,000 / il unless there is a concomitant platelet function disorder. These patients may require platelet transfusion support at any platelet count.[10]

Dose of platelet transfusion:

A platelet concentrate containing approximately 0.7×10^{11} platelets should cause a platelet count increase of 5000 to 10,000 / il in an average sized adult. Most institutions have adopted policies for a standard platelet dose of so many units of pooled platelets. Common local practices have included 4, 6 or 8 to 10 units as their "dose" for adults. However, more hospitals are changing guidelines to more appropriately treat patients of different sizes and weights. They have adopted policies to give one platelet concentrate per 10 kg of body weight. This should increase the platelet count by approximately 40,000 / il. Increasing use of single donor platelet (SDP) is being seen in oncology practice, which is considered equal to 6 to 8 random donor platelet units. One controversy still persisting is the issue of whether it is more economical and cost effective to give 'low' or 'high' doses of platelets to patients. More recent data has shown that the best strategy is to give a 'moderate' dose of 6 single donor units. In general, especially in oncology practice it is preferable to use leukoreduced platelets in patients with hematological malignancies. The rational is to prevent primary alloimmunization to HLA antigens, since many of these patients ultimately will require platelet transfusions. Patients with severely compromised immunogenic function are at risk of transfusion-associated graft versus host disease Oncology patients receiving chemotherapy and c irradiation fall into this category. Platelet concentrate should be irradiated before transfusing these patients. is worth mentioning here that when transfusing platele no other therapy should be given in another IV line[10]. Su therapies include antibiotics or other biochemical age that may inhibit platelet function and render the transfusi ineffective[10].

Improvement in the Preparation of Platele Concentrate

i. Many modifications in the preparation of platele transfusions have occurred in recent years. Platelets prepared by standard techniques are contaminated with a significant number of leukocytes. These leukocytes are subsequently responsible for adverse reactions after platelet transfusion. They cause febrile transfusion reactions, adverse immunomodulatory effects, HLA alloimmunization and transfer of some transfusion-associated viruses like cytomegalovirus. Therefore, realizing this problem, transfusion medicine specialists have developed effective means for their removal. These include bedside filtration and pre-storage filtration. Bedside filtration causes about 4 log reduction of WBC on the average. A disadvantage of this method is that it does not remove cytokines or the WBC fragments released during storage. However, pre-storage filtration is able to circumvent these problems. Usually this method removes WBCs from the original whole blood unit within a few hours after collection. Therefore pre-storage filtration is a superior

method which produces less febrile reaction due to HLA immunization] Apheresis procedures are available which harvest platelets with reduced numbers of WBC. The WBC content of platelet units as reported by International Society of Blood Transfusion working group should be less than 5 X 10^6 WBCs in these units usually.

ii. Additive solution use:

Attempts have been made to increase the shelf life of the platelet concentrates and maintain their function by addition of synthetic additive solutions. The advantages of these non plasma storage media are the prevention of lactate accumulation, removal of products like complement, kallikrin, thrombin and plasmin and removal of platelet micro vesicles.

iii. Making platelet concentrate safer:

A major problem with platelets stored at room temperature is the risk of bacterial contamination. Appropriate precautions of course in the collection, preparation and storage reduce the incidence significantly. Leukodepletion also reduces the risk of bacterial contamination. Finally several studies have demonstrated that photo inactivation of platelet concentrate helps in removing some of the viruses. The most promising method is addition of photochemical reagents such as Psoralen compounds that bind to viral DNA. Psoralen is inactivated by UV light of an appropriate wavelength (UVA 320 – 400 nm). The cross-linked product thus produced interferes with viral replication. Novel products are being synthesized with improved DNA binding capacity, requiring shortened period of UVA exposure and causing better platelet preservation. Also some attempt has been made to inactivate HLA antigen by chloroquine treatment for preventing alloimmunization. But this product was found to be toxic. To reduce the incidence of HLA-alloimmunization of transfused patients efforts have been made to inactivate the HLA antigens of platelets by citric acid treatment. However this affects the quality of the platelets.

When not to transfuse platelet: Transfusions may induce immune resistance, generally transfusions not given in conditions of platelet destruction like Heparin induced thrombocytopenia, Haemolytic uraemic syndrome, thrombotic thrombocytopenia purpura Disseminated intravascular coagulation[4].

Idiopathic(immune)thrombocytopenic purpura(ITP):

It is an acquired disorder characterized by thrombocytopenia due to antibody formation with variable risk of bleeding. Varieties of ITP are Newly diagnosed,Persistent(3 – 12 month),Chronic > 12 month OR (a) Primary **(b)** Secondary **Diagnosis of ITP: (A)** Blood picture of ITP (1) Platelet count normal to d" 10,000/µl (2) Prolonged bleeding time (3) Positive tourniquet test (4) H" 30% have positive anticardiolipin antibody (5) Normocytic normochromic anaemia (6) Anaemia proportional to degree of blood loss. **(B)** Bone marrow picture of ITP: Increase in % of immature megakaryocytes, Moderate increase in lymphocytes, Moderate increase in eosinophil , If severe anaemia present there is Erythroid hyperplasia and depeletion of iron stores.

Pathogenesis of ITP:

(1) The pathophysiology of primary ITP is mainly due to accelerated platelet destruction by anti Gp2b/3a antibody and anti Gp1b/1x antibodyandauto antibodies causes opsonization of platelets leading to destruction by reticulo endothelial system,

(2) Dysregulated T-cell in ITP which enables development of auto antibodies, direct toxic effect on plateletand auto antibodies are predominantly IgG type.

(3) Insufficient platelet production. (4) H.pylori which may initiate or perpetuate ITP by molecular mimicry that is cross reactivity between antibody, bacterial CagA protein and platelet antigen.

Treatment of ITP:

(a) First line therapy (Anti-D immunoglobulin, Corticosteroid, Intravenous immunoglobulin),

(b) Second line therapy (Immunosuppresants, Splenectomy, Danazol, Rituximab, Vincristine, Thrombopoetin receptor agonist (TPO) etc).

(c) Treatment for patients failing first and second line therapy like options with sufficient data: TPO receptor

agonist, combination of first line and second line therapy, combination chemotherapy, Human Stem Cell Transplant[4,5,11].

THERAPEUTIC AGENTS AND THEIR DOSING SCHEDULES IN ITP[4]

Agent	Dosing schedule
Rituximab	375 mg/m2 weekly for 4 doses
Anti-D immunoglobulin	50 – 75 µg/kg, repeated at 3 weeks interval
Cyclophosphamide	150 mg daily for upto 8 weeks
Dexamethasone	40 mg daily for 4 days, repeated after 4 days interval
IVIG	1gm/kg divided doses, repeated at 2 – 4 week interval at 400 mg/ kg
Vincristine	2 mg at 5 – 7 days interval for 2 or more doses
Vinblastin	7.5 mg at 5 – 7 days interval for 3 or more doses
Prednisone	1 mg/kg daily for 14 days
Danazol	400 mg twice daily for 1 month
Colchicine	200mg daily for upto 4 weeks

Treatment of ITP by Splenectomy is Indicated in chronic ITP of adult, failure to 1st / 2nd line therapy with troublesome bleeding for several weeks and responder's shown improvement in capillary fragility, shortening of bleeding time, platelet count increases with few hours to few days[4,5,11].

Thrombopoietin-receptor agonists for the treatment of thrombocytopenia[11] : Most commonly used agents are recombinant human interleukin-11 inChemothe rapy-induced thrombocytopenia(TCP), TCP in patients with cirrhosis at a dose of 50 ig/kg per day (subcutaneous), Romiplostim is used in ITP at a dose of 0.2-10 ig/kg once a week (subcutaneous), HCV-related TCP at a dose of 2 ig/kg once a week (subcutaneous), Eltrombopag is used in ITP at a dose of 50 mg once daily (oral), HCV-related TCP 25 mg once daily (oral)[11].

Trombocytopenia due to Dengue virus (DENV):

Thrombocytopenia has always been one of the criteria used by WHO guidelines as a potential indicator of clinical severity. In the most recent 2009 WHO guidelines, the definitions generally describe a rapid decline in platelet count or a platelet count less than 150,000 per microliter of blood.

A kinetic description of platelet count in DHF/DF showed a significant decrease on the 4th day of the illness. In fact, previous studies reported DHF in adults without shock, in which platelet counts mildly to moderately decreased on the 3rd day until the 7th day of illness and reached normal levels on the 8th or 9th day[9,12]. In children, there is little correlation between platelet count and bleeding manifestations or between platelet count and disease severity . In adults, a platelet count of 5×10^9/ Litre and packed cell volume >50 are significantly associated with bleeding manifestations. However, a study enrolling 245 dengue patients showed no correlation between clinical bleeding and platelet count, and 81 nonbleeding patients had counts of less than 20×10^9/litre[13]. In contrast, another study enrolling 225 dengue patients suggested that bleeding occurred more often in patients with platelet counts below 20×10^9/Litre.

Most clinical guidelines recommend that platelet transfusions be given to patients who develop serious hemorrhagic manifestations or have very low platelet counts, platelet counts falling below 10–20 × 10^9 /Litre without hemorrhage or 50 × 10^9 Litre with bleeding or hemorrhage[14]. The efficacy of platelet transfusions is controversial. In a study of 106 pediatric patients with DSS with thrombocytopenia and coagulopathy, there was no significant difference in hemorrhage between patients who received preventive transfusions compared to those who did not. Patients who received transfusion had a higher frequency of pulmonary edema and increased length of hospitalization . Platelet transfusion did not prevent the development of severe bleeding or shorten the time to bleeding cessation and was associated with significant side effects. **Platelet transfusions should not be routinely performed in the management of dengue[6].**

The mechanisms involved in thrombocytopenia and bleeding during DENV infection are not fully understood. Several hypotheses have been suggested to elucidate the mechanism involved. In this context, DENV could directly or indirectly affect bone marrow progenitor cells by inhibiting their function to reduce the proliferative capacity of hematopoietic cells . Indeed, there is evidence that

DENV can induce bone marrow hypoplasia during the acute phase of the disease. Besides platelets counts, the functional disruption of these cells is associated with a significant deregulation of the plasma kinin system and the immunopathogenesis of dengue. In addition, DENV infection induces platelet consumption due to disseminated intravascular coagulation (DIC), platelet destruction due to increased apoptosis, lysis by the complement system and by the involvement of antiplatelet antibodies . Here, we discuss the relevance of platelets in physiology and their implication in dengue pathogenesis, acting both as a *victim* of infection and an *effector cell* of the antiviral immune response.

Bone Marrow suppression in Dengue: Previous reports have shown that, during the early phase of disease, bone marrow displays hypocellularity and attenuation of megakaryocyte maturation[9]. The precise mechanisms underlying DENV-induced bone marrow suppression during the acute phase remain unclear. However, three main factors have been suggested: (1) direct lesion of progenitor cells by DENV; (2) infected stromal cells; (3) changes in bone marrow regulation. Thrombopoietin (TPO) is a cytokine that specifically regulates megakaryocytopoiesis and platelet production by activating the TPO receptor c-MPL (myeloproliferative leukemia virus oncogene). Because TPO is elevated when platelet production decreases, serum TPO levels may be a useful indicator of megakaryocytopoiesis in dengue. In fact, Matondang et al. showed that TPO levels significantly increased in adult DENV patients in which circulating platelets were markedly reduced and the TPO levels inversely related to the platelet counts.

Increased Destruction of platelets Causes Thrombocytopenia in Dengue: Thrombocytopenia may also be due to (1) platelet consumption during ongoing coagulopathy process, (2) activation of the complement system or (3) increased peripheral sequestration. It has been shown *in vitro* that platelets undergo increased phagocytosis by macrophages in patients with secondary DENV infections by an uncharacterized mechanism. It has also been demonstrated that DENV patients develop anti-platelet antibodies of the IgM isotype. Notably, antiplatelet IgM titers in patient sera were higher in DHF/DSS compared to DF. Anti-platelet antibodies cause platelet lysis, as measured using lactate dehydrogenase activity assays. In accordance with elevated IgM titers, DHF/DSS sera caused increased platelet lysis compared to DF patient sera. In addition, cytotoxicity was much higher in the presence of complement. Autoantibodies against endothelial cells and blood-coagulation-related molecules have also been identified. In fact, molecular mimicry between platelets, endothelial cells, or blood coagulation molecules and dengue virus NS1, prM, and E proteins may explain the cross-reactivity of anti-NS1, anti-prM, or anti-E antibodies to host proteins and play a role in disease pathogenesis. Cross-reactive antibodies may cause platelet dysfunction, endothelial cell damage, coagulation defects, and macrophage activation, which may contribute to some clinical features of DHF. Some studies have shown platelet activation and apoptosis in dengue-infected patients. In this way, platelet apoptosis, platelet phagocytosis, and serum TPO levels significantly increased in patients during the acute and early convalescence phases compared to levels in patients during the convalescence phase and in healthy volunteers, suggesting accelerated platelet clearance. However, this was overcome by TPO-induced enhanced thrombopoiesis in these patients. Another study later confirmed that platelets from DENV-infected patients exhibited classic signs of the intrinsic pathway of apoptosis, which include increased surface PS exposure, mitochondrial depolarization, and caspase-9 and caspase-3 activation. Moreover, all of these changes were observed when platelets from healthy subjects were directly exposed to DENV *in vitro*, which may contribute to thrombocytopenia development in dengue patients

Thrombocytopenia in pregnancy: It is due tobenign thrombocytopenia of pregnancy, ITP, pre-eclampsia,drug related (Heparin, Linezolid, Valproic acid etc), HIV, TTP, HIT, pseudothrombocytopenia

Management of life threatening tromboctopenia in pregnancy: (1) Platelet transfusion (2) Concurrent intra venous immunoglobulin (1 gm/kg divided doses repeated at 2-4 week interval at 400 mg/kg)[4].

Post transfusion thrombocytopenia: Caused by re-exposure to foreign platelet antigen(Ag) by blood transfusion , antibody(Ab) causes destruction of patients own platelet by uncertain mechanism(probably due to coating of patients platelet by donor platelet microparticle) and patientstypically presents as sudden onset of severe thrombocytopenia (d"10000) 5-7 days after transfusion[15].

Diagnosis: By clinical suspicion,demonstration of HPA-1a allo-antibodies in serum.

Treatment: Intra venous immunoglobulin(1 gm/kg divided doses repeated at 2-4 week interval at 400 mg/kg), avoid giving HPA-1a positive platelet, wash RBC to remove passenger platelets.

Refractory Thrombocytopenia (RT): It is characterized in the blood by isolated thrombocytopenia, e"10% dysplasia evaluated on at least 30 megakaryocytes, dysmegakaryocytopoiesis which may include (hypolobated megakaryocytes, multinucleated megakaryocytes, micro-megakaryocytes).Causes are chronic ITP, accessory spleen, familial thrombocytopenia, con-comitant medication, hypersplenism, recurrent viral infection, prior to bone marrow malignancy, ITP with severe ADAMTS13 deficiency[16].

Treatment of RT: Rule out the cause and treat accordingly, stop any offending drug, Search for accessory spleen and operate it, intra venous immunoglobulin (1 gm/kg divided doses), high dose corticosteroids[16].

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Case Report

SYSTEMIC SCLEROSIS-POLYMYOSITIS OVERLAP SYNDROME-A CASE REPORT AND REVIEW OF THE LITERATURE

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ABSTRACT

Overlap Syndromes(OSs) have been defined as entities satisfying classification criteria of at least two connective tissue diseases(CTDs) occurring at the same or different times in the same patient. OSs are well defined clinical entities, not just a mere association. These conditions include systemic sclerosis (SSc), dermatomyositis or polymyositis, Sjogren's syndrome(SS), rheumatoid arthritis(RA) and systemic lupus erythematosus(SLE) in any combination. Presence of a specific autoantibody and different clinical features than the individual CTDs indicate the need to identify these rare syndromes as combined pathology influences the diagnosis, treatment and prognosis. We report an overlap of systemic sclerosis-diffuse cutaneous with polymyositis in a 24 year old lady whose diagnosis and treatment was delayed for four years before she came under our supervision.

INTRODUCTION

Systemic sclerosis (SSc) is a systemic autoimmune disease of unknown aetiology characterized by vascular lesions, autoimmunity and progressive visceral and vascular fibrosis of multiple organs, predominantly in skin, lungs, heart, intestinal tract, joints, and muscles. Scleroderma overlap syndrome is a relatively common condition with SSc-SS and SSc-myositis are the most common combinations. The overall prevalence of myopathies in SSc patients varies from 5% to 81%[1] and may indicate deconditioning, disuse atrophy and malnutrition. However, inflammatory myositis indistinguishable from idiopathic polymyositis may occur, hence the term scleroderma-polymyositis overlap (SSc-PM). The mortality rate in the SSc-PM overlap syndrome is reported to be of 21.1%, higher than in the entire SSc and overlap syndrome groups[1]. Several studies have demonstrated a worse survival and increased prevalence of myocardial involvement in SSc-PM overlap compared with SSc [2]. It indicates the need to identify these patients as early diagnosis and close monitoring are essential in the overall management.

