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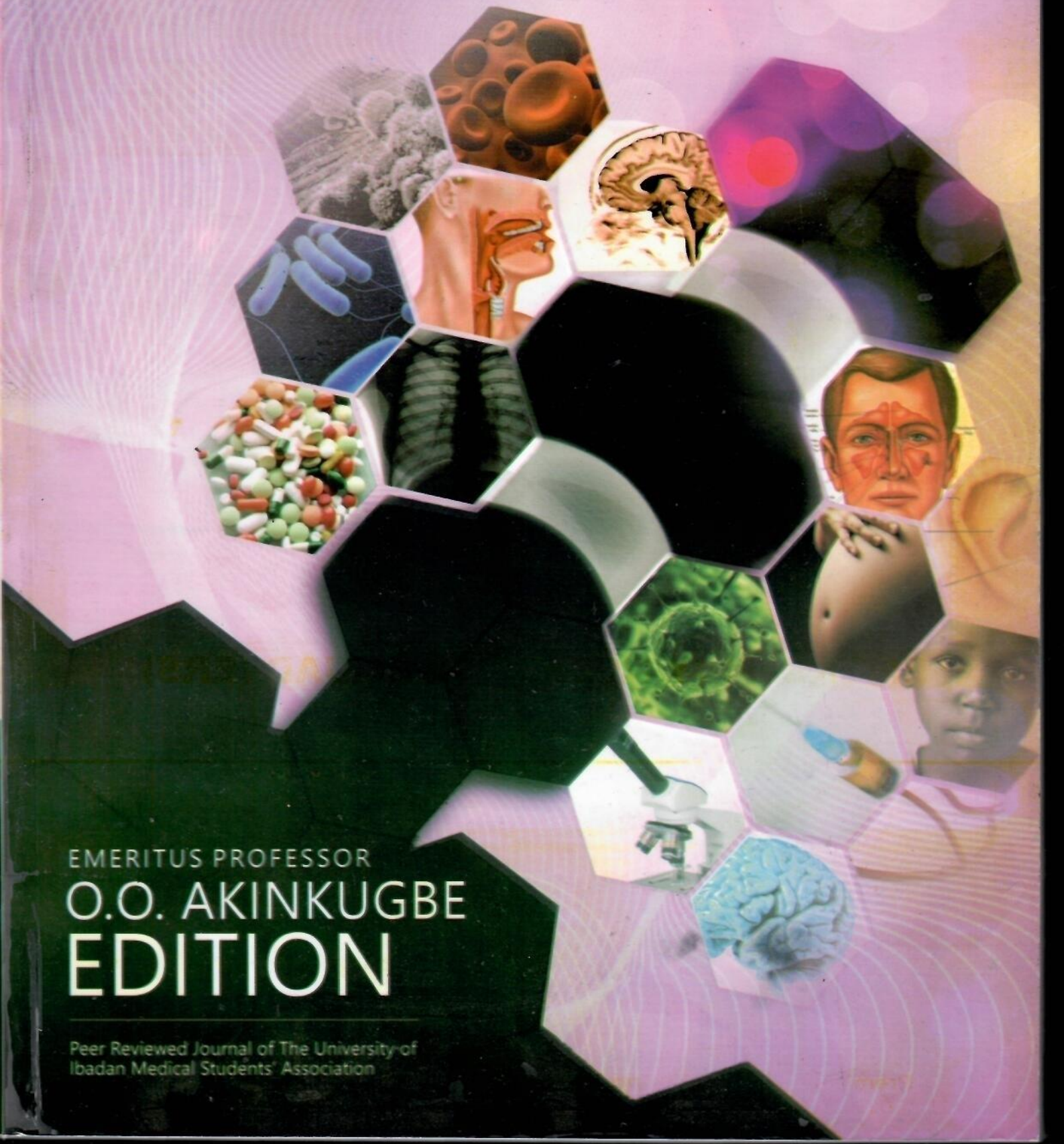

EMERITUS PROFESSOR
O.O. AKINKUGBE
EDITION

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AKINKUGBE
EDITION

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University College Hospital, Ibadan

Emeritus Professor Oladipupo Olujimi Akinkugbe

CON, CFR, NNOM, MD, D.Phil., FRCP Edinburgh, FWACP, FAS , Hon. D.Sc.

Emeritus Professor Oladipupo Olujimi Akinkugbe

CON, CFR, NNOM, MD, D.Phil., FRCP Edinburgh, FWACP, FAS , Hon. D.Sc.

Was born on the 17th of July 1933.

He attended the prestigious Government College Ibadan for his secondary education and went ahead to study medicine at the University College Ibadan from where he graduated in 1958. He went up to Balliol College in Oxford University in 1962 for his doctorate in philosophy the Thesis for the degree in 1964 was on "Angiotensin and the Kidney". He got his MD from the University of London in 1968 and also became a fellow of the Royal College of Physicians (Edinburgh) in the same year. Emeritus Professor Akinkugbe returned to the country to chair department of Medicine, University of Ibadan in 1968. He was subsequently Dean of Medicine in 1970, Head of department of Medicine, University of Ibadan 1972, Principal and Vice Chancellor University of Ilorin (1975-1978), Vice chancellor Ahmadu Bello University, Zaria (1978-1979).

He is a renowned academic with visiting professorships of Medicine at Harvard University 1974-1975, Oxford 1981 and University of Cape Town in 1995. He has served on man WHO expert committees on Cardiovascular Disease and Health manpower development. He was also on WHO global advisor committee on Health Research. Emeritus Professor Akinkugbe was the foundation president of the Nigerian Hypertension Society and Nigerian Association of Nephrology. He has sat as chairman on the board of trustees of Ajayi Crowther University and Bells University, Ota. He was the foundation chairman of JAMB and chairman planning committee of University of Abuja and Ondo State University. He Chaired UCH management board in the year 2000.

Emeritus Professor Akinkugbe was on the Editorial boards of many international journals including Journal of Hypertension 1984-1990, Journal of Human Hypertension 1988, Kidney International and News in Physiological Science 1992-1998.
He has authored or edited books on hypertension, cardiovascular Disease, health & planning and clinical medicine. He co-authored the popular Compendium of Clinical Medicine with Prof. A.O. Falase.

He is a distinguished fellow of the University of Ibadan, Hon. Fellow Balliol College Oxford, England. He has honorary Doctor of Science from seven Nigerian universities including University of Ibadan and Obafemi Awolowo University.

He is an award winning researcher with awards from Searle Distinguished Research Award for his work on hypertension in black populations and The Boerhringer Ingelheim Award of The International Society of Hypertension. He received the Nigerian National Order of Merit award in 1997and the civil honour of the Commander of the Federal Republic of Nigeria in 2004. He also received national award from Cote d'Ivoire. Also recognised as an illustrious son of the soil, he has traditional titles from different states in the south west. They include: Atobase of Ife, Babalofin of Ijebu-Igbo, Adengbuwa of Ondo and Aare Basegun of Ibadan.

He is happily married to Professor Folashade Akinkugbe and blessed with two sons. His hobbies include listening to music, gardening, bird watching and playing golf.

> "Professor Akinkugbe is a www man, endowed with the multiple gifts of words, wisdom and wit"
>
> Dr Tony Marinho
> 2013

INSTRUCTIONS TO AUTHORS

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1. Title page with the full title of the paper and the authors' full names and highest academic degrees and departmental institutional affiliations.
2. Running title of not more than 40 characters (letters and spaces included) and the name, address of author responsible for the correspondence about the manuscript.
3. An abstract or summary of 150-250 words stating the objectives, methods, results and conclusion of the paper.