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CASE REPORT

A 24 year old female presented with chief complaints of intermittent fever, joint pain, difficulty in getting up from sitting position and raising her arms above the head with difficulty in combing hair for 4 years. She also had pigmentation of skin, tightening of skin and bluish discolouration of fingers on exposure to cold for past one and half year. She also complained of dyspnoea on exertion for 6 months. However, there was no history of orthopnea, PND, swelling of feet. There was no oral ulcer or malar rash. For these complaints, she was receiving some ayurvedic medication for the past 16 months. On general examination, there was cushingoid facies, mild pallor, sclerodactyly, thickening of skin over face, chest, arm, forearm. Examination of the musculoskeletal system revealed waddling gait without evidence of arthritis. CNS examination revealed proximal myopathy, normal reflexes with flexor plantar response. Lab investigations: Hb%-10 g%, TLC-7800/cmm, ESR- 40 mm in 1st hour, CRP-7.6

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mg/dl(Normal:6-8), serum urea-24mg%, serum creatinine-0.9mg%, AST-64 IU/L, ALT-44IU/L, RA factor- negative. Ultrasound of the abdomen and pelvis revealed hepatomegaly with fatty change. X-ray chest PA view showed B/L lower zones haziness. 2D-ECHO was normal. Serum creatinine kinase-98 IU/L(Normal-60-174), serum LDH-248U/L(Normal-140-280), EMG showed a myopathic picture and NCS was normal. ANA-3+ speckled, dsDNA-37.5, C3-155, C4- 51 and ENA profile was negative.

Based on the above findings, a diagnosis of SSc-dc with polymyositis overlap was made classification criteria and the patient was put on prednisone (0.5mg/kg wt), tadalafil (10mg), methotrexate(10 mg), calcium and vitamin D3. She was discharged to follow up after one month.

DISCUSSION

The exact prevalence of SSc overlap syndrome is not known although various combinations with RA, SLE, Sjogren syndrome, vasculitis, myositis have been reported. SSc-PM overlap has been described in adults and adolescents with myositis appearingsimultaneously, before or in established SSc. Diffuse cutaneous form of SSc is reported to be more prevalent among the SSc overlap syndromes and is associated with cardiomyopathy[3]. GIT involvement in the form of pneumatosis intestinalis, pseudo-obstruction have been reported in SSc-PM. In a recent case-control study, Ranque B et al have reported increased prevalence of reduced forced vital capacity, heart involvement, defined as clinical congestive heart failure, left ventricular ejection fraction (LVEF) < 60%, arrhythmia or conductive abnormalities, and scleroderma renal crisis among patients with myopathy than in controls[4]. In our patient, normal echocardiography ruled out heart involvement though HRCT could not be done to look for ILD.

Different antibodies are associated with SSc-PM overlap eg, anti-PM/Scl and anti-Ku[5]. Several novel antibodies like anti-U3 RNP, and anti-RuvBL1/2 have also been reported. Presence of these autoantibodies may indicate a specific pattern of organ involvement, eg, limited cutaneous involvement and pulmonary fibrosis in patients with antiPM/Scl, diffuse cutaneous involvement and pulmonary arterial hypertension in anti-U3 RNP. However, these antibodies were absent in the ANA profile study of our patient since the prevalence of these antibodies are usually low.

The myopathology in patients with SSc-PM overlap syndrome shows specific patterns compared to PM patients. Necrotizing muscle fibers are observed in almost all patients with SSc-PM overlap[1]. Presence of linear deposits at endothelial cells of endomysial capillaries in MAC staining differentiates dermatomyositis from polymyositis[6].

Corticosteroids, cytotoxic drugs, azathioprine, mycophenolate mofetil and cyclophosphamide are being used in the treatment of SSc-PM overlap. High dose steroids should be used cautiously in patients with diffuse cutaneous involvement as in can provoke scleroderma renal crisis. Methotrexate should not be used in ILD patients with active alveolitis. The useof anti-TNFα therapy in patients with SSc-myositis is controversial as it aggravates ILD. Rituximab has been shown to be effective in most patients with uncontrolled myositis. There are so trials of IVIG and mycophenolate mofetyl in patients with SSc-myositis.

CONCLUSION

Early diagnosis and routine follow up are critical in the management of patients with SSc-PM overlap syndrome. Since cardiac and pulmonary complications are a major cause of death in this group of patients, periodic cardiopulmonary monitoring is vital in the effective treatment.

CONFLICT OF INTEREST

None

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Fig.1 Sclerodactyly

Case Report

ECTOPIC CUSHING'S SYNDROME DUE TO THYMIC CARCINOID –A CASE REPORT

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INTRODUCTION

Thymic neuroendocrine tumor are aggressive tumors usually present with symptoms due to mass effect or rarely with endocrinopathy. These can rarely be the cause of ectopic Cushing's syndrome and 150 cases have been reported in literature. Here we report a case of thymic neuroendocrine tumor presenting with ectopic adrenocorticotroic hormone(ACTH) production and resultant Cushing's syndrome.

CASE REPORT

A 30-yr female presented with progressive weight gain of about 20 kg ,darkening of skin , acne with oligomenorrhic cycle for last one and half yrs. There was no history of exogenous steroid intake, episodic diarrhea or flushing. On evaluation she had central obesity (BMI-33.87kg/m^2), rounded plethoric face, hypertension (BP-160/100 mm Hg), marked hyperpigmentation(Fig1 a,b,), purple livid striae over abdomen , proximal muscle weakness and easy bruisability favoring a clinical diagnosis of Cushing's syndrome.

A hard fixed nontender left supraclavicular mass (2cm x2cm) was detected. In routine investigation she was found to have anaemia ,impaired glucose tolerance, hypokalemia and dyslipidemia (table 1). Marked hyperpigmentation and short duration of presentation pointed towards ectopic ACTH production. ACTH dependent Cushing's syndrome was documented by raised 11P.M. S.Cortisol and S.ACTH with non-suppressed S. Cortisol by 1 mg over night dexamethasone suppression test (ODS) and 0.5 mg /48hrs low dose dexamethasone suppression test (LD-DST)(table 1). MRI of brain was normal. FNAC of supraclavicular mass revealed metastatic -thymic carcinoid. CT scans of chest showed a solid enhancing mediastinal mass (fig-2) and right supraclavicular cervical adenopathy with abdominal CT being normal. CT guided core needle biopsy of the anterior mediastinal mass showed neuroendocrine tumor (thymic carcinoid). MEN1 was excluded.

Radical en block resection of the anterior mediastinal tumor was done through a median sternotomy along with dissection of left supraclavicular lymph node. The tumor was a grayish black, globular mass of size 6x5x3cm with a thick capsule and bosselated surface(fig3a,). Histo-pathologic evaluation revealed predominantly single cells and occasional small loose clusters of cells with uniformly round or oval contour scanty cytoplasm, evenly distributed finely granular chromatin, and inconspicuous nucleoli, features suggestive of typical thymic carcinoid(fig3b,c).Supraclavicular lymph nodes were positive for metastatic disease.

The perioperative period was uneventful and she recovered remarkably. There was rapid remission of the Cushing's syndrome over a period of 12 weeks) and biochemical parameter improved on repetition after 3 months. A CT scan of the thorax, repeated after 6 month showed no residual lesion

DISCUSSION

In 1972 Rosai and Higa first described carcinoid tumors of the thymus. Thymic carcinoid constitutes 2%-4% of all anterior mediastinal tumors. Because of their aggressive behavior, carcinoid tumors of the thymus have been renamed as thymic neuroendocrine carcinoma (TNC). Histologically they may be well differentiated (typical and atypical carcinoid) or undifferentiated (small and large cell variety). Atypical carcinoid is more aggressive than typical carcinoid. Carcinoid tumors arising from the

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embryonic foregut (stomach, bronchus, thymus, pancreas and thyroid) are often deficient in the enzyme aromatic L-amino acid decarboxylase, and therefore have less serotonin secreting capacity than those arising from the ileum, but they have a greater tendency to peptide hormone production like ACTH &ADH[1]. Carcinoid syndrome is very rare in thymic carcinoid. TNC occur almost in the anterior mediastinum and usually present with symptoms due to mass effect (chest pain, cough, dyspnoea, or superior venacava syndrome) or rarely with endocrinopathy like Cushing's syndrome, SIADH ,MEN-I or MEN -II syndrome.In addition, metastatic spread to mediastinal and cervical lymph nodes, liver, bone, skin, and lungs occurs in 20-30% of patients[2]. About 10% of Ectopic Cushing syndrome is caused by TNC due to ectopic ACTH production. Ectopic Cushing's syndrome in thymic carcinoid usually occurs between 4 to 64 years of age, most commonly between the second and the fourth decades of life[3]. Males are affected three times more commonly than females[1]. Approximately 25% of patients with thymic carcinoid have MEN-1 syndrome. Diagnosis is often missed and a high degree of clinical acumen is required while evaluating the cause of ectopic Cushing's syndrome. In our case supraclavicular mass detected during clinical examination made our task easy underscoring the importance of a thorough clinical examination. Our patients did not have typical features of carcinoid syndrome.

Surgery is the therapy of choice for TNC of the thymus. Aggressive radical resection of these tumors (the entire thymus gland and the perithymic fat) along with the involved structure through a median sternotomy is required to prevent recurrence. Postoperative radiotherapy may help to prevent local recurrence after excision of an invasive carcinoma[4]. The role of radiotherapy, chemotherapy, or both in the treatment of thymic carcinoid tumors has not been adequately established. Single agents or combination drug therapies with fluorouracil, streptozocin, etoposide or cisplatin do not significantly affect survival or recurrence rates[5]. Octreotide has been found beneficial in management of TNC[6]. Despite aggressive therapy, patients with these tumors have poor prognosis which is linked to the degree of tumor differentiation. The 5-year survival rate is approximately 50% for patients with well-differentiated thymic carcinoid tumors. As 20 – 30 % of TNC present with metastasis at the time of diagnosis[2] which may not be picked up by routine CT or MRI, a newer modalities of investigation like Somatostatin receptor scintigraphy or PET scanning with ^{68}Gallium-DOTATATE may be required for detection and subsequent postoperative monitoring. It has been reported that the prognosis is worse for patients with thymic carcinoid who have Cushing's syndrome[7]. A study of 74 patients with thymic carcinoid found that the 10-year mortality rate for those with Cushing's syndrome was 65% compared with 29% for those without endocrinopathic conditions[7].

In our patient, typical thymic carcinoid was detected as the cause of ectopic Cushing's syndrome. Radical en block resection of the tumor lead to resolution of the clinical and biochemical parameters of Cushing's syndrome during follow up without any signs of local recurrence and distant metastasis. From the clinical course of our patient, it is evident that, the prognosis is good, if these tumors are detected early and managed appropriately. Marked hyperpigmentation and therapy resistant hypokalemia as in our case, are clinical indicators to think for ectopic ACTH as the cause Cushing's syndrome.

CONCLUSION

In conclusion, thymic carcinoid is a rare and aggressive tumor, at times presents with endocrinopathies. Early detection, favorable histology and adequate resection may improve clinical outcome. However despite being adequately resected these tumors have tendency for recurrence and metastases which requires periodic follow up every 1-2 year.

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TABLE-1

Lab parameter	Base line	3 month post operative	Referance
Haemoglobin(gm%)	10.2	12.6	11.5-15.5
Serum K(mEq/L)	2.9	4.2	3.5-5.5
FPG (mg/dl)	90	86	70-100
2 hr 75 gm PPG(mg/dl)	186	134	120-140
S.Chol(mg/dl)	224	162	130-200
TG(mg/dl)	127	115	80-170
HDL(mg/dl)	55	47	40-60
LDL(mg/dl)	152	92	<100
S. Calcium(mg/dl)	10.2	10.8	
serum cortisol (µg/dl)-8am	48	12	5-23
serum cortisol (µg/dl)-11pm	42	1.6	<1.8
serum cortisol (µg/dl)-1 mg ODS	34	0.9	<1.8
plasma ACTH (pg/ml)	392	7	9-52
Urine 5-HIAA (mg/24 hrs)	6.7	-	2-8

Figure1a & b(preoperative)

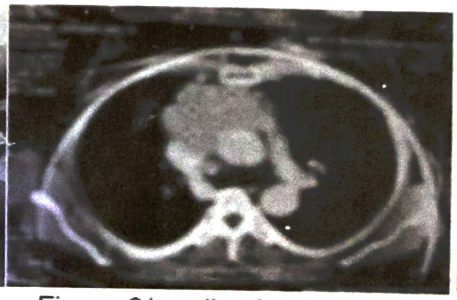

Figure 2(mediastinal tumors)

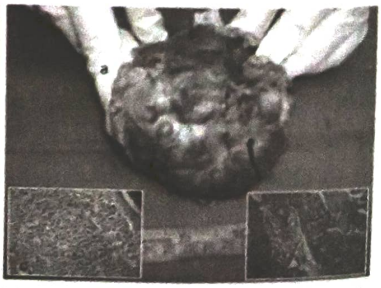

Figure 3a,b,c (Gross and histopathological features)

Case Report

CHRONIC HYPONATREMIA PRESENTING WITH HEMIPARESIS – A CASE REPORT

*S.C.Dash, **B.K.Barik, ***K.K.Jena, ****Amit Kumar

ABSTRACT

Symptoms of hyponatremia are primarily due to neurologic dysfunction induced by cerebral edema and more pronounced in acute hyponatremia. The neurologic deficits due to osmotic demyelination syndrome as a sequel to over aggressive correction of hyponatremia are also well-known. Chronic hyponatremia is rarely symptomatic as the brain adjusts to the hypotonicity and tends to minimize the cerebral edema and its symptoms. However, chronic hyponatremia can also cause neurologic manifestations. A 58years old male, hypertensive for 2 years, on antihypertensive drugs and salt restriction; presented with nausea, vomiting for 7 days and left hemiparesis of 2 days duration. CT Scan and MRI brain were done which showed normal studies of the brain. The patient showed complete recovery from weakness and restoration of normal power on the affected side after correction of hyponatremia with normal saline and hypertonic saline.

Key words: chronic hyponatremia, hemiparesis, normal saline, hypertonic saline

INTRODUCTION

Hyponatremia is a very common electrolyte disorder in clinical medicine[1].The signs and symptoms depend on both the magnitude and rapidity of fall in serum sodium level and are related to osmotic intracellular shift leading to cerebral edema. Mild hyponatremia usually remains asymptomatic and GI manifestations occur with s. Na+ ~ 125 mEq /L. As the s. Na+ level falls further CNS symptoms such as confusion, lethargy, focal neurologic deficits, disorientation and agitation usually manifest. Serious neurologic changes such as seizure and coma are usually seen when the sodium concentration falls acutely below 115 mEq/L.[2]Hyponatremic encephalopathy, a consequence of cerebral edema in acute hyponatremia is associated with substantial morbidity and mortality where as in chronic hyponatremia, adaptive mechanisms counteract brain swelling and is defined as an asymptomatic or mildly symptomatic condition.[1] We report here a case of severe chronic hyponatremia presenting with left hemiparesis and recovered completely after correction of hyponatremia.

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Case report

A 58 years old male was admitted with mild headache, nausea & vomiting for 7 days for which he was taking treatment from a local doctor but developed weakness of left upper & lower limbs since 2 days and brought to our hospital. There was no h/o of fever, altered sensorium, convulsion or difficulty in speech. Patient was hypertensive since 2 years and on metoprolol&telmesartan and salt restricted diet. Examination revealed pulse 68/min, regular, BP 136/70mmHg & mild dehydration. Patient was conscious, oriented and other higher functions, cranial nerves were normal. There was normal tone and grade 3/5 power in left upper & lower limbs and normal power in right upper & lower limbs. Deep tendon reflexes were normally present and plantar reflex was extensor in left and flexor in right. Sensory examination was normal. Other systemic examination was normal.

Investigations showed- Hb-8.7 g/dl, TLC-7,800/cmm, peripheral smear revealed microcytic hypochromic anemia, RBS- 104 mg/dl, urea- 75mg/dl, creatinine - 2.9 mg/dl, s. Na^+ -100mEq/L, s. K^+ -3.0 mEq/L,s. Cl^- -64/mEq/L Urine routine and microscopic test showed only albumin-1+, LFT within normal limits, chest X-ray & ECG were normal.

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Lipid profile: TC- 98.4mg/dl, TGL-85mg/dl, LDL- 48mg/dl, HDL-33.0 & VLDL- 17mg/dl. Ca2+ -8.6mg/dl & Mg2+ - 1.7mg/dl (were WNL). USG abdomen and pelvis findings suggested CKD and no other abnormalities. CT Scan of brain and subsequent MRI brain revealed normal studies of brain(fig1,fig2). EEG was also done which showed normal study. Hyponatremia was corrected gradually with normal saline followed by hypertonic saline (3% Nacl). Patient showed improvement by 3rd day and when sodium concentration reached to124 mEq/L on 5th day, patient got complete recovery by attaining normal power in the affected limbs.