Below the abstract, list in alphabetical order three to eight key words for cross indexing using terms from the medical subject headings (MeSH) list of index medicus.

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1. For standard journal articles: Author's name(s) initials, title of article, year of publication, volume in Arabic numerals (with number in parenthesis) and the number of first and last pages. Eg; Akinkugbe O.O. Nephrology in the tropical setting. Nephron 1978; 22:249-252. If there is more than one author, list all except they exceed four wherein four are given, followed by et al.
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FOREWORD

CELEBRATING THE LAST OF THE AFRICAN MOHICANS

I consider it a great privilege and honour to write the foreword to this commemorative edition of the **DOKITA**, celebrating our living icon Emeritus Professor Oladipupo Olujimi Akinkugbe.

Born to noble parents on, 17th July, 1933, Prof. Akinkugbe represents the best in all that he touched in the field of Education, Health, Literature and Arts. Although known for his immeasurable contributions in Education and Medicine, our celebrant is a prolific writer, poet and lover of music.

The University celebrated this great icon, ably described as our immovable asset and treasure, when he clocked 80 thereby deflating the saying that a prophet is without honour in his country. At the celebration, I likened him to the proverbial elephant touched by 3 or 6 blind men, each giving a vivid description of what he felt, but in aggregate terms describing the complexity of the great animal. It is simply a professorial assignment to describe Emeritus Prof. Akinkugbe. He remains my classic prototype of a Professor.

A teacher of teachers, professor of professors, with an imposing and intimidating physical and intellectual architecture, Professor Akinkugbe stands out with uncommon distinction. A man with a great sense of humour, a gifted orator with supreme command of Queens English, he has a way of keeping you awake during his presentations.

I was not lucky to be thought directly by this great scholar but his works constituted a source of pride to me when I served a period of medical attachment at Royal postgraduate Hospital, Hammersmith in 1985 under the tutelage of Mr Pat Soutter, a committed gynaecologic oncologist. His work on the relationship between abnormal haemoglobins and renal pathologies in blacks, published in the 60's saved a Ghanaian lady her kidney at the hospital.

While we have been unable to clone this great man, I wish to charge his disciples too numerous to count, to continue to propagate his ideals and ensuring his immortality. Long live Emeritus Prof. Akinkugbe, Long live our greatest University of Ibadan, Long live our great country Nigeria

Professor I.F. Adewole
Vice Chancellor,
University of Ibadan
November, 2014

PREFACE

Emeritus Professor O.O. Akinkugbe deserves to be honoured by any students' organization in Nigeria. More so by the students of the University of Ibadan where the erudite Professor taught for more than 30 years. The 37th edition of DOKITA produced in his honour is a reflection of his lasting association with students' friendly attributes. He is one academic Colossus on whose shoulder many students and students' organization have stood to conquer the world.

I met Professor O.O. Akinkugbe in the 1990s while he was still very active as a researcher and teacher. He exuded profound erudition. He interacted with both young and old students generally and welcomed everyone in his office and home. Professor Akinkugbe found time to attend ceremonies organized by his students either individually or as a group, even in remote areas where you least expected he might visit. These attributes have endeared him in many ways to his students, many of whom have become professional and academic giants in their various fields of endeavour. Even the students of today, especially, from this great institution still drink from the fountain of experience and network of Professor O.O. Akinkugbe.

I have personally come to recognize his larger than life attribute, and I respect his views and judgements. The great man, like all great leaders, also respects the opinions of younger ones, and when he disagrees with them, he does so politely without making them to lose face. A man of immense academic and political value, with many firsts and double Vice-Chancellorship. I salute you on your achievement and the long lasting impression you have created in the minds of the students of this great University and elsewhere.

Long live, Professor O.O. Akinkugbe!

Long live the University of Ibadan!!

Long live the Federal Republic of Nigeria!!!

Professor Babatunde L. Salako
Provost, College of Medicine
University of Ibadan
October, 2014

EDITORIAL

This special edition of **DOKITA** in honour of Emeritus Professor O. O. Akinkugbe is a proof that patience, persistence and perspiration make an unbeatable combination for success. Although the journey to this edition (37th in the Series) witness quite a number of daunting challenges, the Editorial Board has worked tirelessly and has successfully produced this excellent piece on behalf of the University of Ibadan Medical Students' Association. It is a general edition that contains well written articles from consultants and most especially medical students,who conceived the idea of **DOKITA** in 1960. This edition is intended to celebrate one of the fathers and a doyen of medicine in Nigeria, Emeritus Professor O. O. Akinkugbe.

This edition covers a wide range of specialties from Obstetrics and Gynaecology with *Cord Clamping: A Neglected Component of the Active Management of the Third Stage of Labour* to Paediatrics with *Childhood Hypertension*, and a fusion between both of them *Prevention of Mother to Child Transmission*. Pathology offers us *Pituitary Adenoma* and *Molecular and Metabolic Interelationship among Micronutrient: Prepathologic and Clinical Significance*. Chronic Illnesses are not left out with contributions on *Diabetic Retinopathy* and *Hypertensive Emergencies*, Psychiatry further provides a balanced read with *Suicide and Suicidal Behaviours in Nigeria: A Review*. Out of the dark room comes the beautiful piece on *Radiology and Psychiatry*. *Suppurative Otitis Media; Recurrent and Contemporary Issues* from Otorhinolaryngology.

My heartfelt gratitude goes toMr. Stephen Adeseko and members of the 2014 Journal Committee who through so much groaning in labour have made sure this child comes forth; our Supervisor for this edition, Professor E. O. Olapade-Olaopa, who has exhibited his prowess as a researcher to make sure all articles meet up with recognized standards; all our peer-reviewers for being thorough in order to maintain the standard set by our founding fathers; the members of the Advisory Council especially the Board Chairman, Professor A. O. Omigbodun for always being there for the Board; all past Board members especially Drs. Chima Okwumezie and Taiwo Ojedoja for their advice and assistance; all current Board members for their cooperation and the team spirit that made the difference in this edition.

Finally, to God be the glory for the past, present and the future.

Have a pleasant reading ride.

Yeka Wusa Nmadu
Editor-in-Chief
November, 2014.

"

DOKITA started with a robust record of impeccable clinial scientific editing skills and has sustained this reputation through the past five decades, thanks to the enduring commitment of its successive Editorial Boards.

"

O.O. Akinkugbe
2010

SUPPURATIVE OTITIS MEDIA: RECURRENT AND CONTEMPORARY ISSUES

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ABSTRACT

The risk factors for Suppurative Otitis Media are highly prevalent in Nigeria; more than 70% of Nigerian children with Chronic Suppurative Otitis Media in the first year of life. Vaccination and the immunobiologic status of the patient are paramount in the outcome and development of disease. the article reviews the recurrent issues of diagnosis, biology and prevention of Suppurative Otitis Media.

Keywords: *suppurative otitis media, risk factors, vaccine, immunobiology, review*

INTRODUCTION

Otitis media simply refers to inflammation of the middle ear mucosa and its integument, sometimes including the Eustachian tube. Traditionally, otitis media is traditionally classified as acute or chronic, mucopurulent or cholesteatomatous; however, advancement in science has brought classification such as vaccine preventable otitis OM [1]. Acute otitis media (AOM) and otitis media with effusion (OME) are highly prevalent in the pediatric population and represent major disease burdens worldwide. Following the Korea National Health Survey performed in 2009, otitis media (OM) was ranked as the seventh most frequent disease responsible for hospital visits among patients younger than 18 yr old [1, 2]. AOM is a very common disease in children younger than 3 yr old. Two of three children experience AOM once, and about one in three children could have more than three episodes of AOM. The prevalence of AOM in Korea has not been reported, although previous studies have revealed AOM incidence rates of 62% and 83% in children under 1 and 3 yr old, respectively [3]. The incidence rate differs according to age; the incidence is low in the neonatal period but rises markedly after 6 months old, peaking at around 2 yr old, with another slightly lower peak from 4 to 7 yr old. Despite its considerable economic impact, there have been no prospective studies regarding the incidence of AOM in Korea. According to the 2008 statistics of the Health Insurance Review and Assessment Service, the yearly cost of AOM was 140 billion Won, which is 9.3% that of acute respiratory tract infections.[4] In USA, 90% incidence in children under the age of 2 years and 60% in preschool attendees [5]. In Nigeria, community prevalence of chronic suppurative otitis media (CSOM) among children was reported to be 21.2% [6] while hospital and school prevalence ranged between 1.01% and 25% [7, 8] In addition, more than 70% of the children with CSOM in Nigeria had developed OM in the first year of life (Lasisi and Ajuwon 2001). The lower prevalence figure of OM in Nigeria compared to USA is noteworthy and contrary to expectation. This might be due to many factors: inaccessible healthcare, poverty and local beliefs among others. However, the findings from Nigeria suggested that the development of otitis media in the first year of life – Early otitis media (EOM) may result in the propensity to chronicity and hearing loss.

DIAGNOSIS

The diagnosis of acute otitis media is not as simple as it is widely thought, it may be difficult and in fact AOM tends to be overdiagnosed. An international study[9] has shown GPs to be certain of the diagnosis of AOM in 58% of children under 1 year, increasing to 73% in children older than two and a half years. Reasons for diagnostic uncertainty could not be extracted from the study. Diagnostic certainty is, however, influenced by the diagnostic criteria used, diagnostic equipment used, the GP's knowledge of the topic and practical examination problems such as cerumen or a crying child. Knowledge of the importance of factors compromising diagnostic certainty is essential when trying to improve performance. The diagnosis of AOM is often based on the criteria of presence of acute onset of symptoms, signs of middle ear inflammation, and effusion. Examination of the tympanic membrane (TM) for colour, position, mobility, and translucency might be difficult owing to an uncooperative child or obstruction with cerumen.[9,10] However, the mobility and position of the TM appear to be most important for diagnosis of acute OM. In acute OM the tympanic membrane may be dull or red and bulging. This further underscores the importance of otoscopy in the diagnosis of ear diseases in children with fever.[10]

Others features which are non sensitive and non specific are otalgia, ear-rubbing, fever, irritability, restless sleep, diminished appetite, and excessive crying.

However, when otorrhoea sets in, the diagnosis becomes easier as the disease becomes suppurative otitis media which may be acute or chronic.

Table 1 shows the list of features for the diagnosis of acute otitis media according to the American Academy of

Otorhinolaryngology, Head and Neck Surgery [13]

Table 1:

Definition of AOM

A diagnosis of AOM requires

1. A history of acute onset of signs and symptoms,
2. The presence of MEE, and
3. Signs and symptoms of middle-ear inflammation.

Elements of the definition of AOM are all of the following:

1. Recent, usually abrupt, onset of signs and symptoms of middle-ear inflammation and MEE
2. The presence of MEE that is indicated by any of the following:
   a. Bulging of the tympanic membrane
   b. Limited or absent mobility of the tympanic membrane
   c. Air-fluid level behind the tympanic membrane
   d. Otorrhea
3. Signs or symptoms of middle-ear inflammation as indicated by either
   a. Distinct erythema of the tympanic membrane or
   b. Distinct otalgia (discomfort clearly referable to the ear[s] that results in interference with or precludes normal activity or sleep)

Risk Factors

These are listed as follows [14, 15]:

- Bottlefeeding
- Adenoid
- Malnutrition
- Allergy
- Low social status
- smoking
- Congestion in a household
- Recurrent Upper Respiratory Tract Infection
- Allergy
- Low social status
- Day-care attendance
- Missed vaccination

VACCINE PREVENTABLE OM

The prevalence of antibiotic-resistant S. Pneumonia has increased globally before the pre-vaccine era. The pattern of changes in antimicrobial susceptibility varies among serotypes and geographic regions [16]. Prior to PCV7 introduction, the major problem with antimicrobial resistance in S. pneumoniae worldwide was nonsusceptibility to penicillin, macrolides and multidrug resistance[17]. Currently, Streptococcus pneumoniae along with nontypeable Haemophilus influenzae are the major pathogens of AOM cases, although a few serotypes are responsible for most cases of AOM worldwide, including serotypes 3, 6A, 6B, 9V, 14, 19A, 19F, and 23F [18, 19]. Pneumococcal conjugate vaccines (PCVs) are currently licensed for use in children and they have showed modest efficacy against AOM overall [20]. In children aged < 5 years with AOM, the PCV7, PCV10 and PCV13 covered 54%, 60% and 85% of the pneumococcal serotypes, respectively [21]. Additionally, H. influenzae type b (Hib) conjugate vaccine has been included for routine immunization of infants as part of a pentavalent vaccine in some other countries.[22] In the US, evaluation of cohorts of children born after the introduction of PCV7 found 17% and 28% reductions in frequent otitis media, and 16% and 23% declines in myringotomy tube placement in children up to two years of age from Tennessee and New York, respectively.[23] These declines have been offset, to some extent, by increases in nonvaccine serotype disease. Serotype 19A, which is often highly resistant to antibiotics, has become predominant.

MOLECULAR BASIS OF OTITIS MEDIA

Viral URTI believed to induce OM due to generation of cytokines and inflammatory mediators leading to ETD and increased adherence and colonization by bacteria. Viral culture in middle ear effusion has been reported in 24 – 42% of middle ear aspirates [24, 25]. The role of cytokines in the pathogenesis of OM include up-regulating the mucin mRNA expression in the middle ear epithelium and induction of chemo-attraction of macrophages to the site of infections [26]. Tumour necrosis factor alpha (TNF α), IL-4 and IL-13 have been identified in 77-91%, 67- 97% and 92-100%, respectively, of chronic middle ear effusions [24-26]. The concentration of TNF α, IL-1β have been found to correlate with the concentration of endotoxin in the purulent secretion while IL-8 has been found in higher levels in more viscous effusion [26-29]. In addition, high levels of these cytokines in MEE have been correlated with persistence and chronicity of OM, suggesting the regulation of these cytokines as the possible sites of future therapeutic interventions in OM. [28, 29]. Middle ear effusions have also been found to contain mediators of the allergic response, such as IgE and eosinophil cationic protein children [30-32].

PRINCIPLES OF MANAGEMENT

The aim of management is to identify the risk factors, control the course of disease and treat complications. This will entail good history, physical examination including neurological examination and laboratory investigations.