Discussion

Clinical manifestations of hyponatremia depend on multiple factors including the chronicity of the symptoms, the absolute level of sodium and the patient's overall health.[3] When hyponatremia develops slowly (>48 hours), even very low concentration of sodium can be present without resulting in cerebral edema. The brain adjusts to the hypotonicity by extruding intracellular inorganic solutes to the extracellular space within few hours. These exiting solutes drag water with them, thereby reducing cellular swelling (rapid adaptation). The restoration of normal brain volume occurs in several days through loss of organic osmolytes from brain cells (slow adaptation). Low osmolality in the brain persists despite the normalization of brain volume. Proper correction of hypotonicity reestablish normal osmolality without risking damage to the brain.[1,3,4]

Chronic hyponatremia is seldom symptomatic. The degree of cerebral edema and therefore, the likelihood of neurologic symptoms is much less with chronic than with acute hyponatremia. However, chronic hyponatremia can cause severe neurologic manifestations and when doubt exists, it is safer to consider hyponatremia as chronic.[5]When patients with chronic hyponatremia have symptoms, the serum sodium concentration is generally below 110 mEq/L, and there has usually been an acute exacerbation of the hyponatremia.[6]

Recent studies have demonstrated that mild chronic hyponatremia can cause gait impairment, attention deficit, increased risk of falls and chronic moderate hyponatremia impaired memory in rats and correction of hyponatremia with tolvaptan could reduce this effect.[4,7] The osmotic theory cannot explain these effects of chronic hyponatremia and it has been suggested that low sodium directly affects the cellular homeostasis through oxidative stress.[4]

Chronic hyponatremia cannot be determined by using presently available clinical tools. History, prior measurement of sodium, and the neurological feature at presentation are the only available clinical criteria for determining chronicity.[5]

Hyponatremia can be of 3 types- hypertonic hyponatremia, isotonic hyponatremia or hypotonic hyponatremia. The hypotonic hyponatremia is the most common type and often called true hyponatremia. Hypotonic hyponatremia is further categorized in 3ways based on patient's volume status- hypervolemichyponatremia, euvolemichyponatremia and hypovolemic hyponatremia

Most patients with hypovolemic hyponatremia can be treated successfully with isotonic saline, but in the presence of severe symptoms, hypertonic saline infusion is required. There are 2 indications for saline infusion in hyponatremia. Overt manifestations of hyponatremia are treated with hypertonic saline, whereas symptoma c hypovolemia associated with hyponatremia without ov t symptoms is usually treated with isotonic saline. [4,5]

Our case was having left hemiparesis due to seve e chronic hyponatremia and the patient responded to infusio n of normal saline followed by hypertonic saline with slo v correction of sodium. Patient recovered completely from left hemiparesis after correction of hyponatremia.

Conclusion

Although, chronic hyponatremia is traditionally defined as a benign condition, there are emerging evidences suggesting different neurologic manifestations of chronic hyponatremia. Therefore, this apparently benign condition should also be considered for the neurologic complications.

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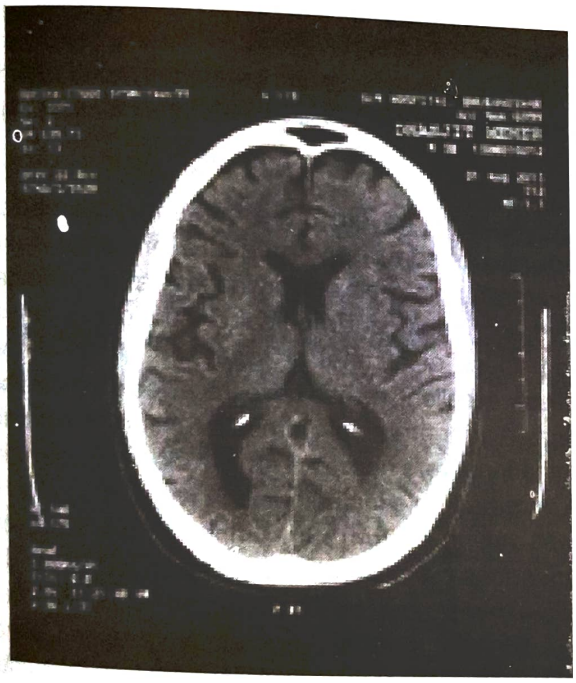

Fig 1. Normal CT Scan of Brain

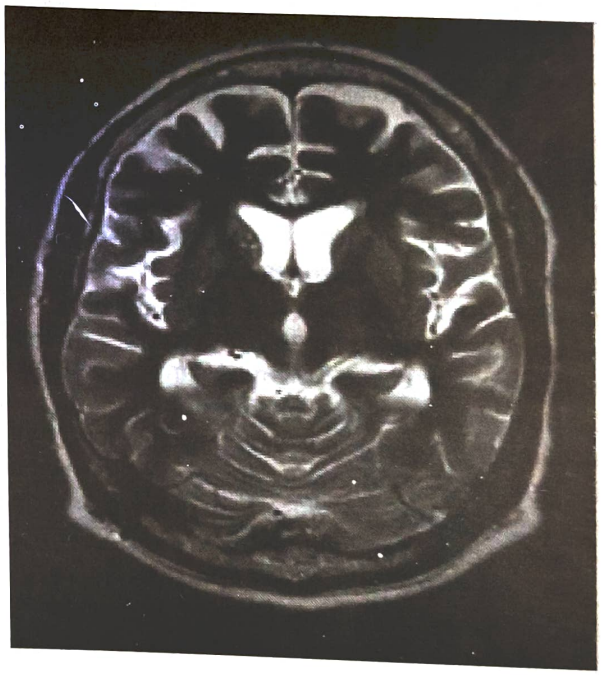

Fig.2. Normal MRI Brain

Case Report

HERPES SIMPLEX ESOPHAGITIS IN IMMUNOCOMPETENT HOST : A CASE REPORT

Ayaskanta Kar*, Kashinath Padhiary**, Malati Murmu***, Dipak Gaikwad****, Biswajeet Kar****, Sangya Das****

ABSTRACT

Herpes simples Esophagitis (HSE) is usually observed in immunosupressed individuals. It is rare in immunocompetent patients. It is suspected clinically by an acute onset symptomatic triad of odynophagia, retrosternal pain and fever. Herpes simplex type 1 virus is the most common cause. Upper GI Endoscopy establishes the diagnosis. We present a case of acute herpetic esophagitis in an immunocompetent adult male who presented with acute onset of severe retrosternal pain and odynophagia. Endoscopic findings revealed severe exudative well circumscribed multiple ulcers in the mid and distal esophagus with typical histological features in the biopsy and positive serological marker for HSV1 (Harpes Simplex virus 1) and dramatic response of the patient to oral famciclovir therapy. Due to rarity of HSE in immuno competent host, we report this case.

Key Words : Immuno suppressed, Upper GI Endoscopy.

INTRODUCTION :

Herpes simplex virus (HSV) is a double standard DNA virus classified into two subtypes HSV 1 & HSV 2[1]. HSV infections are found worldwide. Gingivostomatitis and pharyngitis are the most frequent clinical manifestations of first episodes of HSV 1 infection most commonly seen in children and young adults[1]. The esophagus is the most commonly involved visceral oragan in Herpes virus infection[1]. Herpes simplex esophagits (HSE) in immuno-compromised host is well documented[2]. It represents both reactivation of virus during immuno supression and primary infection although the former is common[2]. Few papers have described immunocompetent individuals with herpes simplex esophagitis (HSE)[1]. Although HSE is rare in immunocompetent individuals, it should be considered as a diagnostic hypothesis for clinical conditions characterized by acute odynophagia and retrosternal pain without other obvious cause of ulcers, evidenced endoscopically in the mid-distal esophagus[3]. Here in we present a case of immuno competent adult with HSE who had dramatic response to oral Famciclovir therapy.

CASE REPORT :

A 42 years old male presented to medicine outdoor with complaint of acute onset of severe retrosternal burning pain and odynophagia for last 07 days. He had no singnificant medical or surgical history and denied abuse of alcohol or tobacco. His health was previously excellent, he had never received corticosteroids. He denied prior orolabial Herpes Infection. His physical examinations were normal & routine blood investigations were unremarkable including negative serology for HIV. He was taking proton pump inhibitor (Rabeprazole), Domperidone tablets and antacid syrup for last 07 days for GERD prescribed by Physician but without success. Upper Gastrointestinal Endoscopy revealed severe exudative Esophagitis with multiple deep circumscribed Ulceration with hyperemia at the base. These were more prominent in gastro esophageal junction and mid esophagus (Fig. 1, Fig. 2) and minor lesions over the upper esophagus (Fig. 3). Histological changes in the esophageal biopsies were compatable with Herpes Infection as it showed acute severe inflammation, multinucleated Giant cells with Ground glass Intra nuclear

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eosinophilic inclusion bodies characteristic of herpes virus infection. Serological marker for HSV 1 antibody IgM was found to be positive.

After the diagnostic confirmation, the treatment was started with oral Famciclovir (250 mg.) thrice daily for 10 days. There was dramatic response noted on 3rd day and complete resolution of symptoms was achieved in 1st week.

DISCUSSION :

Herpes simplex virus (HSV) is a double stranded DNA virus classified into two subtypes, HSV1 & HSV2[1]. HSV infections are found worldwide. After candidasis, HSV type 1 is the most common cause of infectious esophagitis[4]. Herpes simplex esophagitis (HSE) is most commonly seen in immunocompromised patients with AIDS, an underlying malignancy, a debilitating illness in patients who have been treated with radiation, steroid or antibiotic chemotherapy[4]. HSE in immunocompetent hosts is rare and it may represent either a primary disease or reactivation of a latent infection[4].

Esophagitis may result from the direct extension of Oropharyngeal disease into the Esophagus or may occur by reactivation of HSV spread of virus to the esophageal mucosa by the way of the vagus nerve[1]. The typical presentation of HSE is that of a young healthy male who presents with acute odynophagia, dysphagia or heartburn with or without prodormal symptoms (i.e. fever, pharyngitis, respiratory symptoms) or oral lesion. Prior exposure to a family member with possible HSV infection have been reported in 20% cases[5,6]. Our patient is a young male and presented with similar fashion with severe retrosternal chestpain, odynophagia without prodormal symptoms.

Most symptomatic immunocompetent patients with HSE will present with an acute onset of esophageal complaints, but a subset of patients (24%) will present with prodrome of symptoms including odynophagia (76%), fever (44 – 63%) and respiratory symptoms, Sorethroat (in 23%). Other common complaints associated with HSE may include retrosternal pain (60%), dysphagia (21%), myalgia (21%)[5]. Oral manifestations (Herpes Labialis) may preceed the onset of odynophagia by 1 – 4 days, concide with or overlap 1 – 5 days after wards[5].

Diagnosis is usually established with upperGlendoscopy. HSE has characteristic endoscopic appearnces. The distal and mid esophagus is commonly involved in more than 50% cases and in 26% of cases the entire esophagus is affected. In the early stage, vesicles are seen, which then slough to form descrete, circumscribed ulcers with raised edges. These lesions have punched out or volcano line appearance. cobblestoning can be seen due to clusture of the lesions. Exudates are present in the majority of cases[2]. In our case the mid and distal esophagus is mostly affected and the upper esophagus has few lesions with typical circumscribed ulcers (Fig. 1, Fig. 2, Fig. 3) with overlying exudates (Fig1)). In case of esophageal erosions or if HSE is clinically suspected, biopsies from the ulcer edges should be obtained for both histopathology and viral culture. Virus isolation by cell culture has traditionally been considered as the diagnostic 'Gold standard' for HSV infection[2].

The characteristic histological appearance is the presence of multinucleated giant cells with eosinophilic intranuclear inclusions, called cowdry type A intranuclear inclusions and nuclear chromatin with a ground glass appearance[4]. In recent years, HSV DNA PCR is considered the most sensitive, cost effective, rapid and easiest diagnostic tool of HSV infection[4] with sensitivity of 92 – 100% and 100% specificity. Serology is of limited value as a majority of healthy individuals will have prior exposure to HSV, unless there is a seroconversion[4]. Endoscopic appearance of herpetic esophagitis can be confused with eosinophilic esophagitis or with esophagitis caused by candida Sp. Or cytomegalo virus (CMV).

Antivial therapy in early stage is advisable to hasten the recovery and to rapidly achieve symptomatic relief[2]. Treatment with oral nucleoside analog, acyclovir or famciclovir or valacyclovir has been shown to be effective for HSE. The duration of the illness ranges from 4 to 9 days in those receiving antiviral therapy compared with 10 to 17 days in those receiving symptomatic treatment alone[4]. Among the reported cases of adults who received acyclovir therapy, most achieved a clinical response with in 24 – 72 hours and all became asymptomatic within 4

to 14 days without complications. In severe cases Intravenous acyclovir is given.

HSE is generally a self limiting condition but cases of immuno competent patients experiencing significant complications, including GI bleeding, esophageal perforation, mediastinitis, tracheo esophageal fistula has been reported[4].

In our case the diagnosis of HSE is made based on clinical symptoms, typical endoscopic findings, positive serological marker (IgM for HSV-I) and characteristic histological features of esophagial ulcer biopsy.

CONCLUSION:

Herpetic esophagitis should be taken into consideration in Immunocompromised patients. However HSE should be suspected in otherwise healthy subjects with symptoms (Odynophagia, Heart burn) suggestive of esophagitis without obvious cause. Particularly in patients with ulceration in mid and distal Esophagus at Endoscopy. In these cases endoscopic biopsy from the edge of the ulcers should be examined microscopically and viral culture and PCR should be done to establish the diagnosis. HSE in immunocompetent host is self-limiting but antiviral therapy may shorten the illness if started early.

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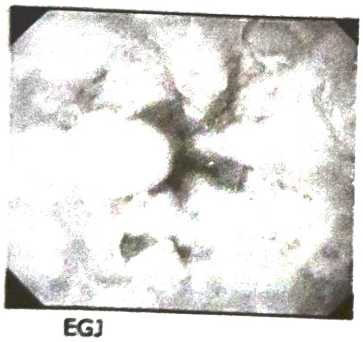

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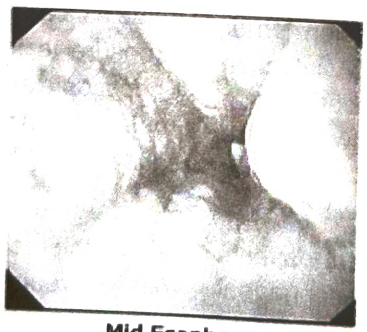
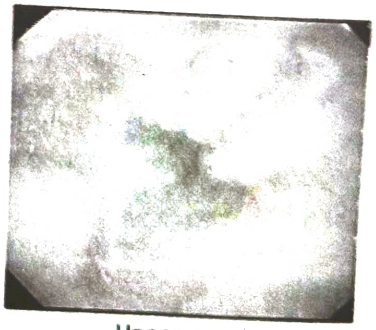
Fig. - 1



Mid Esophagus

Fig.- 2



Upper esophagus

Fig.-3

Original article

AN UNUSUAL PRESENTATION OF PAPILLARY THYROID CARCINOMA

Swayamsidha Mangaraj*, Debarchan Jena*, Arun Kumar Choudhury**,
Binoy Kumar Mohanty***, Anoj Kumar Baliarsinha****

ABSTRACT

Thyroid malignancies are relatively rare malignancies accounting for <1% of all cancers of body. Differentiated cancers of thyroid include papillary and follicular subtypes. Distant metastasis is a rare occurrence in papillary thyroid carcinoma which usually metastasize to lymph nodes in contrast to bone and lung metastasis seen with follicular thyroid carcinoma. Distant metastasis as a presenting feature of papillary thyroid carcinoma is seldom described in medical literature. We report a case of 56 year old female who was diagnosed to have papillary thyroid carcinoma while evaluating for painful swelling in the right iliac bone.

Case report

A 56 year old female presented with painful swelling in right iliac region and progressive difficulty in movement of right leg for last six months. It had resulted in complete restriction of movement of the affected limb at the time of presentation. There was no history of trauma, bone pain, hypertension, diabetes, malignancies in self or family members or any other chronic illness.

On examinat on, she had pallor, a pulse rate of 84/min and a blood pressure of 140/90 mm Hg. Neck palpation showed a small firm goiter with nodules in right lobe of thyroid and level IV and VI cervical lymphadenopathy on same side. On abdominal palpation, she had a tender soft tissue swelling of size 4 cm x 5 cm in right iliac region in continuity with iliac bone. Rest of systemic examination did not reveal any abnormality. CT scan showed presence of soft tissue mass invading the iliac bone (with mild post contrast enhancement) and extending on both sides of it [Figure 1 and 2]. There was presence of a linear fracture through the iliac bone. A guided FNAC from the lesion was suggestive of malignant deposits with a papillary pattern pointing towards the possibility of thyroid being the primary site. USG of thyroid revealed enlarged thyroid lobes (right >>left) with heterogeneous right lobe studded with iso to hypoechoic nodules with microcalcification. A FNAC from thyroid gland nodule was consistent with papillary thyroid carcinoma (PTC). FNAC from above said cervical lymph nodes was suggestive of metastatic disease. Biochemical investigations revealed normal thyroid function test. Blood sugar, renal function tests and liver function tests were normal. CT scan of head, chest and abdomen along with MRI of spine did not reveal presence of any additional metastatic deposit. Basing on the above findings she was diagnosed to have papillary thyroid carcinoma with distant bone metastasis. She was referred to department of experimental surgery for total thyroidectomy with modified radical neck dissection and resection of metastatic mass along with iliac bone in consultation with orthopedic surgeon. Post surgical plan included an ablative radioiodine I^{131} therapy and I^{131} WBS (whole body scan) for evaluation of possible tumor metastasis remnant.

Discussion

The most common thyroid malignancy, PTC constitutes 50% to 90% of differentiated thyroid cancers worldwide.[1,2] Although PTCs can occur at any age, most patients are between 30 and 50 years of age (mean age, 45 years).[1] Women are affected more frequently than men (female predominance, 60% to 80%).[2] Most primary tumors are 1 to 4 cm in size; they average about 2 to 3

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cm in greatest diameter.[1] PTC is frequently multifocal when it occurs in a single lobe, and it is bilateral in 20% to 80% of cases.[1] Only 1% to 7% of PTC patients have distant metastases at diagnosis.[2,3] Commonly reported osseous sites include the vertebrae, skull, pelvis and femur.[4]. The various subtypes of papillary carcinoma of thyroid include *follicular variant, diffuse sclerosing variant, tall cell variant and coloumnar cell variant.*

Follicular carcinomas have been reported to show a greater prevalence to metastasize distally than papillary or anaplastic subtypes. Whilst, lymph node metastases are often present at diagnosis, haematogenous spread is a rare and late event in case of PTC. Clinical symptoms of lung involvement are uncommon; in contrast, pain, swelling, or fracture occurs in more than 80% of patients with bone metastases.[1] Bone metastases are osteolytic and are often difficult to visualize on radiography or bone scintigraphy; bone involvement is better visualized by MRI. FDG-PET scanning is useful in these patients for determining the extent of disease and for prognostic assessment. The prognosis is favorable in differentiated thyroid carcinoma with a 10-year survival rate of 80-95% but this is decreased to 50% when distant metastases are present.[5] Furthermore, age at diagnosis of papillary thyroid carcinoma is a consistent prognostic indicator with the risk of recurrence and death increasing with age, especially in those over 40 years. [5]

Current guidelines advise bone metastases should be treated with a combination of surgery, external beam radiotherapy, and 131Iodine therapy. Improved survival and quality of life has been shown following removal of up to five bone metastases and hence surgical excision is recommended for accessible, solitary, isolated metastases.[5] Small metastases may be treated with radioiodine, but their persistence after two or three treatments should lead to surgery. A recurrence that is palpable or easily visualized with ultrasonography or CT scanning should be excised. Palliative surgery is required for bone metastases if there are neurologic or orthopedic complications or a high risk of such complications.[1] Radiofrequency ablation and cement injection may be effective alternatives.[1] Surgery may also be performed with a curative intent in patients who have only one or a few bone metastases. External radiotherapy is given to bone metastases visible on radiographs, even in the presence of iodine uptake. Among the factors responsible for distant metastases and increased mortality in patients with DTC are age over 45 years and the involvement of multiple organs, both are independently associated with cancer mortality. Bone metastases are associated with a poorer prognosis in comparison to metastases to the lung. In patients with bone metastases, whether isolated or associated with lung metastases, the prognosis is markedly poor with 10-year survival rates reported from 13-21%. [6]Nevertheless, recognizing the patterns of rare metastases from DTC has a significant impact on the clinical decision making and prognosis of patients. Because of its high sensitivity and specificity, post-therapeutic ^{131}I-WBS and ^{131}I single photon emission computed tomography/computed tomography (^{131}I-SPECT/CT) currently remain indispensable for the management of patients with DTC.

Our case represents a rare manifestatio of papillary thyroid carcinoma. Here a solitary dis nt symptomatic bone metastasis was the presenting fe re of PTC. It also underscores the fact that rarely di nt bone metastasis can also be seen in PTC at diagr is while it is a more common entity in follicular thy d carcinoma. Radiological differentials to the soft tis e mass invading iliac bone observed in our case inclu d chondrosarcoma, plasmacytoma and lymphoma. Sim ir to our case, S Siddiq et al have also reported a cas n which asymptomatic pelvic bone metastasis was e presenting feature of underlying PTC. [7]

Conclusion

Therefore, we would like to emphasize upon this rare manifestation of distant metastasis being sole presentation of underlying PTC. Moreover, while dealing with bone metastasis like our case, metastasis from thyroid should always be kept as differential even in absence of overt thyroid pathology. A meticulous evaluation and prompt management is pivotal for a better clinical outcome.

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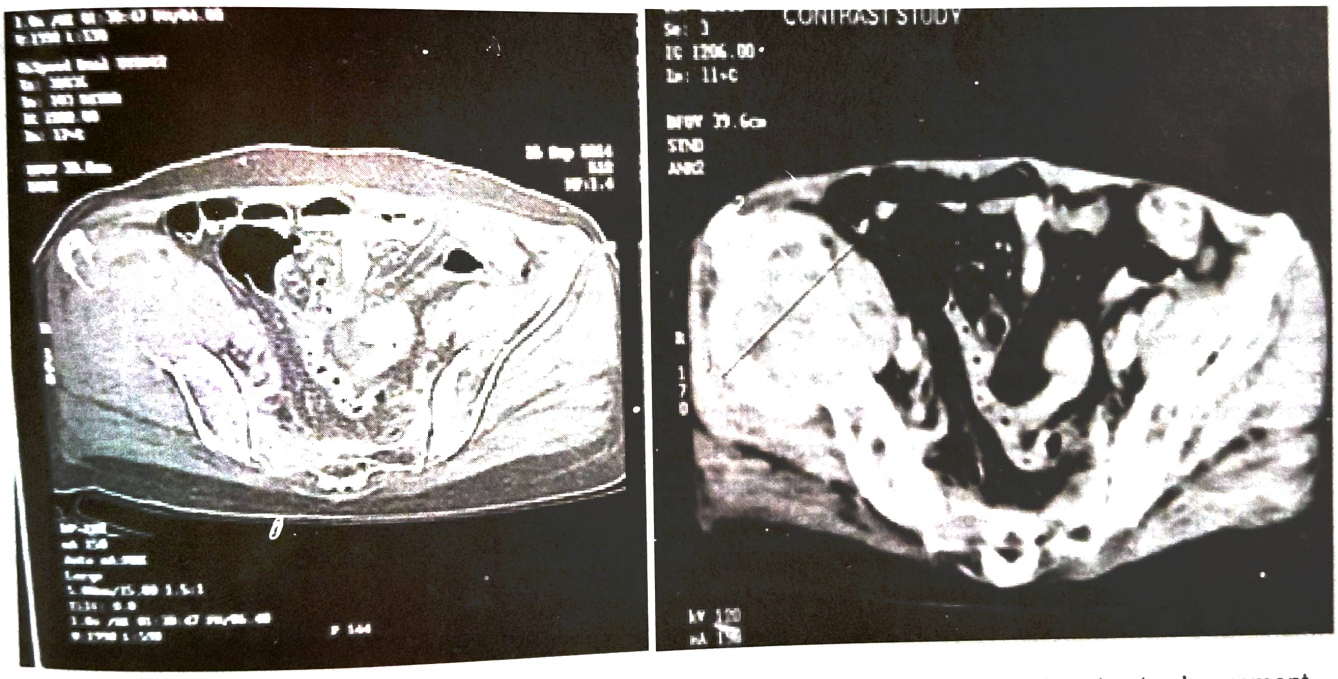

Figure 1 and 2- Soft tissue mass invading and destroying right iliac bone with mild post contrast enhancement.

Case report

RHINO-OCULO-CEREBRAL SYNDROME – A CASE REPORT

Biswajyoti Rath*, Ashok Kumar Mallick**

ABSTRACT

Mucormycoses are a group of invasive infections caused by filamentous fungi of the Mucoraceae family, with the rhinocerebral form of the disease being the most common in large case series. Uncontrolled diabetes and increased serum iron are regarded as the two leading predisposing factors for the development of the disease.We present a 43 year old male with recently diagnosed diabetes presenting with features of orbital apex syndrome and short term memory loss found to have rhino-oculo-cerebral mucormycosis on histopathological and radiological evaluaton .

Key word : diabetes , rhino-oculo-cerebral mucormycosis

Introduction:

Mucormycosis is an invasive fulminant fungal infection first described by Paulltauf A in 1885 .The disease may present with various manifestations, but there is a predilection for the paranasal sinuses.[1] ROCM is typically seen in patients with poorly controlled diabetes mellitus .[2]Despite the advances in diagnosis and treatment, invasive rhino-orbito-cerebral infection is still the most lethal clinical form of the disease.[3,4] The mortality rate is reported to be as high as 20% even if the diagnosis and aggressive treatment are not delayed.[5] The common presenting symptoms and signs are headache, fever, acute sinusitis, decreased vision, unilateral periorbital or facial swelling, facial pain, alterations in mental state and necrotic ulcer in the nasal or oral mucosa.[2,6] Although rare, orbital apex syndrome which presents with ptosis, proptosis, sensorial deficit and visual loss may be the initial manifestation of the disease

Case report

A 43 year male, a newly diagnosed diabetic presented with ocular pain for 1 month with sudden onset complete opthalmoplegia and loss of vision in his left eye . In the next day he developed altered sensorium . Emergency CT and MRI scan of brain was showed diffuse mass lesion involving the left nasal cavity with mucosal thickening ,heterogenous mass along the medial aspect orbit of left eye(figure 1-3) .A presumptive diagnosis of muormycosis was made and i.v. amphotericin was started and he improved .CNS examination showed left orbital apex syndrome and involvement of V ,V3 divisions. He was treated with insulin ,i.v. amphotericin . Endoscopic sinus surgery (frontal maxillary ethmoidal) done, histopathological diagnosis was mucormycosis . His ophathalmoplegia did not improve ,had impairment of short term memory , MMSE score was 23/30 On repeat MRI of brain T2Wi MRI showed hyperdense lesion (mycetoma) involving the medial aspect of left orbit (both intra- and extraconal components) with relative sparing of left optic nerve ,extending through optic canal backwards to involve the ipsilateral cavernous sinus with mucosal thickening of frontal ,left ethmoidal and sphenoidal sinuses and cerebritis of left medial temporal lobe.He was referred to ophalmologist for enucleation.

Discussion

Mucormycoses are a group of invasive infections caused by filamentous fungi of the Mucoraceae family. The most frequently isolated species is *Rhizopus oryzae* followed by *Rhizopus microsporus*, and *Absidia corymbifera*. [7]Based on clinical presentation and site of involvement six manifestations of the disease can be

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described: rhinocerebral, pulmonary, cutaneous,gastrointestinal, disseminated and localized infections not otherwise belonging in the previous categories[8].

The rhinocerebral form of the disease has been the most common in large case series[9], accounting for 30% to 50% of all cases of mucormycosis and has been predominantly associated with poorly controlled diabetes mellitus and diabetic ketoacidosis[10]. Other risk factors include immunocompromised state due to organ transplantation, hematologic malignancies, chronic corticosteroid treatment and haemochromatosis. Impaired neutrophil and phagocyte response and increased available serum iron are the two underlying conditions in the majority of mucormycosis patients.

The spread of rhinocerebral mucormycosis has not been adequately described. Based on their observations in a series of 10 patients, Hosseini et al regard the pterygopalatine fossa as a reservoir of the disease through which it can spread to neighboring structures including the retroglobal space of the orbit and infratemporal fossa.

Rhinocerebral mucormycosis most commonly presents in an acute setting, reminiscent of sinusitis or periorbital cellulitis[8]. Facial pain and unilateral facial swelling are also important parts of the clinical picture of the patient with variable grade fever being present although not in all cases. The only disease specific finding described in the relative literature is blackened necrotic eschars of the nasal mucosa or palate. However, in large case series it has been noted in less than half of the patients. The clinical picture may further progress to include unilateral opthalmoplegia representing involvement of the orbital contents either by infection or vascular compromise. Contralateral ophtalmoplegia suggests cavernous sinus thrombosis, although bilateral rhinocerebral mucormycosis albeit rareshould be considered. Progression of the infection to central nervous system is heralded by development of confusion and disorientation, with bloody nasal discharge also reported as a potentially early sign of disease extension to the brain. Central nervous system damage may also result from cavernous sinus thrombosis and internal carotid artery encasement leading to cerebral infractions[12] and hematogenous dissemination of the disease to other organ sites.

Early diagnosis of rhinocerebral mucormycosis is considered a step of grave importance . Symptoms compatible with mucormycosis in a predisposed patient call for prompt initiation of treatment[13] while appropriate steps are taken towards confirmation of diagnosis. Histopathological examination of surgical specimens can confirm the clinical diagnosis with the appearance of right-branching aseptate hyphae, which are considered typical of mucor species, along with evidence of angioinvasion and tissue necrosis. Fungal cultures can provide further confirmation. Imaging methods are of little help during the early stages of rhinocerebral mucormycosis with thickening of the sinus mucosa or extraocular muscles[8]. CT scans can be used to evaluate the progression of disease .MRI scans may be more accurate in evaluating the extent of disease due to fungal invasion of soft tissues . Both CT and MRI scans should be frequently obtained due to the rapidity of disease progression and for appropriate planning of surgical interventions. Reversal of underlying predisposing conditions is of paramount importance. Euglycemia should be restored rapidly and any immunosuppressive conditions reversed if possible. The surgical approach should be based on the clinical state of the patient with timely interventions for appropriate debridement of infected areas. Polyene based therapy (amphotericin B)as the main course of action. Iron chelation therapy and posaconazole should be considered in cases of refractory infection or polyene intolerance.

Cases of localized sinonasal rhinocerebral mucormycosis have been reported to have low mortality rate(10%). Progression of the disease is associated with worse prognosis, with. CNS involvement considered fatal.In conclusion, rhinocerebral mucormycosis remains still a poorly understood disease with high mortality rate.

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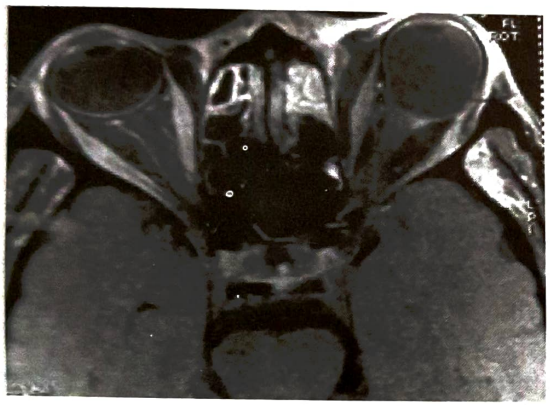

FIGURE 1 – T2Wi MRI showing hyperdense lesion (mycetoma) in the left ethmoidal ,maxillary and frontal paranasal sinuses sparing the left orbit

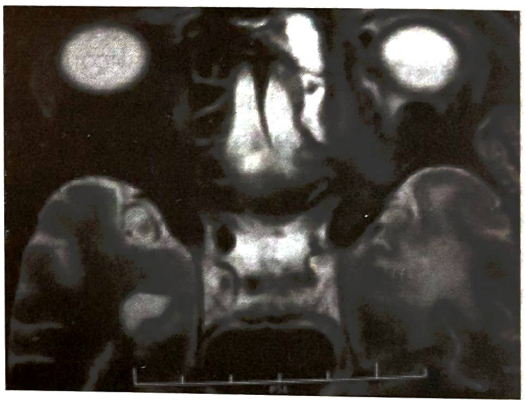

FIGURE 2 – T2Wi MRI showing hyperdense lesion (mycetoma) involving the medial aspect of left orbit (both intra- and extraconal components) with relative sparing of left optic nerve ,extending through optic canal backwards to involve the ipsilateral cavernous sinus and enhancement of extra-ocular muscles ,mucosal thickening of frontal ,left ethmoidal and sphenoidal sinuses

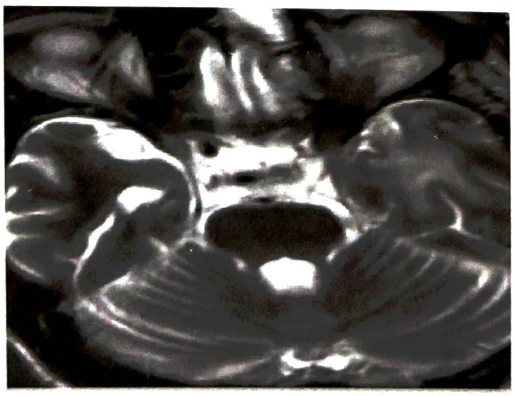

FIGURE 3 - T2Wi MRI showing cerebritis involving left temporal lobe

Case Report

FAMILIAL AMYLODOSIS POLYNEUROPATHY- TWO CASE REPORTS WITH VARIED PRESENTATIONS

*B.K.Barik, **.S.S.Jena, ***Dr.K.K.Jena, ***Dr. Amit Kumar, ****S.C.Dash

ABSTRACT

We report two rare cases of Familiai amyloidosiswith varied presentations.