The investigation can be classified as follows:

Radiology

The plain radiograph of the temporal bone appears outdated in most parts of the world, though still done in may developing sub saharan African countries. However the computerized tomography of the temporal bone and brain is often needed to show presence of middle ear polyp, abscesses and ossicular erosion, It is expedient in ruling out intracranial involvement.

A chest radiograph may assist in diagnosing pulmonary tuberculosisi in cases of tuberculous otitis media and also assess the patients' fitness for surgery.

Audiology

The pure tone audiogram is needed to diagnose presence and severity of hearing loss accompanying suppurative ear disease. Usually, the hearing loss is conductive, shown by an air bone gap more than 20 decibel, however, it could be sensorineural or mixed in cases of associated labyrinthitis.

Tympanometry may show type b tympanogram in otitis media with effusion.

Hematology

This will be handy in assessing the blood count which may show leucocytosis with neutrophillia in acute suppurative OM.

Microbiology

The microscopy and culture of the organisms responsible for the infection will help in the choice of antibiotic for medical management.

Table 2:

Criteria for Initial Antibacterial-Agent Treatment or Observation in Children with AOM

AGE	CERTAIN DIAGNOSIS	UNCERTAIN DIAGNOSIS
<6months	Antibacterial therapy	Antibacterial therapy
6months - 2years	Antibacterial therapy	Antibacterial therapy if severe illness; Observation option* if non-severe illness
>2years	Antibacterial therapy if severe illness; Observation option* if non-severe illness	

The conservative treatment involves the following:

1. Aural toileting
2. Topical antibiotics drop
3. Topical ear dressing

Table 2 shows the criteria followed by the American Academy of Otorhinolaryngology Head and \neck Surgery for the use of antibiotics in suppurative otitis media.

SURGERY

The principles of surgery are:

1. Control of Infection
2. Drainage
3. Hearing rehabilitation

Generally, surgery is indicated in cases of persistence of disease despite adequate conservative treatment and those with complications.

The types of mastoid surgeries for suppurative otitis media are as follows:

- SIMPLE MASTOIDECTOMY
- MODIFIED RADICAL MASTOIDECTOMY
- RADICAL MASTOIDECTOMY
- HEARING REHABILITATION
  - Tympanoplasty/Ossiculoplasty
  - Hearing Aid
  - Bone Anchored Hearing Aid (BAHA)
  - Intratympanic hearing implant
  - Cochlear implant

COMMON COMPLICATIONS OF SUPPURATIVE OTITIS MEDIA

Intracranial group
Meninigitis
Lateral sinus thrombophlebitis
Encephalitis
Subdural empyema
Brain Abscess
Otitis hydrocephalus
Extracraial extratemporal group
Mastoid Abscess
Mastocutaneous fistula
Citelli's Abscess
Bezold's Abscess
Extracranial intratemporal group
Labyrinthitis – Toxic and purulent
Labyrinthine fistula

In conclusion, the prevalence of childhood Suppurative Otitis Media has been noted to be high in Nigeria, the risk factors and role of vaccines and immunobiology has been discussed. The various treatment modalities and hearing rehabilitation depend on the clinical status of the patient at presentation and the availability of facilities and manpower.

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DIABETIC RETINOPATHY: A REVIEW

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A B S T R A C T

Background
According to the 2012 International Diabetes Federation (IDF) estimates, more than 371 million people in the world are living with diabetes mellitus and half of them do not know that they have the disease. Nigeria leads in Africa with 3.2 million cases, followed by South Africa with 1.9 million cases. Diabetic retinopathy is a microvascular complication of diabetes mellitus, characterized by retinal changes marked by microaneurysms, exudates, haemorrhages, and in some cases neovascularisation. Diabetic retinopathy is rare in prepubescent patients with type 1 diabetes, but nearly all patients with type 1 and 60% of patients with type 2 diabetes develop some degree of retinopathy after 20 years.
The aim of the review is to emphasise the importance of early detection of diabetic retinopathy and appropriate management through evidence-based knowledge of recent advances in diabetic retinopathy.

Materials and Methods
The materials used in this review article come from studies and publications on diabetes and diabetic retinopathy

Keywords: *Blindness, Diabetes, Microvascular, Retinopathy.*

INTRODUCTION

Diabetic retinopathy is a well-characterised, sight-threatening, chronic microvascular complication that eventually afflicts virtually all patients with diabetes mellitus. Diabetic retinopathy is characterized by gradually progressive alterations in the retinal microvasculature, leading to areas of retinal nonperfusion, increased vasopermeability, and pathologic intraocular proliferation of retinal vessels. These complications associated with increased vasopermeablity, termed *macular oedema*, and uncontrolled neovascularisation, termed *proliferative diabetic retinopathy* (PDR), can result in severe and permanent visual loss.[1]

Diabetic retinopathy is one of the leading causes of blindness in adults aged 20-74 years in developing countries such as India and Nigeria [2] and is the leading cause of visual loss in people of the same age-group in developed countries, despite the widespread use of laser photocoagulation and control of blood glucose. [1-6] In spite of decades of research, there is still no cure for diabetic retinopathy [1, 6]. However, with appropriate medical and ophthalmologic care, more than 90% of visual loss resulting from diabetic retinopathy can be prevented. [1, 6]

EPIDEMIOLOGY AND IMPACT

More than 371 million people in the world are living with diabetes mellitus, but only half are aware that they have the disease. [2, 7] On the global scale, China leads with 92.3 million cases, followed by India and USA with 63.0 million and 24.1 million cases respectively. Fifteen million people have diabetes mellitus in Africa. Nigeria leads with 3.17 million cases, followed by South Africa (1.98 million cases) and Ethiopia (1.39 million cases). The prevalence rate in Africa is 4.3%. Furthermore, 81.2% of the cases in Africa remain undiagnosed. Currently Africa has the highest mortality rate from diabetes and it is estimated that in the next 20 years, the number of people with the disease in this region will double.[7]

Diabetic retinopathy accounts for about 1% of visual impairment and blindness, worldwide (WHO 2010) [8] and is a leading cause of new-onset blindness in adults. [1-6, 8] It is important to note that the WHO figures essentially represent diagnosed cases, when in reality; half of diabetics do not know they have diabetes and diabetes is also implicated in other ocular diseases such as cataract and glaucoma which also cause visual impairment. There is a higher risk of more frequent and severe ocular complications in type 1 diabetes. Approximately 25% of patients with type 1 diabetes have retinopathy after 5 years, with the figure increasing to 60% and 80% after 10 and 15 years respectively.[1] However, because there are more adult-onset cases than juvenile cases, type 2 disease accounts for a higher proportion of patients with visual loss. [1, 3, 5]

The most sight-threatening form of retinopathy: Proliferative Diabetic Retinopathy (PDR), is present in approximately 25% of type 1 patients with diabetes of 15 years' duration. [1] In type 2 diabetes, the progression of retinopathy is usually in the macular

and paramacular region, resulting in macula oedema and consequent loss of vision.[1, 3, 5, 9] However, there are a few cases where patients with type 2 diabetes go on to develop proliferative retinopathy and patients with type 1 go on to develop maculopathy.[3, 5]

NATURAL COURSE OF DIABETIC RETINOPATHY

There are five fundamental pathologic processes in diabetic retinopathy: (a) formation of retinal capillary microaneurysms, (b) excessive vascular permeability, (c) vascular occlusion, (d) proliferation of new blood vessels and accompanying fibrous tissue on the surface of the retina and optic disc, and (e) contraction of these fibrovascular proliferations and the vitreous.[9]

The clinical picture of diabetic retinopathy in an individual patient depends on the relative contributions of these five processes. Microaneurysm formation, unless accompanied by excessive vascular permeability or capillary occlusion, is a benign process with no visual consequences. When microaneurysms and/or retinal capillaries become excessively permeable, the resulting clinical picture is that of retinal oedema and hard exudate formation, often involving the centre of the macula and leading to moderate impairment of vision. Vascular occlusion appears to begin in the capillary bed and initially is of little clinical importance. As the vaso-occlusive process worsens, involvement of terminal arterioles becomes apparent and larger patches of capillaries become occluded, presumably causing elaboration of one or more growth factors.[1, 3, 9, 10] There is resultant stasis, increased stickiness of platelets and release of inflammatory mediators.

Vasoproliferation follows, first within the retina and then on its anterior surface. The resulting preretinal new vessels are the principal source of the vitreous haemorrhage that is a characteristic feature of the proliferative stage of diabetic retinopathy (PDR) and a common cause of severe visual loss. Equally characteristic are the fibrous proliferations that accompany the new vessels. Contraction of these proliferations is the principal mechanism leading to tractional retinal detachment, also common causes of visual losses in PDR.[1, 5, 6, 9]

PATHOPHYSIOLOGY

The earliest histologic effects of diabetes mellitus in the eye include loss of retinal pericytes (supporting cells for retinal endothelial cells), thickening of vascular endothelium basement membrane, and alterations in retinal blood flow. With increasing loss of retinal pericytes, the retinal vessel wall develops outpouchings (microaneurysms) and becomes fragile.[1, 3, 5, 9] Early in their evolution, microaneurysms are seen with direct ophthalmoscopy as tiny dots of the same deep red colour as the retinal veins.[9] Clinically, microaneurysms and small retinal haemorrhages may not always be readily distinguishable and are evaluated together as "haemorrhages and microaneurysms".[1, 9] Rheologic changes occur in diabetic retinopathy resulting from increased platelet aggregation, integrin-mediated leukocyte adhesion, and endothelial damage.[1]

When the number of microaneurysms in an eye exceeds 10, fluorescein angiography usually demonstrates retinal capillary abnormalities, consisting of focal fluorescein leakage from microaneurysms or more diffuse leakage from capillaries, capillary dilation and/or capillary non perfusion (capillary dropout)[9]. Disruption of blood retinal barrier may ensue, characterised by increased vascular permeability. The subsequent leakage of blood and serum from the retinal vessels results in retinal haemorrhages, retinal oedema, and hard exudates.[1, 3, 9] Hard exudates are made up mainly of lipid, most of which has presumably leaked from the plasma across the excessively permeable walls of microaneurysms and adjacent leaky capillaries.[9] They are yellowish and vary in size. They may be confluent or arranged in a circinate pattern around a cluster of microvascular abnormalities. Scattered hard exudates often come and go, but continued focal leakage will result in plaques that can cause permanent functional impairment if located on the fovea.[3] The posterior pole is the most common location of retinal oedema and hard exudates[9], and when the retina within a disc diameter or two of the centre of the macula is involved (macula oedema); visual acuity is threatened, although it does not actually become impaired until the centre of the macula is involved. Moderate visual loss follows if the fovea is affected by the leakage.[1, 3, 6, 9]

With time, increasing sclerosis and endothelial cell loss lead to narrowing of retinal vessels, decreasing vascular perfusion and may ultimately lead to obliteration of capillaries and small vessels.[1, 9] As the retinopathy becomes more severe, larger patches of nonperfused capillaries are seen. Frequently it is evident that such patches were supplied by terminal arterioles that have become occluded. Adjacent to patches of nonperfused capillaries, clusters of microaneurysms and tortuous, perfused vessels are often present. It is difficult to determine whether these vessels are dilated pre-existing capillaries or intraretinal new vessels; the term intraretinal microvascular abnormalities (IRMA) is used to include both possibilities.[9] The ophthalmoscopic counterpart of capillaries that have recently closed following occlusion of terminal arteriole in the nerve fibre layer is cotton-wool spot (soft exudate). In diabetic retinopathy, these lesions are characteristically less intensely white and fade less rapidly (often over 3-6 months)[3] than is the case in hypertensive retinopathy.[3, 5, 9] As capillary closure becomes more extensive, it is common to see many dark-red blot haemorrhages and/or segmental dilation of retinal veins (venous beading). When these lesions (cotton wool spots, IRMA, venous beading and retinal haemorrhages) are prominent, non proliferative diabetic retinopathy (NPDR) is considered *severe*, or *preproliferative*, and new vessels are likely to appear soon on the surface of the retina or optic disc (See Table 1). Some studies assert that of these four lesions, cotton-wool spots are the least predictive of the subsequent development of PDR.[9] When capillary closure becomes extensive, these intraretinal lesions tend to disappear, leading to a featureless appearance (featureless retina) and this is a sign of severe retinal hypoxia.[1-2, 9]

The vascular occlusion described above, leads to ischaemia. The resultant ischaemia is a potent inducer of angiogenic growth factors.[1-3, 5, 10-11] Several angiogenic growth factors have been isolated from eyes with diabetic retinopathy, including Insulin-like Growth Factors (IGFs)[1-2], basic Fibroblast Growth Factor (bFGF),[1-2] Hepatocyte Growth Factor (HGF),[1]

and Vascular Endothelial Growth Factor (VEGF).[1-3, 5, 10-11]. These factors promote the development of new vessel growth and retinal vascular permeability. Indeed, inhibition of molecules such as VEGF and their signalling pathways can suppress the development of retinal neovascularisation and retinal vascular permeability.[1-2, 10-11] When new vessels appear on the surface of the retina or optic disc, diabetic retinopathy is said to have entered the proliferative stage.

New vessels arise most frequently posteriorly, within 45 degrees of the optic disc, and are particularly common on the disc itself. Eyes with new vessels on the disc are at greater risk of visual loss, and new vessels here (on or within one disc diameter of the disc, or in the vitreous cavity anterior to this area) are commonly designated NVD and considered separately from new vessels elsewhere (NVE).[1, 9] NVD begin typically as fine loops or networks lying on the surface of the disc or adjacent retina, or bridging across the physiologic cup. In their earliest stages, they may easily be mistaken for normal vessels during ophthalmoscopy, but can usually be correctly identified by stereoscopic examination with slit-lamp and contact lens, or by their characteristic leakage on fluorescein angiography. When well established, NVD are easily identified using direct ophthalmoscopy. Early NVE are easily overlooked and may be difficult to distinguish from IRMA. As they become larger, NVE are easily identified, either by their tendency to form networks or by their course across both arterial and venous branches of the underlying retinal vessels, a pattern never occurring in the normal vasculature. The most striking networks are roughly circular patches resembling carriage wheels, with vessels radiating like spokes from the centre of the patch to a circumferential vessel bounding its periphery. The centres of such patches often lie over retinal veins, from which the vessels appear to arise.[9]