KEY WORDS:

Amyloidosis, autosomaldominantdisorder, transthyretin gene, *autonomic dysfunction,* multi system disorder.

INTRODUCTION:

Familial amyloidosis is a rare disease an autosomal dominant inherited disorder caused by abnormal deposition and accumulation of proteins in the tissues of the body. Amyloid deposits are primarily made up of protein fibers known as amyloid fibrils. These amyloid fibrils are formed when normally soluble body proteins aggregate (clump together) and then remain in the tissues instead of safely going away. About 30 different proteins are known to form amyloid deposits in humans. These amyloid forming ("amyloidogenic") proteins are known as "precursor proteins." Amyloid deposits cause disease by gradually accumulating within organs and thereby disrupting the structure and damaging the function of the affected tissues. Different types of amyloidosis are named according to the precursor proteins which form the amyloid fibrils. All have the initial "A" denoting amyloidosis and letter(s) identifying the particular precursor protein which forms amyloid fibrils within the amyloid deposits. In ATTR amyloidosis, a blood protein called transthyretin (TTR) is the amyloid precursor protein that forms the amyloid deposits. Familial amyloid polyneuropathy (FAP) is one of three distinct, different types of ATTR amyloidosis. It is the most commonly recognized form of hereditary systemic amyloidosis worldwide.

Transthyretin (TTR)[3]- —Transthyretin (TTR) is a normal blood protein, present in everybody. In healthy people, normal, so-called "wild-type" TTR functions as a transporter of thyroid hormone and vitamin A (retinol) within the bloodstream, hence the name: "trans-thy-retin". Most TTR in the body is made in the liver and a small amount is made in the eye and the brain. People who are born with inherited mutations (alterations) in the TTR gene produce abnormal, ("variant") TTR throughout their lives. The "variant" TTR protein is amyloidogenic (amyloid forming). Over the course of several decades, usually after the age of 30 and often much later, people with inherited TTR gene mutations may develop symptoms of disease caused by the build-up of amyloid deposits. More than 100 different mutations in the TTR gene have been observed. Many of these can cause the disease called familial amyloid polyneuropathy (FAP), in which amyloid deposits containing "variant" TTR affect the nerves, often the heart, and sometimes the kidneys and eyes. Some people with inherited TTR gene mutations develop amyloid cardiomyopathy in which amyloid deposits containing "variant" TTR affect only the heart. Some people without any mutations in the TTR gene develop senile systemic amyloidosis with advancing age in which amyloid deposits containing normal "wild type" TTR affect only the heart.

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The symptoms of FAP may appear as early as age 20, or as late as age 80. Symptoms may include: Peripheral neuropathy, autonomic neuropathy, heart failure that results from stiffening of the heart due to amyloid deposits (restrictive cardiomyopathy) and symptoms due to amyloid deposits in the: eye, kidneys, thyroid gland, adrenal glands, blood vessels.

CASE REPORT-1.

SKM35yr gentle man from Dhenkanal , Odisha came with complain of abnormal uncontrolled movements of limbs, unable to walk, diarrhea, irrelevant speech for the past 3 months.

He is symptomatic since 2006. Insidiously he complained of intermittent postural giddiness, and black outs upon standing from supine and sitting position. Then he developed urinary urgency, frequency, urge incontinence, bed wetting in the night, erectile dysfunction and altered bowel habit after 3 year. He complained of disturbances of sweating (increased sweating also in winter), reduced lacrimation, dryness of tongue, change in the taste, migratory transient weakness and numbness in the limbs and face. In 2010, he developed insidious weakness in lower limb > upper limbs with positive sensory symptoms. 2011 he had a head injury with neuro imaging revealed sub arachnoid hemorrhage left parietal area. It was managed conservatively. Since then he has intermittent headache with nausea and vomiting. He has intermittent low grade fever, without any specific localizing signs. Progressively he required support to walk from 2011 and he was bed bound since last two years. He is having continuous indwelling urinary catheter for past four years.There is no loss of consciousness, seizures, focal neurological deficit.

Family history revealed that his father had a similar illness and he expired at the age of 39 years. His younger brother also suffers from postural giddiness, urinary urgency, erectile dysfunction and episodic vomiting since three years.

On examination he was conscious. General examination revealed peri-orbital puffiness, mild pallor, pitting pedal edema, and ecchymotic patches in peri-orbital region, trunk and extremities. He didn't have hepatospleenomegaly. There was orthostatic fall of blood pressure (Supine 130/70 Hg , sitting -70/50 mm of Hg.).

Neurological Examination revealed impaired attention and inability to perform complex calculation in mental status examination. Pupil is mid dilated and not reacting to light with defective color vision to red and green. Visual acuity and fundus was normal. Other cranial nerves were normal. Motor system examination revealed hypotonia in the limbs and ankle contracture and generalized arflexia. Joint Position Sense and vibration sense were absent in limbs. Cerebellar signs were absent.

Investigations showed hematological, renal, hepatic parameters were within normal range. Serum electrophoresis normal. 2-D ECHO suggest restrict e cardiomyopathy. CSF study showed protein 437gm , sugar 59mg %, cells 5 lymphonuclear cell. Ner e conduction study suggest severe motor and sens axonal neuropathy with autonomic involvement.24h urinary protein showed subnephrotic proteinur Abdominal fat pad aspirate and punch skin biopsy of lo limb revealed amyloid deposits. MRI of brain and spi showed leptomeningeal enhancement with cerebr atrophy. Sural nerve biopsy also showed amylo deposition. Vasculitis markers were negative. Assay f alpha galactosidase enzyme(Fabry's disease) usin fluorometry method using artificial substrate was 25.9 nmol/hr/mg(> 69.87 nmol/hr/mg). Targeted Mutation analysis for gene IKBKAP for familial dysautonomia(Riley day's syndrome) were negative. The hormonal analysis were in normal range. The Schrimer's test showed decreased lacrimation.

In view of progressive autonomic nervous dysfunction, generalized areflexia, restrictive cardiomyopathy with similar illness in his younger brother, father, a familial autosomal dominant disorder was thought of. His abdominal fat, skin, nerve biopsy revealed amyloid deposits. So familial amyloid polyneuropathy was confirmed. He was on symptomatic treatment and possible liver transplant was needed for his survival.

CASE REPORT-2

S M, 32 yr old gentle man came with complain of vomiting, giddiness and fall whenever he stands and unable to walk and bed wetting. He is smptomatic since 2012. Insidiously he complained of intermittent postural giddiness, and black outs upon standing from supine and sitting position. Then he developed similar urogenital disturbances. For the past one year, he developed insidious weakness in lower limb > upper limbs with positive sensory symptoms. He has altered behavioral disturbances and reduced cognition for the past nine months. He is independent in activity of daily living. He is on indwelling urinary catheter since last six months due to incontinence of urine.There is no loss of consciousness, seizures, focal neurological deficit. Family history showed that his father had a similar illness and he expired at the age of 39 years. His elder brother also suffers from postural giddiness, urinary urgency, erectile dysfunction and episodic vomiting since eight years and now bed bound.

On examination he is conscious, oriented. He didn't have hepatospleenomegaly. There is orthostatic fall of blood pressure (Supine 130/70 Hg , sitting -70/50 mm of Hg.). MMSE -23/30. He has impaired attention and parietal lobar dysfunction. He could not appreciate primary taste sensation. Pupil is mid dilated and not reacting to light. Visual acuity and fundus is normal. Other cranial nerves are normal. Motor system examination revealed hypotonia in the limbs and ankle contracture and normal deep tendon reflexes. JPS and vibration sense is impaired in limbs. Cerebellar signs are present.

Investigations showed that his hematological, renal, hepatic parameters were within normal range. Serum electrophoresis normal. 2-D ECHO suggest left ventricular hypertrophy with normal ejection fraction.CSF study showed protein 437gm%, sugar 59mg %, cells 5 lymphonuclear cell. Autonomic function test showed severe autonomic dysfunction. Nerve conduction study suggest severe motor and sensory axonal neuropathy with autonomic involvement. USG abdomen showed b/l hydroureteronephrosis with chronic cystitis. 24hr of urinary protein showed subnephrotic proteinuria. EEG showed diffuse slowing. Abdominal fat pad aspirate and punch skin biopsy of lower limb revealed amyloid deposits. MRI of brain and spine showed leptomeningeal enhancement in brain and spinal cord with cerebral atrophy.Sural nerve biopsy also showed amyloid deposition. Vasculitic markers were negative.

In view of progressive autonomic nervous dysfunction, generalized areflexia, restrictive cardiomyopathy with similar illness in his younger brother, father, a familial autosomal dominant disorder was thought of. His abdominal fat, skin, nerve biopsy revealed amyloid deposits. So familial amyloid polyneuropathy was confirmed. He was on symptomatic treatment and possible liver transplant was advised.

DISCUSSION:

FAP was first described in 1952 in a number of families in Portugal. Since then it has been diagnosed in families from Japan, Sweden and County Donegal in North-West Ireland. Worldwide, most people with FAP have ancestors originating in one of these regions. In the UK, FAP is most common in people with Irish ancestry. It is estimated that 1% of the people in County Donegal have a TTR gene mutation.

The familial amyloid polyneuropathies (FAP) is complex and requires a neurological and cardiological multidisciplinary coverage and also symptomatic treatment.

It includes specific treatments to control the progression of the systemic amyloidogenesis, the symptomatic treatment of the peripheral and autonomic neuropathy (digestive, urinary, sexual, postural hypotension) and the treatment of organs severely involved by amyloidosis (heart, eyes, kidneys). First line specific treatment of met30 TTR-FAP is liver transplantation (LT) which allows to suppress the main source of mutant TTR, to stop the progression of the neuropathy in 70 % of cases at long-term (with an experience of 18 years) and to double the median survival. In case of severe renal or cardiac insufficiency, a double transplant kidney-liver or heart-liver can be discussed. The tafamidis(in temporary

authorization of use in France) is a stabilizing medicine of the tetrameric TTR which showed in very early stages of met30 TTR-FAP short-term capacities to stop the progress of the peripheral neuropathy in 60 % of the cases versus 38 % with placebo. It should be proposed in case of contraindication of TH (age>70 years [20 % of the cases]), of very early stages (very low NIS-LL score), or for the period of wait of LT. Other innovative medicines issued from biopharmaceutical companies have been developed to block the hepatic production of both mutant and wild TTR which are noxious in the late forms NAH (>50 years old) (RNAi [RNA interference] therapeutics, AntiSensoligonucleotids), for removing the amyloid deposits (monoclonal antibody anti-SAP), or to slow down the formation of deposits of TTR and amyloidosis (combination of doxycycline-TUDCA). Clinical trials should be first addressed to the patients with a late onset of FAP or non-met30 TTR-FAP who are less responding to LT and patients with contraindications in the LT. Initial cardiac assessment and periodic cardiac investigations are important for the FAP according to the frequency of cardiac impairment which is responsible of high rate of mortality. Conduction disorders (atrio-ventricular blocks) require the implantation of a pacemaker in about one third of the cases during the evolution of the disease. A myocardial infiltration is detected in two third of the cases and is for a long time latent; it remains often limited to a diastolic dysfunction which can be responsible for hemodynamical difficulties during the LT; it evolves sometimes, late, towards a systolic dysfunction of bad prognosis. A combined liver-heart transplantation is proposed in cases of severe cardiac involvement which are contraindication to the LT only, essentially in forms "not met30". In every case of FAP, a regular cardiological follow-up is required for life, because of the progress of the cardiac involvement, which is not always stopped by the liver transplantation. The symptomatic treatments are indispensable to improve the quality of life of the patients: neurogenic pains, urinary disorders, liqueurs, sexual impotence, postural hypotension. The familial screening of the carriers of the TTR gene mutation and their regular follow-up by appropriate clinical examination and complementary investigations are major to detect early the onset of the disease to start as soon as possible specific therapy.

Most of the TTR in the bloodstream is made in the liver. Liver transplantation is therefore a treatment option for some patients with FAP. The liver which makes the abnormal "variant" TTR is removed and replaced by a donor liver making normal, "wild type" TTR. The aim is to prevent the formation of further amyloid deposits by reducing the supply of the amyloid-forming precursor TTR. Unfortunately, amyloid deposits in the heart sometimes continue to progress even after liver transplantation. It seems that amyloid deposits composed of abnormal (variant) TTR, present before liver transplantation, act as a template encouraging deposition of normal TTR as amyloid. Thus the normal TTR protein ("wild type" TTR) produced by the new liver builds up on top of the existing 'variant' TTR amyloid deposits. This problem has appeared most often in older patients with variants other than TTR Val30Met.

Combined heart and liver transplant has been performed in a few dozen patients with FAP around the world. This operation is only an option for a minority of patients, and it carries significant risks.

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Fig-1. MRI BRAIN SHOWING LEPTOMENINGEAL ENHANCEMENTS

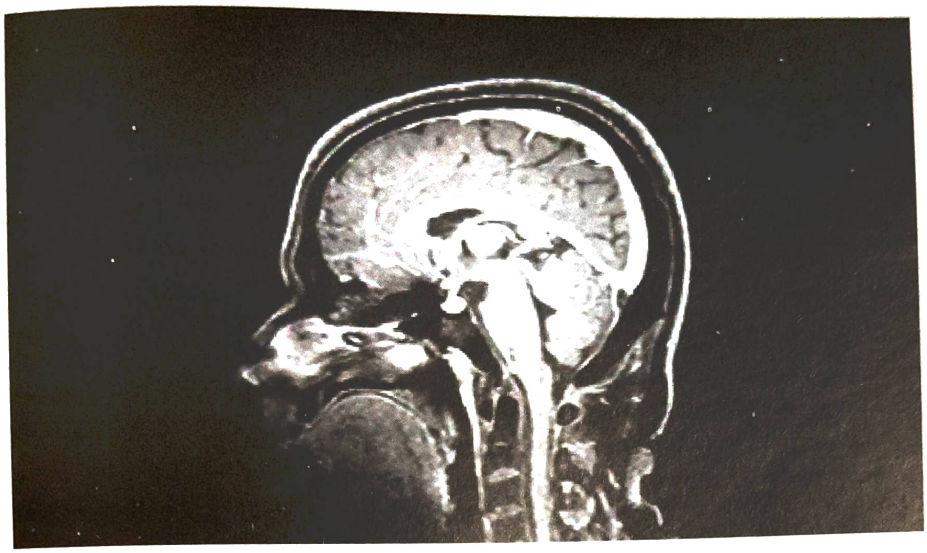
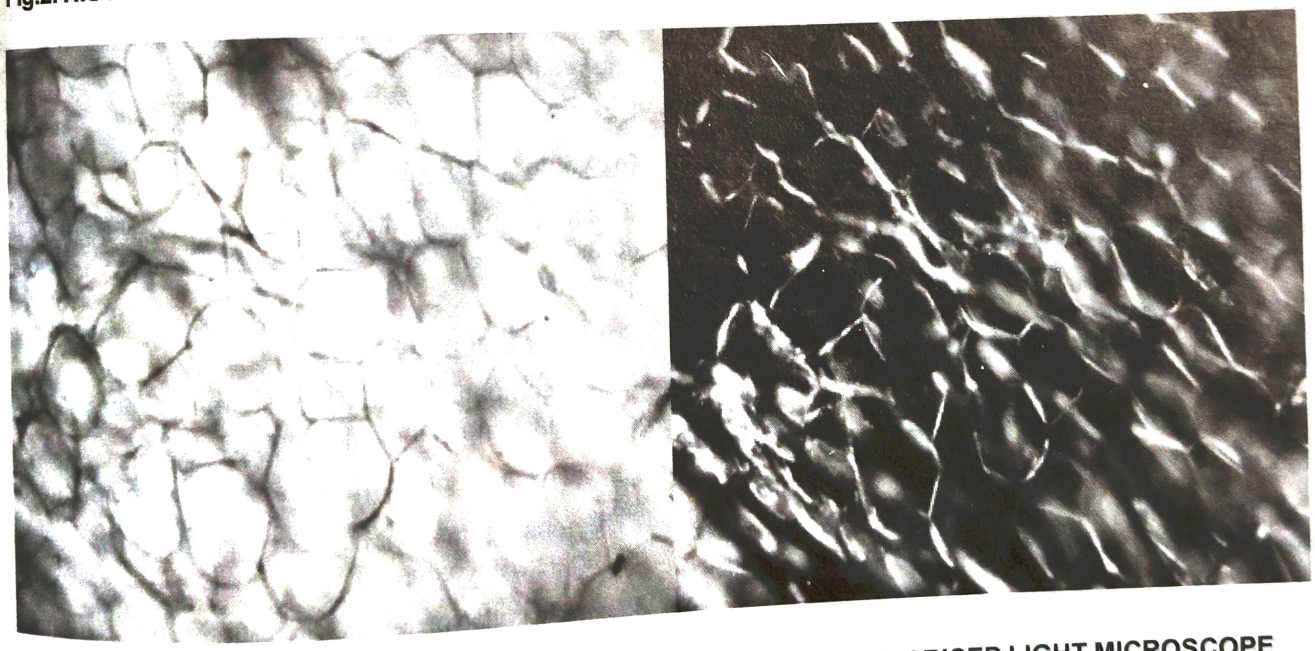


Fig.2. HISTOPATHOLOGY PICTURE OF THE FAT BIOPSY



A) FAT BIOPSY WITH CONGO RED STAIN

B) UNDER POLARISED LIGHT MICROSCOPE

GUIDELINES FOR TREATMENT OF DENGUE FEVER

*Manoj Kumar Kissan, *Ashutosh Ratha

NATIONAL VECTOR BORNE DISEASE CONTROL PROGRAMME(NVBDCP) - 2014

INTRODUCTION

Dengue is the rapidly spreading mosquito- borne viral disease of mankind.The agent of dengue i.e. dengue virus belongs to family flavivirus.There are four serotypes of dengue virus designated as DENV-1,DENV-2,DENV-3,DENV-4.Dengue is transmitted from infected person to other by bite of infected female aedes mosquito.Aedes aegypti is the main vector in most urban areas.Other are Aedes albopictus,Aedes polynesiensis,Aedes niveus.