Proliferating new vessels in diabetic retinopathy have a tendency to bleed, which results in preretinal and vitreous haemorrhages (VHs).[1, 3-6] Although the presence of a large amount of blood in the preretinal space or vitreous cavity per se is not damaging to the retina, these intraocular haemorrhages often cause prolonged visual loss by blocking the visual axis. Membranes on the retinal surface can be induced by blood and result in wrinkling and traction on the retina. Although all retinal neovascularisation eventually becomes quiescent, as with most scarring processes there is progressive fibrosis of the new vessel complexes that is associated with contraction.[1]

Posterior vitreous detachment is a process occurring in most normal eyes during or after the sixth or seventh decade.[9] However, posterior vitreous detachment tends to occur at an earlier age in patients with PDR. In the area free of fibrovascular proliferations, the posterior vitreous surface pulls away from the retina. Where proliferations are present, they are pulled forward, and with them the retina from which they arise, often producing localised areas of tractional retinal detachment and retinal tears that may result in severe and permanent visual loss if left untreated.[1, 3, 5-6, 9, 12] As contraction begins, traction is exerted upon the new vessels. Vitreous haemorrhage often occurs concomitantly, probably in part because of the traction. The severity of visual symptoms varies with the extent of vitreous haemorrhage, from a few floating specks lasting only an hour or two (until the blood disperses or settles inferiorly) to loss of all but hand movement or light perception vision. It is unusual that for the first vitreous haemorrhage that occurs in an eye to be a massive one, but large haemorrhages often follows an initial small one within a few days or weeks; thus, even a very small vitreous haemorrhage is an urgent indication for prompt ophthalmologic attention. The rate at which haemorrhages clear is highly variable, from a few weeks (when they are small) to months, years or never, when they are large. Haemorrhages tend to recur periodically, usually without any obvious precipitating event and often during sleep.[9]

CLINICAL FEATURES

Clinical findings associated with background and progressing diabetic retinopathy include haemorrhages or microaneurysms (H/Ma), cotton-wool spots (CWSs), hard exudates, intraretinal microvascular abnormalities (IRMA), and venous calibre abnormalities (VCABs), such as venous loops, venous tortuosity, and venous beading. VCABs are a sign of severe retinal hypoxia.[1, 3, 5, 9, 12] The intraretinal haemorrhages can be "flame-shaped or dot/blot"-like in appearance, reflecting the architecture of the layer of the retina in which they occur.[1, 3, 5, 9]

Diabetic retinopathy and its various stages are diagnosed by stereoscopic examination of the fundus with the pupil dilated.[1-2, 5, 9, 12] Ophthalmoscopy and evaluation of stereoscopic fundus photographs represent the gold standard.[12] Fluorescein angiography is used to determine if laser treatment is indicated. The presence of rubeosis iridis is confirmed or excluded in slit-lamp examination with a mobile pupil, i.e. without the use of a mydriatic, and by gonioscopy of the angle of the anterior chamber.[1, 9, 12]

Vision loss from diabetic retinopathy generally results from persistent, non-clearing vitreous haemorrhages, traction retinal detachment, or diabetic macular oedema. Neovascularisation with fibrous tissue contraction can distort the retina and lead to traction retinal detachment. The new vessels may bleed, causing preretinal or vitreous haemorrhage. The most common cause of vision loss from diabetes, however, is macular disease and macular oedema. Macular oedema is more likely to occur in patients with type 2 diabetes, which represents 90%[1] of the diabetic population. In diabetic macular disease, macular oedema involving the fovea or nonperfusion of the capillaries in the central macula is responsible for the loss of vision.[1, 3, 5-6]

CLASSIFICATION OF DIABETIC RETINOPATHY

Diabetic retinopathy is broadly classified into *non-PDR* (NPDR) and *PDR* categories. Macular oedema may coexist with either group and is not used in the classification level of retinopathy.[1, 3, 5-6, 9, 12] Generally, diabetic retinopathy progresses from no retinopathy, through mild, moderate, severe and very severe nonproliferative disease and eventually on to PDR. Level of NPDR is determined by the extent and location of clinical manifestations of retinopathy. Mild NPDR is characterised by limited microvascular abnormalities such as H/Ma, CWS, and increased vascular permeability. Moderate and severe NPDR are characterised by increasing severity of H/Ma, VCABs, IRMA, and vascular closure.

PDR is characterised by vasoproliferation of the retina and its complications, including new vessels on the optic disc (NVD), new vessels elsewhere on the retina (NVE), preretinal haemorrhage (PRH), vitreous haemorrhage, and fibrous tissue proliferation (FP). On the basis of the extent and location of these lesions, PDR is classified as *early PDR* or *high-risk PDR*.[1] Larger areas of these complications as well as new vessels that are near the optic disc are associated with greater risks of visual loss. The level of NPDR establishes the risk of progression to sight-threatening retinopathy and dictates appropriate clinical management and follow-up.[1,3,5,9,12]

RISK FACTORS

1. *Age and duration* of diabetes is closely associated with the onset and severity of diabetic retinopathy. Diabetic retinopathy is rare in prepubescent patients with type I diabetes, but nearly all patients with type I diabetes and more than 60%[1,3] of patients with type 2 diabetes develop some degree of retinopathy after 20 years.[1,3,5,9-10] PDR has generally been considered to be a more important problem in type I diabetes, and macular oedema more important in type 2.[1,3,5,9]

2. *Poor glycaemic control* is another significant risk factor for the onset and progression of diabetic retinopathy.[1,3,5,9] The Diabetes Control & Complications Trial (DCCT) demonstrated a clear relationship between hyperglycaemia and diabetic microvascular complications, including retinopathy in 1441 patients with type I diabetes.[1]

3. *Renal disease* as manifested by microalbuminuria and proteinuria, is yet another significant risk factor for onset and progression of diabetic retinopathy.[1,3,9]

4. *Hypertension* is associated with PDR and is an established risk factor for the development of macular oedema.[1,3,5,9]

5. *Elevated serum lipid levels* are associated with extravasated lipid in the retina (hard exudates) and visual loss.[1,3,5,9]

6. *Pregnancy* is a significant predictor of progression of diabetic retinopathy, and women with type I diabetes who get severe retinopathy in pregnancy are at excess risk of giving birth to a child with congenital abnormalities.[1,3,5]

OTHER OCULAR MANIFESTATIONS OF DIABETES

All structures of the eye are susceptible to complications of diabetes.

Neuropathies

Mono- or polyneuropathies of the third, fourth, and sixth cranial nerves may arise in association with diabetes, with the fourth cranial nerve being least likely diabetes-associated. These neuropathies are usually due to small vessel occlusion and are associated with paralysis of the corresponding muscles. Ptosis is present in third nerve (oculomotor nerve) palsy because the levator palpebrae superioris muscle which is supplied by the oculomotor nerve is paralysed. Diabetes-induced third-, fourth-, and sixth- nerve palsies are usually self-limiting and should resolve spontaneously in 2 to 6 months. Palsies may recur or subsequently develop in the contralateral eye.[1,3,5,12]

Lids and Conjucntiva

Recurrent styes and blepharoconjunctivitis are sometimes the first indications of diabetes and should prompt tests to exclude it.[3] Xanthelasma, a fatty deposit in the subcutaneous tissue of the lids, is commonly seen in diabetics, especially with associated hyperlipidaemia. Others include, keratoconjunctivitis sicca, microaneurysms of the bulbar conjunctiva and chalazion.[1,3,12]

Cornea

Corneal sensitivity is commonly impaired in diabetes, and is inversely related to the severity of retinopathy. This sensory deficit may predispose to bacterial corneal ulcers, neurotropic ulcers and difficulties with contact lenses; indeed, diabetic patients who wear contact lenses must take extra care with lens hygiene and be warned to seek advice early if trouble develops. Intrinsic abnormalities of the epithelial basement membrane complexes, with impaired barrier function, lead to superficial punctate keratitis and poor healing after trauma and the formation of persistent epithelial defects. Epithelial defects and recurrent corneal erosions can develop after photocoagulation and vitrectomy. The treatment in most cases is topical lubricants; in some cases bandage contact lenses are required.[1,3]

Glaucoma

A potentially serious diabetic ocular complication is neovascularisation of the iris (NVI). This leads to closure of the angle of the eye by fibrovascular network, resulting in neovascular glaucoma.[1,3,9,12] Proliferative diabetic retinopathy remains a leading cause of neovascular glaucoma, second only to central retinal vein occlusion[3] and it accounts for 32%[1] of cases.[1,3,12] Rubeosis iridis (neovascularisation in the iris) in proliferative diabetic retinopathy is tantamount to loss of the eye as rubeosis iridis is a relentless and irreversible process.[12] Open angle glaucoma is 1.4 times[1] more common in the diabetic population than in the nondiabetic population.[1,3] The prevalence of glaucoma increases with age and duration of diabetes, but medical therapy for open-angle glaucoma is generally effective.[1,3,12]

Optic disc

The optic disc can be affected by diabetes in a variety of ways other than NVD or NVE. Optic disc pallor can occur following spontaneous remission of proliferative retinopathy or remission following scatter (panretinal) laser photocoagulation. Because diabetes poses an increased risk for development of open-angle glaucoma, the disc pallor following remission of retinopathy or panretinal photocoagulation must be considered when evaluating the optic nerve head for glaucoma.[1]

Lens

Diabetes effects on the crystalline lens can result in transitory refractive changes, alterations in accommodative ability and cataracts.[1,3,12] Cataract is 1.6 times[1] more common in people

with diabetes than in those without diabetes. Cataracts occur earlier in life and progresses more rapidly in the presence of diabetes.[1, 3]

Pupil abnormalities

Some diabetic patients have small pupils in dim illumination which dilate poorly to mydriatic agents. The cause is an autonomic neuropathy partially denervating the sphincter and the dilator muscles.[3] Also, pupil-sparing third nerve palsy is seen in some diabetic patients.

Orbit

Mucormycosis is a rare but frequently fatal orbital fungal infection (Mucorales fungi). The disorder often spreads from infected paranasal sinuses. The clinical picture is similar to those of inflammatory orbital disorders.[1, 12]

Other Vitreo-Retinal Abnormalities

Central and branch retinal vein occlusions (CRVO and BRVO) are over-represented in diabetes and must be distinguished clinically from the various stages of retinopathy. In both, the deterioration of vision is more sudden. Among the predisposing causes to be excluded are hypertension, hyperlipidaemia and hyperviscosity syndromes. These occlusions can lead to retinal ischaemia and retinal and optic disc neovascularization.[3]

DIABETIC RETINOPATHY AND COGNITIVE DECLINE

Diabetic retinopathy is now more accurately defined as a neurovascular rather than a microvascular disease as neurodegenerative disease precedes and coexists with microvascular changes.[11] Recent studies have shown that Treatment with an Erythropoietin-Derived Peptide after diabetes is fully established can significantly protect against neuroglial and vascular degenerative pathology without altering haematocrit or exacerbating neovascularisation.[13]

Cerebral microvascular disease associated with type 2 diabetes may exacerbate the effects of aging on cognitive function. A considerable homology exists between the retinal and cerebral microcirculations; a hypothesized association between diabetic retinopathy (DR) and cognitive decline was examined in older people with type 2 diabetes. In the population based Edinburgh Type 2 Diabetes Study, 1,046 men and women aged 60–75 years with type 2 diabetes underwent standard seven-field binocular digital retinal photography and a battery of seven cognitive function tests. DR was independently associated with estimated lifetime cognitive decline in older men with type 2 diabetes, supporting the hypothesis that cerebral microvascular disease may contribute to the accelerated age-related cognitive decline observed in diabetic populations.[14]

MANAGEMENT OF DIABETIC RETINOPATHY

Diabetic retinopathy cannot be cured but effective treatments have been established that preserve vision and dramatically reduce the risk of vision loss. These treatments include laser treatments and vitrectomy surgery. Additionally, it is crucial to note that tight blood glucose control and control of accompanying conditions such as high blood pressure, kidney disease, elevated cholesterol, anaemia, and obesity greatly reduce the risk of onset and progression of diabetic retinopathy.[1-6, 9, 12]

The recent discovery of inhibitors of vascular endothelial growth factor is revolutionizing the management of diabetic retinopathy, particularly diabetic macular oedema.[1-2, 10-11] However, not all patients respond to anti-vascular endothelial growth factor agents, reinforcing the fact that diabetic retinopathy is a multifactorial disease.[10-11] Furthermore, other pharmacological agents such as the angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are not effective in halting the progress of diabetic retinopathy as compared to their effectiveness in diabetic nephropathy. This is a further evidence that diabetic retinopathy is not simply a microvascular, but neurovascular problem.

During laser photocoagulation, a laser beam is focussed on the retina. This laser scars the areas of the retina to stop the formation of new blood vessels and to shrink any new vessels that are present. Laser photocoagulation is also used to seal leaking blood vessels that may cause oedema or swelling in the macula area of the eye. Laser surgery and appropriate follow-up care can reduce the risk of blindness by 90 percent.[1, 6] The primary goal of laser surgery is to prevent further vision loss and not to restore vision that has already been lost, which is why finding diabetic retinopathy early is the best way to prevent vision loss.[1-3, 5-6, 9, 11-12] Currently, laser photocoagulation is the mainstay of treatment for proliferative diabetic retinopathy, but is gradually being superseded for diabetic macular oedema and the technique involves the use of argon laser.[11]

The laser should be directed at the new vessels and, in addition, to the associated areas of capillary nonperfusion (ischaemia). If the proliferative retinopathy has progressed to new vessels developing on the optic disc then a technique known as panretinal photocoagulation (PRP) is carried out. This involves multiple laser burns to the peripheral retinopathy again to the areas of capillary non-perfusion. The presence of new vessels on the disc carries the worst prognosis and therefore laser therapy should be carried out as rapidly as possible. If bleeding has occurred and there is a good view, then laser treatment should be applied. If the bleeding is recurrent and affecting vision and/or if there is the presence of fibrous tissue giving rise to traction on the retina, then vitrectomy is indicated.[1, 5-6, 9]

Vitrectomy is the surgical removal and replacement of the vitreous body with Ringer's solution, gas, or silicone oil.[12] It may be done when there is a retinal detachment, because removing the vitreous gel gives better access to the posterior segment of the eye. The vitreous gel may also be removed if vitreous haemorrhage does not clear on its own.[1-2, 6, 9, 12, 15] A vitrectomy is performed under either local or general anaesthesia.[6] During a vitrectomy, small instruments are inserted into the eye, cutting the vitreous gel, and suctioning it out. The three instruments (infusion cannula, light source, and vitrectome), all 1mm in diameter, are introduced into the globe through the pars plana, which is why the procedure is referred to as a *pars planavitrectomy*(PPV). This site entails the least risk of iatrogenic retinal detachment.[12] Removal of the vitreous gel is usually followed by treating the retina with a laser (photocoagulation), cutting or removing fibrous or scar tissue from the retina, flattening areas where the retina has become detached, or repairing tears or holes in the retina or macula.[1, 6, 9, 12] At the end

of the surgery, the vitreous body is replaced with Ringer's solution, silicone oil or a gas to restore normal pressure in the eye.[2, 15-16]