CLINICAL CRITERIA FOR DENGUE FEVER(DF)/ DENGUE HAEMORRHAGIC FEVER(DHF)/

DENGUE SHOCK SYNDROME(DSS)

Clinical features of DF:

Acute febrile illness of 2-7 days duration with two or more of the following manifestation: headache , retro-orbital pain,myalgia,arthralgia,rash,haemorrhagic manifestations.

Dengue haemorrhagic fever(DHF):

a)A case with clinical criteria of DF

PLUS

b)Haemorrhagic tendencies evidenced by one of the following:

1.positive torniquet test

2.petechiae,ecchymosis,purpura

3.bleeding from mucosa,gastrointestinal tract,injection sites or other sites

PLUS

c)Thrombocytopenia(platelet count less than 1 lakh/cumm)

PLUS

d)Evidence of plasma leakage due to increase vascular permeability,manifested by one or more of the following:

1. a rise in average haematocrit(Hct) for age and sex more than or equal to 20%
2. a more than 20% drop in haematocrit following volume replacement treatment compared to baseline
3. signs of plasma leakage(pleural effusion, ascites, hypoproteinaemia)

Dengue shock syndrome(DSS): All the above criteria for DHF with evidence of circulatory failure manifested by rapid and weak pulse and narrow pulse pressure,hypotension for age,or cold and clammy skin and restlessness.

CASE DEFINITION

Probable DF/DHF

A case compatible with clinical criteria of dengue fever during outbreak OR Non ELISA based NS1 antigen/ IgM positive

Confirmed dengue fever

A case compatible with clinical criteria of dengue fever with atleast one of the following:

1.Isolation of dengue virus from serum,plasma,leucocytes

2.Demonstration of IgM antibody titre by ELISA positive in single serum sample

3.Demonstration of dengue virus antigen in serum sample by NS1-ELISA

4.IgG seroconversion in paired sera after two weeks with fourfold increase in IgG titre

5.Detection of viral nucleic acid by polymerase chain reaction(PCR)

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GRADING OF DF/DHF

DF: Fever of 2-7 days duration with two or more of the following manifestation: headache,retro-orbital pain,myalgia,arthralgia with or without leucopenia,thrombocytopenia and no evidence of plasma leakage.

DHF I: Above criteria plus positive torniquet test and evidence of plasma leakage.Thrombocytopenia with platelet count less than 1 lakh/cumm and hematocrit rise of more than 20% above baseline.

DHF II: Above plus some evidence of spontaneous bleeding in skin or other organ(black tarry stool,gum bleeding,epistaxis) and abdominal pain.Thrombocytopenia with platelet count less than 1 lakh/cu.mm and hematocrit rise of more than 20% above baseline.

DHF III(DSS): Above plus circulatory failure(weak rapid pulse,narrow pulse pressure<20mm hg,hypotension,cold clammy skin,restlessness).Thrombocytopenia with platelet count less than 1 lakh/cumm and hematocrit rise of more than 20% above baseline.

DHFIV(DSS): Profound shock with undetectable blood pressure or pulse.Thrombocytopenia with platelet count less than 1 lakh/cumm and hematocrit rise of more than 20% above baseline.

TREATMENT

MANAGEMENT OF DENGUE FEVER:

I) Management of DF is symptomatic and supportive.

II) Bed rest during acute phase.

III) Use cold sponging to keep temperature below 38.5 degree celcius.

IV) Antipyretics may be used to lower the body temperature.Paracetamol is preferred. Doses are 10mg/kg/dose for children and 500mg/dose,that can be repeated every 6 hourly depending upon fever and bodyache.

V) Oral fluid and electrolyte therapy is recommended for excessive vomiting and sweating.

VI) Patient should be monitored for 24 to 48 hours after they become afebrile for development of complications.

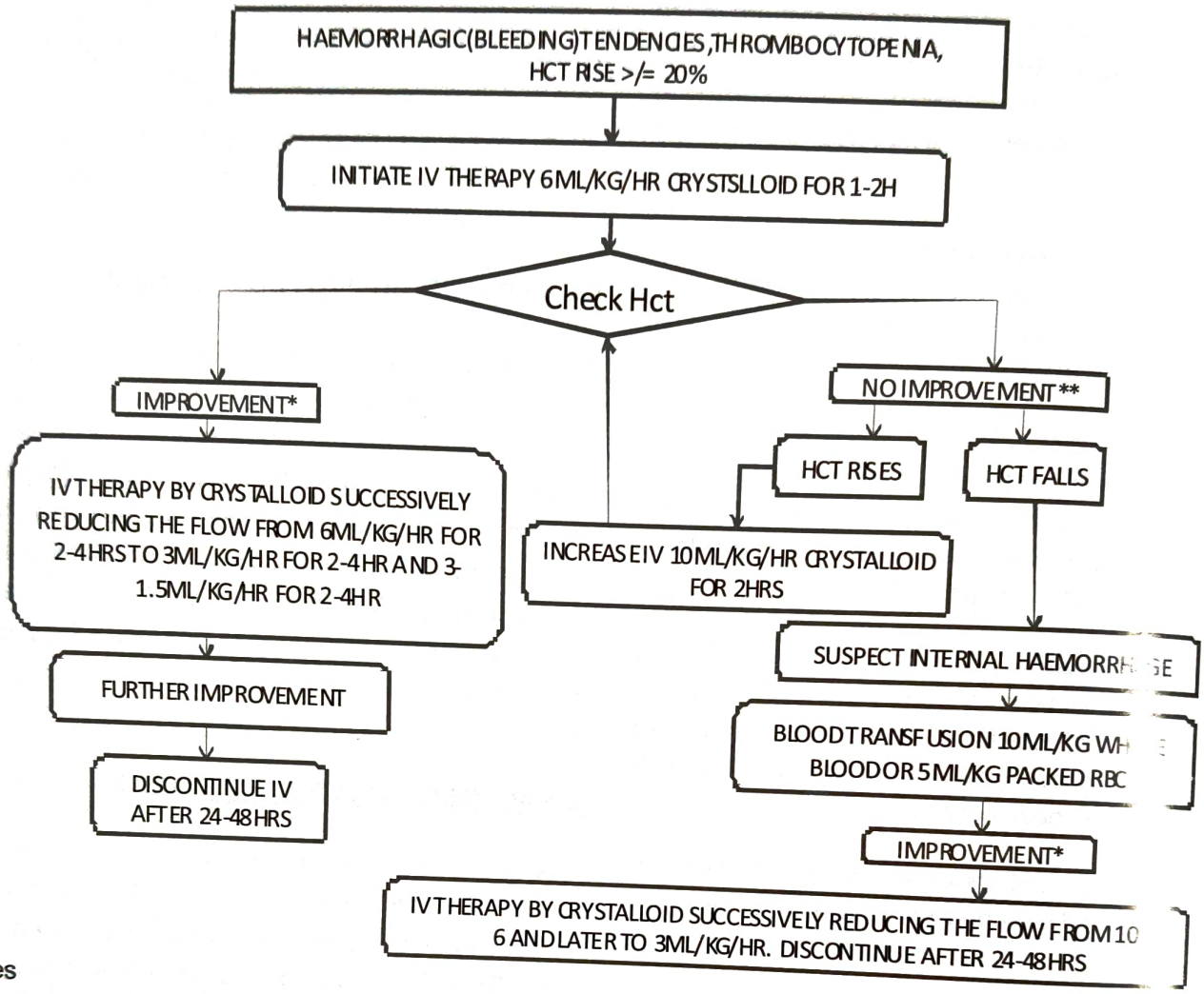
MANAGEMENT DURING FEBRILE PHASE:

Paracetamol should be used to keep temperature below 39 degree celcius.oral rehydration solution(ORS) and/or fruit juices are preferred over plain water.Intravenous fluid is used in case of persistently vomiting patient or patient refusing oral feeding.Patient should be closely monitored during critical period that usually occurs during transition from febrile to afebrile stage,i.e. after third day of illness.Haematocrit should be determined daily specially from third day until patient remain afebrile for one to two days.

MANAGEMENT OF DHF GRADE I AND II:

Any fever with thrombocytopenia,high haemoconcentration and present with abdominal pain,tarry black stool,epixtasis,bleeding from gums etc.need to be hospitalized. All patients should be looked for signs of shock that occurs usually after third day of illness.Rise of haemoconcentration indicates plasma leakage and volume loss for which proper fluid management is instituted.If signs of shock persists despite treatment then the management for grade III/IV DHF/DSS should be started.Oral rehydration ,paracetamol along with cold sponging is given as described above.

VOLUME REPLACEMENT ALGORITHM FOR PATIENT WITH DHF GRADE I AND II



Notes

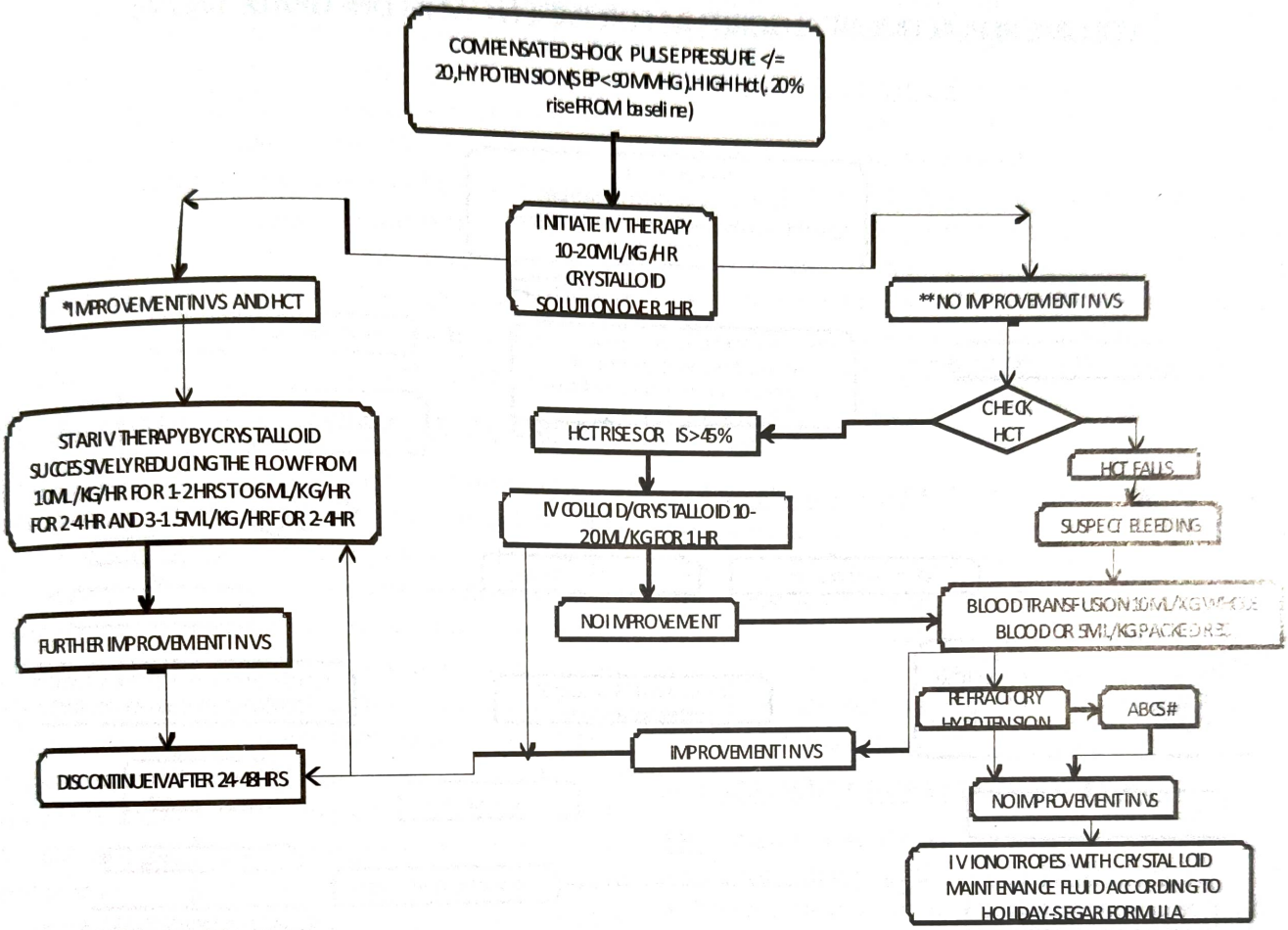
*Improvement-Hct falls,pulse rate & blood pressure stable,urine output rises

**No improvement-Hct or pulse rises,pulse pressure fall below 20mm HG,urine output falls

MANAGEMENT OF SHOCK(DHF GRADE III/IV):

Immediately after hospitalization haematocrit value,platelet count,and vital signs should be examined to assess patient's condition and iv fluid should be replaced.If the patient had already received 1ltr of fluid,it should be changed to colloidal solution preferably dextran 40 or if haematocrit further decreases then whole blood transfusion 10-20ml/kg/dose should be given.In case of persistent shock after initial resuscitation with iv fluid,plasma expander and haematocrit continues to decline then internal bleeding is suspected.And in this case small volume of blood transfusion at 10ml/kg/hr is given.Oxygen should be given to all patient in shock.

VOLUME REPLACEMENT ALGORITHM FOR PATIENT WITH DHF GRADE III



CRYSTALLOID:Normal saline,Ringer lactate

COLLOID:Dextran 40/Degraded gelatine polymer(polygeline)

#ABCS-Acidosis,Bleeding,Calcium(Na++& K+),Sugar

Notes:

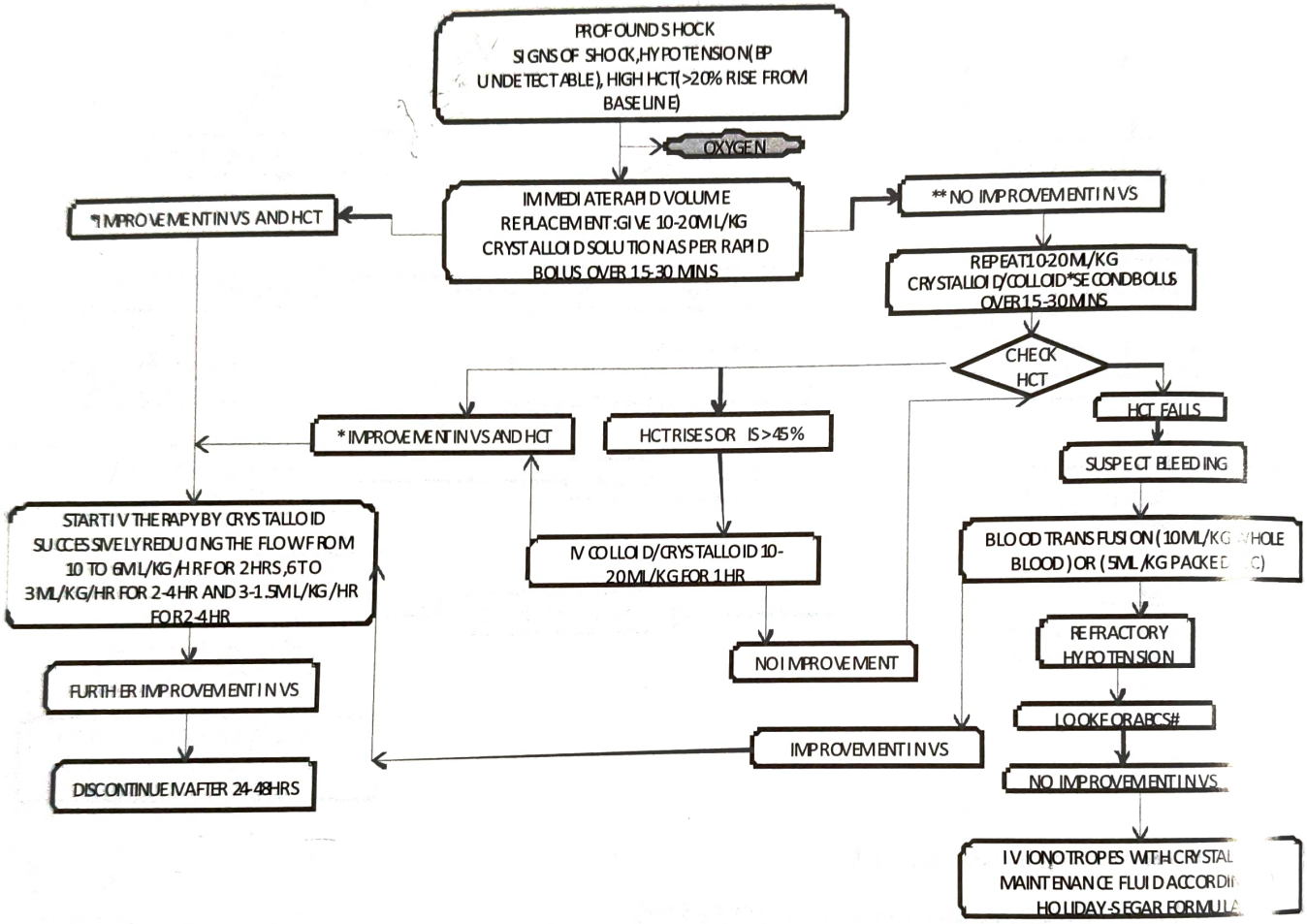
*Improvement :Hct falls,pulse rate & blood pressure stable,urine output rises

**No improvement :Hct or pulse rate rises,pulse pressure falls below 20mm Hg, urine output falls

- Unstable vital signs : Urine output falls, signs of shock
- In case of acidosis , hyperosmolar or ringer lactate solution should not be used.
- Serial Hct and platelet determination : Drop in platelet and rise in Hct are essential for diagnosis of DHF.

Cases of DHF should be observed every hour for vital signs and urine output.

VOLUME REPLACEMENT ALGORITHM FOR PATIENT WITH DHF GRADE IV(DSS)



CRYSTALLOID:Normal saline,Ringer lactate

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- Unstable vital signs : urine output falls, signs of shock
- In case of acidosis , hyperosmolar or ringer lactate solution should not be used.
- Serial Hct and platelet determination :drop in platelet and rise in Hct are essential for diagnosis of DHF.
- Cases of DHF should be observed every hour for vital signs and urine output.

MANAGEMENT OF SEVERE BLEEDING:

In case of severe bleeding patient should be hospitalized ,cause of bleeding and site of bleeding is determined and attempts are made to stop bleeding.Sometime internal bleeding like GI bleed occurs and patient present with profound shock,in that case urgent blood transfusion is given.If blood is not available then iv fluid and plasma expanders can be used.If patient is having thrombocytopenia and active bleeding then blood transfusion and later platelet transfusion is given.In more severe bleeding other causes of bleeding like coagulopathy and severe liver dysfunction are ruled out.

MANAGEMENT OF DF WITH CO-MORBID ILLNESS:

Dengue viral hepatitis-some patients may have liver function abnormality due to dengue virus infection.They may have high AST/ALT ratio or prolonged PT.Hepatic involvement in DF is commonly found in patients having pre-existing liver diseases like cirrhosis of liver,chronic viral hepatitis and hepatomegaly due to any other cause.Patient may also develop hepatic encephalopathy due to hepatic failure.Patients with chronic liver disease having low serum albumin have more risk of developing severe DHF and bleeding.GI bleeding is common in these condition and patient may develop DSS.In this case appropriate fluid management and blood transfusion is neccessary.And patients having hepatic encephalopathy should be treated with hepatic failure regimen and those having prolonged PT intravenous vitaminK1 can be given.

Dengue myocarditis-Myocarditis in DF is rare that can give rise to development of DSS.Cardiac complication may be seen in presence of coronary artery disease(CAD),hypertension, diabetic and valvular heart disease.Shock in these group of patient sometimes become difficult to treat due to cardiac Dysfunction.Some patients with cardiac diseases may be taking aspirin and antiplatelet drugs which can further aggravate the bleeding and these drugs should be stopped.Proper fluid management is required in these group of patients as they can develop congestive cardiac failure that can lead to pulmonary edema as a result of excessive fluid infusion.

DF in diabetes-Sometimes diabetic patients may develop severe complication due to dengue infection especially among those who have diabetic retinopathy, nephropathy, neuropathy,cardiomyopathy, vasculopathy and hypertension. Strict blood sugar control is recommended.

Renal involvement in DF-Acute tubular necrosis(ATN) can occur in DSS that can lead to acute kidney injury(AKI).It may be reversible if shock is treated within a short span of time.Urine output is regularly monitored as it is helpful in assessing renal function.Other investigation like routine urine examination,blood urea& creatinine,GFR,ABG should be performed in severe DF/ DHF.Dengue patients may develop DHF who suffers from diabetic nephropathy,hypertensive nephropathy,connectve tissue disorders(SLE) and other pre-existing chronic diseases.

CNS involvement in DF-Altered sensorium can occur in dengue patient due to many causes like DSS,intracranial bleed,electrolyte imbalance,hypoglycemia,hepatic encephalopathy and also due to CNS infection by dengue virus.But this encephalopathy is clinically difficult to distinguish it from cerebral malaria and enteric encephalopathy during epidemics.Dengue serology(IgM) in CSF confirms the diagnosis.

MANAGEMENT OF DF WITH CO-INFECTION:

TB-Patients may develop breathlessness,massive hemoptysis,pleural effusion and ARDS.If patient is on ATT,then close monitoring should be done for respiratory complication to prevent mortality and morbidity.

HIV-HIV patients infected with dengue may develop complications like DHF,DSS,significant bleeding and organ involvement.Prognosis is poor among HIV & AIDS patient with oppertunistic infection and very low CD4 count.Multiorgan failure is the main reason of mortality in DF of these group of patient.Treatment should be undertaken with a HIV specialist consultation.

Malaria-Malaria is a common co-infection with dengue.Early diagnosis of malaria is done and prompt treatment with antimalarial is started to prevent complications.

Chikungunya-Acute complications are sometime severe in DF in presence of chikungunya.In case of predominant joint involvement in dengue patient,proper investigation is done early to rule out chikungunya.

Enteric fever-Water borne diseases like enteric fever and gastroenteritis are more common during monsoon and so as dengue.In the initial phase of DF patient may be more complicated with typhoid fever if antibiotic is started late.Hence,blood culture is sent early for diagnosis of enteric fever in highly suuspicious cases.

MANAGEMENT OF DENGUE IN PREGNANCY: Dengue in pregnancy carries risk of more bleeding,foetal complication,low birth weight and premature birth.Risk of vertical transmission also increases.Pleural effusion,ascites,hypotension are common.Multiorgan failure like renal failure,hepatic failure,respiratory failure can also occur.IV fluid should be used carefully so as to prevent pulmonary edema.Regular BP monitoring,frequent platelet count, and coagulation profile testing should be performed in DF in pregnant women. DF in pregnancy should be taken seriously to reduce the morbidity and mortality of mother as well as the foetus.

MANAGEMENT OF DENGUE IN NEONATES: After delivery the baby may go in to shock which is misdiagnosed as septic shock or birth trauma.In that case history of febrile illness during pregnancy may help to diagnose DSS in neonates and infants.Close observation,symptomatic and supportive treatment remains the mainstay of the treatment.

MANAGEMENT OF DENGUE IN INFANTS:

Management of dengue among infants without warning signs-Oral rehydration with ORS,fruit juice and other fluid containing electrolytes and sugar along with breast feeding and formula feed are encouraged.The parents are instructed to bring back the child to hospital if any of the warning sign develops.

Management of dengue among infants with warning signs-In this case intravenous fluid is indicated.Initially ringer's lactate(RL),ringer's acetate(RA) or 0.9% normal saline should be used.The capillary leak resolves spontaneously after 24-48hrs in most of the patients.

Management of infants with severe dengue:treatment of shock-Volume replacement in infants in dengue shock is very challenging and should be done during the period of defervescence.

CRITERIA FOR ADMISSION OF A PATIENT:

If a DF patient presents with significant bleeding from any site ,signs of hypotension,persistent high grade fever,rapid fall of platelet count,sudden drop in temperature should be admitted in hospital.Patients with organ involvement should be hospitalized for monitoring and management.All patients with warning signs and symptoms should be hospitalized for monitoring and management.

CRITERIA FOR DISCHARGE OF PATIENT:

The admitted patient who have recovered from acute dengue infection having no fever for at least 24hrs,normal blood pressure,adequate urine output,no respiratory distress,persistent platelet count of >50,000/cu.mm should be discharged from hospital.

NOTES:

1. Warning signs and symptoms:Respiratory distress;oxygen desaturation;severe abdominal pain excessive vomiting;altered sensorium; confusion;convulsion;rapid and thready pulse;narrowing of pulse pressure less than 20mmHG;urine output <0.5ml/kg/hr;laboratory evidence of thrombocytopenia/ cogulopathy;rising Hct;acidosis;derrangement of liver / kidney function tests.
2. Indication for blood transfusion:loss of blood(overt) 15% or more of total blood volume;refractory shock despite adequate fluid administration and declining Hct;
3. Indication of platelet transfusion:platelet count<10,000/ cu.mm even in the absence of bleeding manifestation;prolonged shock with coagulopathy and abnormal coagulation;haemorrhage with or without thrombocytopenia.
4. Holiday and segar formula for calculating maintenance fluid

Body wt. in kgs	Maintenance volume for 24hrs
<10	100ml/kg
10-20	1000+50ml/kg body weight exceeding 10kg
>20	1500+20ml/kg body weight exceeding 20kg

GUIDELINES FOR TREATMENT OF MALARIA- WHO 2015

*Manoj Kumar Kissan, Dukhia Murmu

INTRODUCTION

Malaria is a protozoan disease transmitted by the bite of infected anopheles mosquitoes.It is transmitted in 108 countries containing 3 billion people and causes nearly 1 million deaths each year.Five species of the genus plasmodium cause nearly all malarial infections.They are- P.falciparum, P.vivax, P.ovale, P.malariae, P.knowlesi.Most death are caused by falciparum malaria.

WHO TREATMENT GUIDELINES FOR MALARIA 2015

TREATMENT OF UNCOMPLICATED P.VIVAX,P.OVALE,P.MALARIAE OR P.KNOWLESI MALARIA:

Diagnosis of *vivax malaria may be made by the use of RDT (Bivalent) or microscopic* examination of the blood smear.If the malaria species is not known then treat as for uncomplicated P.falciparum malaria.On confirmation following treatment is to be given:

Drug dose & schedule

1. Chloroquine: For chloroquine sensitive case—25 mg/kg body weight divided over three days i.e.10 mg/kg on day 1,10 mg/kg on day 2 and 5 mg/kg on day 3.

Treat adults and childrens having uncomplicated P.vivax,P.ovale,P.malariae or P.knowlesi with either ACT (except pregnant women in their first trimester) or chloroquine,in chloroquine susceptible areas.And in chloroquine resistant areas treat them with ACT (except pregnant women in their first trimester).In case of pregnant women in their first trimester in chloroquine resistant areas,quinine is used.

2. Primaquine*:Given in both P vivax and P ovale 0.25 mg/kg body weight daily for 14 days to prevent relapse.

Primaquine is contraindicated in individuals with G6PD deficiency,where 0.75mg/kg body weight once in a week for 8 weeks is given under supervision.It is also contraindicated in pregnant women,infants aged <6 months,women breastfeeding infants aged<6 months,women breastfeeding older infants, unless they are known not to be G6PD deficient.

In pregnant or breastfeeding women give weekly chemoprophylaxis with chloroquine till delivery and breast feeding are completed,then on the basis of G6PD status primaquine can be given to prevent future relapses.

TREATMENT OF UNCOMPLICATED P. *FALCIPARUM MALARIA*

Diagnosis of *falciparum malaria may be made by the use of RDT (Monovalent or Bivalent)* or microscopic examination of the blood smear. It is imperative to start the treatment for falciparum malaria immediately on diagnosis.The treatment for falciparum malaria is as follows:

1. Artemisinin based Combination Therapy(ACT): Treatment given for 3 days.

A) Artemether + lumefantrine- It is given twice a day for 3 days(total 6 doses).The first two doses should,ideally be given 8 hours apart. A total dose of 5-24 mg/kg bw of Artemether and 29-144 mg/kg bw of lumefantrine,is the target dose range of this combination.Fixed-dose combination formulation available are tablets containing 20 mg Artemether and 120 mg lumefantrine and 40 mg Artemether and 240 mg lumefantrine respectively.

B) Artesunate + amodiaquine- It is given once daily for 3 days.The target dose (and range) are 4 (2-10) mg/kg bw per day artesunate and 10 (7.5-15) mg/kg bw per day amodiaquine.A total therapeutic dose range of 6-30 mg/kg bw per day artesunate and 22.5-45 mg/kg bw per dose amodiaquine is recommended.Fixed-dose combination

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tablets available are 25+67.5 mg, 50+135 mg, 0r 100+270 mg of artesunate and amodiaquine,respectively.

C) Artesunate+mefloquine- It is also given once daily for 3 days.The target dose(and range) are 4 (2-10) mg/kg bw per day artesunate and 8.3 (5-11) mg/kg bw per day mefloquine.Fixed-dose combination tablets available for childrens are paediatric tablets containing 25 mg artesunate and 55 mg mefloquine hydrochloride (equivalent to 50 mg mefloquine base) and adults are adult tablets tablets containing 100 mg artesunate and 220 mg mefloquine hydrochloride(equivalent to 200 mg mefloquine base).

D) Dihydroartimisnin+piperaquine- A target dose(range) of 4(2-10) mg/kg bw per day dihydroartemisinin and 18(16-27) mg/kg bw per day piperaquine given once a day for adults and childrens weighing more than or equal to 25kg.In childrens weighing <25 kg the target dose (and range) are 4(2.5-10) mg/kg bw per day dihydroartemisinin and 24(20-32) mg/kg bw per day piperaquine respectively.Fixed-dose combination tablets available are 40+320 mg adult tablets and 20+160 mg paediatric tablets of dihydroartemisinin and piperaquine, respectively.

E) Artesunate+sulphadoxine+pyrimethamine- Target dose(range) of 4 (2-10) mg/kg bw per day artesunate given once a day for 3 days and a single administration of atleast 25/12.5 (25-70/1.25-3.5) mg/kg bw sulfadoxine/ pyrimethamine given as a single dose on day 1.No fixed-dose combination tablet is available.Only available as blister-packed,scored tablets containing 50mg artesunate and fixed-dose combination tablets comprising 500mg sulfadoxine + 25mg pyrimethamine.

2. Primaquine: In low transmission areas, give 0.25mg/ kg body weight single dose with ACT to patients with P. falciparum malaria (except in pregnant women,infants less than 6 months,women breastfeeding infants of less than 6 months) to reduce transmission.

TREATMENT OF UNCOMPLICATED *P.FALCIPARUM CASES IN PREGNANCY:*

1st Trimester : Quinine salt 10mg/kg 3 times daily + clindamycin 10mg/kg body weight for 7 days.

Quinine may induce hypoglycemia; pregnant women should not start taking quinine on an empty stomach and should eat regularly, while on quinine treatment.

2nd and 3rd trimester: Area-specific ACT as per dosage schedule given above.

TREATMENT OF P.FALCIPARUM CASES IN INFANTS WEIGHING <5 Kg:_Treat with ACT at the same mg/kg body weight target doses for children weighing 5 Kg.

TREATMENT OF UNCOMPLICATED P.FALCIPARUM CASES IN HIV PATIENTS: Use ACT other than artesunate+sulfadoxine & pyrimethamine if the patient is taking clotrimoxazole.And use ACT other than artesunate + amodiaquine if the patient is taking efavirenz or zidovudine.

TREATMENT OF UNCOMPLICATED P.FALCIPARUM IN NON-IMMUNE TRAVELLERS:_Treat travellers with uncomplicated P.falciparum malaria returning to non-endemic areas with ACT.

TREATMENT OF MIXED INFECTIONS (*P.VIVAX* + *P.FALCIPARUM*) CASES: All mixed infections should be treated with full course of ACT and Primaquine 0.25 g per kg body weight daily for 14 days.

TREATMENT OF P. OVALE AND P. MALARIAE: In India these species are very rarely found in few places. P.ovale P.malariae should be treated as P. vivax.If species is not known then treat as uncomplicated P falciparum.

TREATMENT OF SEVERE MALARIA:

Parenteral(intravenous or intramuscular) artesunate should be used in children and adults including infants,pregnant women in all trimesters,and lactating women, irrespective of chloroquine resistance status of the area in following ways:

1. Artesunate: 2.4 mg/kg i.v. or i.m. given on admission (time=0), then at 12 h and 24 h, then once a day.After parenteral artesunate therapy for a minimum of 24 hours,when the patient tolerates oral therapy;oral ACT is given for 3 days.

Children weighing less than 20 kg should receive a higher parentral dose of artesunate(3mg/kg/dose) than larger

children and adults(2.4mg/kg/dose) to ensure equivalent drug exposure.

2.Parenteral alternatives if artesunate is not available: When parenetral artesunate is not available use intramuscular **Artemether** in preference to **quinine** for treating severe malaria in childrens and adults.

Artemether: 3.2 mg/kg bw i.m. given on admission then 1.6 mg/kg per day.

Quinine : Quinine: 20mg quinine salt/kg body weight on admission (IV infusion or divided IM injection) followed by maintenance dose of 10 mg salt/kg 8 hourly; infusion rate should not exceed 5 mg salt/kg per hour.If patient does not improve within 48 hours then reduce the dose of quinine to one-third i.e.10mg salt/kg every 12 hourly. Those patients who received parenteral Quinine therapy should receive oral Quinine 10 mg/kg body weight three times a day to complete 7 days (including the days when parenteral Quinine was administered) ***plus*** Doxycycline 3mg/kg BW once a day (except in pregnant women and children under 8 years of age) or Clindamycin 10 mg/kg body weight 12-hourly for 7 days.

RECURRENT FALCIPARUM MALARIA:

It can occur due to reinfection or treatment failure.Treatment failure may be due to drug resistance or inadequate exposure to drug due to sub-optimal dosing,vomiting,unusual pharmacokinetics in an individual or substandard medicines. Lack of resolution of fever and parasitemia or their recurrence within 4wks of treatment are considered failures of treatment with currently recommended ACTs.

Failure within 28 days- second line treatment with alternative ACT known to be effective in that region.

Failure after 28 days- considered as new infection and treated with first line ACT.

CHEMOPROPHYLAXIS:

Intermittant preventive treatment of malaria in pregnancy (IPTp)- Sulphadoxine-pyrimethamine for total of three doses,with a gap of one month between each dose in first and second trimester is given in malaria endemic areas of Africa.

Intermittent preventive treatment in infants (IPTi)- Sulphadoxine-pyrimethamine(SP) is given to infants <12 months along with the third round of vaccination with diphtheria,pertusis and tetanus(DTP) and vaccination against measles in areas of moderate to high transmission in Africa,where SP is still effective.

Seasonal malaria chemoprophylaxiss (SMC)- Monthly Amodiaquine+SP is given to children <6yrs of age to a maximum of four doses,beginning at start of transmission season and during the transmission season,in the sub-sahel region of africa.

INSTRUCTIONS TO AUTHORS

About the Journal : Orissa Physicians Journal (OPJ) is the official publication of Association of Physicians, India, Odisha state chapter.

Scope of the journal: The objective of the journal is to promote clinical research and develop academic quality among the members of API, Odisha branch. Therefore, it publishes any type of clinical studies, research, ethical, social issues, and educative articles related to General Medicine.

The Editorial Process: A manuscript will be reviewed for possible publication with the understanding that it is being submitted to OPJ at that point of time and has not been published anywhere, simultaneously submitted, or already accepted for publication elsewhere. The journal expects that authors would authorize one of them to correspond with the Journal for all matters related to the manuscript. The articles will be peer reviewed by two experts.

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Preparation of Manuscripts:

Manuscripts must be prepared in accordance with "Uniform requirements for Manuscripts submitted to Biomedical Journals" developed by the International Committee of Medical Journal Editors (October 2008). However, the requirements for OPJ are as follows.

Types of Manuscripts for OPJ.

1. **Chairman's address:** From this year it has been decided that OPJ will publish the address of Chairman of API, Odisha chapter as such. OPJ also welcomes Ex-Chairman's address for publication.

2. **Original articles:**

These include randomized controlled trials, intervention studies, studies of screening and diagnostic test, outcome studies, cost effectiveness analyses, case-control series, and surveys with high response rate. The text of original articles amounting to up to 3000 words (excluding Abstract, references and Tables) should be divided into sections with the headings Abstract, Key-words, Introduction, Material and Methods, Results, Discussion, References, Tables and Figure legends.

Abstract: Authors should write structured abstract for original article. In structured abstract the headings are Introduction, Material methods, results, Discussion, and conclusion. It should be within 300 words. For case reports and review articles unstructured abstracts should be given.

Key-words: Three to five key words should be given. Key words should not include the words mentioned in the title of the paper.

Introduction: State the purpose and summarize the rationale for the study or observation.

Materials and Methods: It should include and describe the following aspects:

Ethics: When reporting studies on human beings, indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

Evidence for approval by local Ethics Committee (for both human as well as animal studies) must be supplied by the authors on demand. Only a *statement on ethics committee permission and ethical practices must be included in the 'Materials and Methods' section.*

Study design:

Selection and Description of Participants: Describe your selection of the study participants (patients or laboratory animals, including controls) clearly, including eligibility and exclusion criteria and a description of the source population. *Technical information:* Identify the methods, apparatus (give the manufacturer's name and address in parentheses), and procedures in sufficient detail to allow other workers to reproduce the results. Give references to established methods, including statistical methods (see below); provide references and brief descriptions for methods that have been published but are not well known; describe new or substantially modified methods, give reasons for using them, and evaluate their limitations. Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration.

Statistics: Whenever possible quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Authors should report losses to observation (such as, dropouts from a clinical trial). When data are summarized in the Results section, specify the statistical methods used to analyze them. Avoid non-technical uses of technical terms in statistics, such as 'random' (which implies a randomizing device), 'normal', 'significant', 'correlations', and 'sample'. Define statistical terms, abbreviations, and most symbols. Specify the computer software used. Use upper italics (*P*= 0.048). For all *P* values include the exact value (If unable to produce the exact value mention < or > than 0.05 or 0.001). Mean differences in continuous variables, proportions in categorical variables and relative risks including odds ratios and hazard ratios should be accompanied by their confidence intervals.

Results: Present your results in a logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat in the text all the data in the tables or illustrations; emphasize or summarize only important observations.

When data are summarized in the Results section, give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated, and specify the statistical methods used to analyze them. Restrict tables and figures to those needed to explain. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Where scientifically appropriate, analysis of the data by variables such as age and sex should be included.

Discussion: Include summary of *key findings* (primary outcome measures, secondary outcome measures, results as they relate to a prior hypothesis); *Strengths and limitations* of the study (study question, study design, data collection, analysis and interpretation); *Interpretation and implications* in the context of the totality of evidence (is there a systematic review to refer to, if not, could one be reasonably done here and now?, what this study adds to the available evidence, effects on patient care and health policy, possible mechanisms); *Controversies* raised by this study; and *Future research directions* (for this particular research collaboration, underlying mechanisms, clinical research).

Do not repeat in detail data or other material given in the Introduction or the Results section as such. References: About 30 references can be included.

Number of authors: These articles generally should not have more than six authors.

3. Review Articles:

It is expected that these articles would be written by individuals who have done substantial work on the subject or are considered experts in the field.

The prescribed word count is up to 3000 words excluding tables, references and abstract. The manuscript may have about 25 references. The manuscript should have an unstructured Abstract (250 words) representing an accurate summary of the article. The section titles would depend upon the topic reviewed. Authors submitting review article should include a section describing the methods used for locating, selecting, extracting, and synthesizing data. These methods should also be summarized in the abstract.

4. Case reports:

New, interesting and rare cases can be reported. They should be unique, describing a great diagnostic or therapeutic challenge and providing a learning point for the readers. Cases with clinical significance or implications will be given priority. These communications could be of up to 1000 words (excluding Abstract and references) and should have the following headings: Abstract (unstructured), Key-words, Introduction, Case report, Discussion, Reference, Tables and Legends in that order.

The manuscript could be of up to 1000 words (excluding references and abstract) and could be supported with up to 8 references. Case Reports could be authored by up to four authors.

5. Letter to the Editor:

These should be short and decisive observations. They should preferably be related to articles previously published in the Journal or views expressed in the journal. Preliminary observations that need a later paper for validation can be given as letter to the Editor. The letter could have up to 500 words and 3 references. It could be generally authored by not more than four authors.

6.Others:

Editorial, Guest Editorial, Pictorial CME, Documentation, Commentary and Opinion are solicited by the editorial board.

References

Use the style of the examples below, which are based on the formats used by the NLM *in Index Medicus*. The titles of journals *should be abbreviated* according to the style used in Index Medicus. Use complete name of the journal for non-indexed journals. Avoid using abstracts as references. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source. Avoid citing a "personal communication" unless it provides essential information not available from a public source, in which case the name of the person and date of communication should be cited in parentheses in the text.

How to write the names of Authors in citation: Though the names have been written in sequence of First, Middle, and Last name the citation is written from Last name followed by First and Middle name in abbreviation.

Example (From above): Mohapatra MK, Acharya S, Ranj... M. TLR-2 I/D polymorphism protects from multiple complications in falcipaum malaria. The journal of Infectious diseases, Photon. 2013;112:215-221.

The details of writing the citation in the references are given below.

1.Articles in Journals:

Example: 1. Mohapatra MK, Das SP. The Malaria Severity Score: a method for severity assessment and risk prediction of hospital mortality for falciparum malaria in adults. *J Asso Phys Ind* 2009;57:119-25.

When there are more than 4 authors et al should be written after mentioning the name of 4th. author. The name of the journal should be written in italics and in short form without a stop in between.

2. *Reference from a book*. While referring a text book the details of the book has to be mentioned along with the article.

Example-1: Mohapatra MK. Current status of drug resistance malaria in India. *Med Update* Ed. Agarwal AK 2009; Part-I: 9-25.

Example-2: Jameson JL, Kopp P. Principles of Human Genetics, In Harrison's Principle of Internal Medicine, McGraw Hill, 17th edn., Eds, Fauci AS, Braunwald E, Kasper DL, Hauser SL, et al. 2008; Vol-1:385-406.

3.Electronic Sources as reference

Journal article on the Internet:

Patel DK, Mohapatra MK, Thomas AG, Patel S, Purohit P. Procalcitonin as a biomarker of bacterial infection in

sickle cell vaso-occlusive crisis. *Mediterr J Hematol Infect Dis.* 2014, 6: e2014018, DPI:10.4084/MJHID.2014.018. http://www.mjhid.org/article/view/12525.

Tables

- Tables should be self-explanatory and should not duplicate textual material.
- Tables with more than 10 columns and 25 rows are not acceptable.
- Number tables, in Arabic numerals, consecutively in the order of their first citation in the text and supply a brief title for each.
- Place explanatory matter in footnotes, not in the heading.
- Explain in footnotes all non-standard abbreviations that are used in each table.
- For footnotes use the following symbols, in this sequence: *, †, ‡, §, ||,¶ , **, ††, ‡‡

The tables along with their number should be cited at the relevant place in the text

Illustrations (Figures)

Images: Submit good quality color images. **Each image should be less than 2 MB in size.** Size of the image can be reduced by decreasing the actual height and width of the images (keep up to 1600 x 1200 pixels or 5-6 inches). Images can be submitted as jpeg files. Do not zip the files. Legends for the figures/images should be included at the end of the article file.

- Upload the images in JPEG format. The file size should be within 1024 kb in size while uploading.
- Figures should be numbered consecutively according to the order in which they have been first cited in the text.
- Labels, numbers, and symbols should be clear and of uniform size. The lettering for figures should be large enough to be legible after reduction to fit the width of a printed column.
- Symbols, arrows, or letters used in photomicrographs should contrast with the background and should be marked neatly with transfer type or by tissue overlay and not by pen.
- Titles and detailed explanations will be mentioned in the legends for illustrations not on the illustrations themselves.
- The photographs and figures should be trimmed to remove all the unwanted areas.
- If photographs of individuals are used, their pictures must be accompanied by written permission to use the photograph or the authors should provide that if necessary.
- If a figure has been published elsewhere, acknowledge the original source and submit written permission from the copyright holder to reproduce the material. A credit line should appear in the legend for such figures.
- Legends for illustrations: Type or print out legends within maximum 40 words.
- A maximum of 3 photographs will be allowed.
- The Journal reserves the right to crop, rotate, reduce, or enlarge the photographs to an acceptable size.

Protection of patients' rights to privacy: Identifying information should not be published in written descriptions, photographs, sonograms, CT scans, etc., and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian, wherever applicable) gives written informed consent for publication. Authors should remove patients' names from figures unless they have obtained written informed consent from the patient. When informed consent has been obtained, it should be indicated in the article and copy of the consent should be attached with the covering letter.

Re submitting the revised manuscript: The revised version of the manuscript should be submitted online in a manner similar to that used for submission of the manuscript for the first time. However, there is no need to submit the "First Page" or "Covering Letter" file while submitting a revised version. When submitting a revised manuscript, contributors are requested to include, the 'referees' remarks along with point to point clarification at the beginning in the revised file itself. In addition, they are expected to mark the changes as underlined or colored text in the article.

ASSO OF PHYSICIANS OF INDIA
ODISHA STATE BRANCH
IMA HOUSE, MEDICAL ROAD, RANIHAT,
CUTTACK-753007

RECEIPT & PAYMENT ACCOUNT FOR THE PERIOD FROM 1-NOV-2014 TO 31-OCT-2015

Receipt	Amount (Rs)		Payment		Amount(Rs.)
Opening Balance					
Cash-at-Bank	48,435.70	48,435.70	Seed Money BBSR Confernce 15		50,000.00
Cash in Hand	-		1st EC Meeting		14,117.00
		39,405.00	2nd EC Meeting		13,379.00
Dr Manoranjan Behera Loan		2,44,472.00	35th APICON Bhubaneswar		9,487.00
Fixed Deposit		1,95,862.00	APICON 14 Berhampur for Local Utilization		75,000.00
Refund of Loan & Seed Money 34 Rd		8,396.00	Bank chrages		114.00
Interest		2,000.00	CME Jaipur Exp		78,114.00
Membership Fees		1,40,800.00	34th APICON Confernce Expenses		1,70,151.00
Recived on Account of CME Jaipur		93,900.00	Electricity Expenses		4,889.00
OPJ Advertisement			Office Expenses		2,828.00
			OPJ Vol-11 & 12		1,18,209.00
			Salary		14,000.00
			Web Service		29,700.00
			Closing Balance		
			Cash-at-Bank	1,73,282.70	
			Cash in Hand	20,000.00	1,93,282.70
TOTAL		7,73,270.70	TOTAL		7,73,270.70

As per information and explanation produce before us.

For Asso of Physicians of India
Odisha State Branch

Secretary

FOR PATRO & CO.,
Chartered Accountants
FRN : 340100E

(Ambika Prasad Mohanty)
Partner
M.No.057820

Place: Cuttack
Date: 03.11.2015

Fixed Deposits as on 31.10.2015

FD Account details	Amount
30168562477	174320
30168571061	156274
30169638551	145427

Audited Acounts of 34th APICON Berhampur

Receipts and Payments account for the year ended 31/03/2015

Receipts	Rs.	Payments	Rs.
Opening Cash Balance :	0	Cost of bags for delegates	17700
Opening Balance at SBI, MCC Br.	20000	Cost of foods and beverages	50700
Delegates Registration fees received	88732	Tent House payments	25700
Donation from Pharma Cos. & others :	1381200	Light, Music and Entertainment exp.	8600
Bank interest on savings a/c	2220	Building Rent	4675
		Lodging and Boarding	5384
		Travelling and Conveyance	4476
		Printing and stationaries	10761
		Electronic media charges	1000
		Bank charges	117
		Sweeper charges	15
		Closing Cash Balance	
		Closing Balance at SBI, MCC Br.	20086
	1492152		149215

Balance Sheet as on 31.03.2015

Liabilities	Rs.	Assets	Rs.
Opening Fund Balance :	20000	Cash-in-hand	0
Add : Excess of Income over Expenditure	175862	Cash-at-Bank	
Closing Fund Balance :	195862	(at State Bank of India, MCC Br., Berhampur savings a/c no.33717354124)	200862
Current Liabilities :			
Audit and Consultancy fees payable :	5000		
	200862		200862

Place : Berhampur,
Date : 10-04-2015.

For Association of Physicians of India
(Orissa State Branch)

Dr.Umashankar Mishra
Organizing Secretary
APICON ODISHA 2014

Income and Expenditure a/c of Confenrence for the year ending 31.03.2015

	Rs.		Rs.
To Cost of bags for delegates	177000	By Registration fees receipts	88732
To Cost of food and beverages	507000	By Donation from Pharma Cos. & others :	1381200
To Tent House payments	257000	By Bank Interest on savings a/c	2220
To Light, Music and Entertainment exp.	86000		
To Building Rent	46750		
To Lodging and Boarding	53846		
To Travelling and Conveyance	44764		
To Printing and stationaries	107610		
To Electronic media charges	10000		
To Bank charges	1170		
To Sweeper charges	150		
To Audit and Consultancy fees	5000		
To Excess of Income over expenditure :	175862		
	1472152		1472152

With Best Compliments From :