CONCLUSION

Diabetic retinopathy remains the most prevalent cause of visual impairment in the working-age population despite established screening programmes, early diagnosis and treatment of the condition.[1-6, 9, 11] The recent discovery of inhibitors of vascular endothelial growth factor is revolutionizing the management of diabetic retinopathy, particularly diabetic macular oedema.[1-2, 10-11] However, not all patients respond to anti-vascular endothelial growth factor agents, reinforcing the fact that diabetic retinopathy is a multifactorial disease.[10-11]

Finding and treating the eye disease early, before it causes vision loss or blindness, is the best way to control eye disease in people with diabetes. Failure to perform regular ophthalmologic screening examinations in patients with diabetes mellitus is a negligent omission that exposes patients to the risk of blindness. Therefore, all type 2 diabetics should undergo ophthalmologic examination upon diagnosis of the disorder, and type I diabetics should undergo ophthalmologic examination within five years [12] of the diagnosis. Thereafter, diabetic patients should undergo ophthalmologic examination once a year or more often if diabetic retinopathy is present. Pregnant patients should be examined once every trimester.[1, 5, 12] Also glucose levels and other health problems such as high blood pressure, kidney disease (manifested by microalbuminuria and proteinuria), and elevated cholesterol should be closely monitored.[1-6, 9, 12]

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Retinopathy grade	Retinal abnormality (cause)	Action needed
Peripheral retina		
Non-proliferative/background	Dot haemorrhages (capillary microaneurysms) (usually appear first)	Annual screening only
	Blot haemorrhages (leakage of blood into deeper retinal layers)	
	Hard exudates (exudation of plasma rich in lipids and protein)	
Pre-proliferative	Venous beading/loops	Non-urgent referral to an ophthalmologist
	Intraretinal microvascular abnormalities – IRMAs	
	Multiple cotton wool spots	
Proliferative	New blood vessel formation/neovascularization	Urgent referral to an ophthalmologist
	Preretinal or subhyaloid haemorrhage	
	Vitreous haemorrhage	
Advanced retinopathy	Retinal fibrosis Traction retinal detachment	Urgent referral to an ophthalmologist – but much vision already lost
Central retina		
Maculopathy	Hard exudates within one disc-width of macula	Referral to an ophthalmologist soon

Note: Hard exudates have a bright yellowish white colour and are often irregular in outline with a sharply defined margin. Cotton-wool spots are greyish white, have indistinct margins and a dull matt surface, unlike the glossy appearance of hard exudates.

Table 1: Grading of pathological changes in the retina in diabetic retinopathy: the action needed[4]

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SUICIDE AND SUICIDAL BEHAVIOURS IN NIGERIA: A REVIEW

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A B S T R A C T

Suicide is a major cause of mortality worldwide. It is a human tragedy that accounts for an estimated one million deaths annually. This translates to at least one death resulting from suicide every forty seconds. The magnitude of the problem is further compounded by the fact that the incidence of attempted suicide is about twenty-five times more than that of completed suicide. Every act of suicide impacts on at least six other individuals. Suicide rates have increased by about 60% over the last 45 years, thus constituting a major public health burden. These rates are grossly underreported globally and many developing countries, including Nigeria, do not have meaningful records of deaths and their causes. There is paucity of information as regards the incidence of suicide and suicidal behaviours in Nigeria, with the exception of a few recent studies. A systematic online review of published literature on suicide and suicidal behaviours in Nigeria was conducted and relevant articles reviewed. This article chronicles the evolution of research on suicide and suicidal behaviours in Nigeria, from isolated reports in the 1960s to more recent, large-scale epidemiological surveys in the last decade. It further highlights the need for an efficient system of health records with efficient documentation of deaths and their causes, and a change in the country's legislation with respect to suicide and suicidal behaviours.

Keywords: *suicide, suicidal behaviours*

INTRODUCTION

Mental, neurological and substance use disorders make a substantial contribution to the global burden of disease (GBD), which is estimated with the disability-adjusted life years (DALY) metric, assigned to each disease/disorder. The DALY is the sum of two composite measures: the years lived with disability (YLD) and the years of life lost (YLL) due to a specified disease within the total population. Suicide accounted for 1.8% of the total disease burden as at 1998, but is projected to rise to 2.4% by the year 2020.[1] Mental and behavioural disorders are common, and will affect one in every four persons at some time during their lives.[2]

The World Health Organization (WHO) defines suicide as 'the act of killing oneself, deliberately initiated and performed by the person concerned in the full knowledge or expectation of its fatal outcome'.[3] While several definitions exist, suicide simply means the intentional act of ending one's own life.

Suicide is the third leading cause of death among young people, aged 15 to 44 years, and ranks second for adolescents between ages 15 and 19 years old.[4] These reports have prompted the WHO to become vigorously involved in campaigning to bring the public health burden and impact of suicide to the attention of governments, policymakers and the public through the collation and dissemination of statistics, and the development of preventive programs.

It is estimated that globally, about one million deaths occur from suicide every year; which roughly translates to one suicide death every forty seconds. The incidence of attempted suicide is twenty-five times more common than completed suicide. It is also the most important cause of violent death worldwide, accounting for 49% of all cases. Other major contributors to violent deaths worldwide include homicide (32%); with conflicts and wars making up the remaining 19%. It should be borne in mind that the act of committing suicide, is neither a disease nor a pathological condition; but mental disorders are frequently found to be associated with it, especially depression.[5]

Beyond counting the numbers of suicide and suicidal attempts however, is the often unexplored psychological burden from feelings of guilt, sorrow and anguish, which is often experienced by the family members and close associates of individuals who commit suicide. Every act of suicide, affects averagely six other people, at the very minimum.[5] This impact becomes amplified, when a suicide occurs in a public situation, such as in a school or work environment.

Non-fatal suicidal thoughts and behaviours usually precede

successful suicide acts and should be seen as important cries for help and intervention, when they occur. They may be classified into three categories:

- Suicidal ideation, which refers to thoughts of engaging in behavior, aimed at ending one's life.
- Suicidal plan, which refers to the formulation of a specific method and preparations towards ending his own life.
- Suicidal attempt, which refers to engagement in potentially self-injurious behaviour with some degree of expressed intent to die.

AETIOLOGY

The following factors have been found to be associated with suicide.[6]

1. Social: These include factors such as the absence of meaningful family ties or social interactions which could result in egoistic suicide. Estrangement or a break in the relationship between an individual and the society due to social or economic diversity may result in anomic suicide; while excessive integration and submersion into a given society may lead to altruistic suicide, purportedly for the greater good of that society.
2. Psychological: This includes aggression and hostility turned inward against the self, as stated by Sigmund Freud; overwhelming feelings of hopelessness as suggested by Aaron Beck; and cognitive constriction of choices as observed by Edward Scheidman among individuals with suicidal tendencies.
3. Biological: Suicidal behaviours have been linked with diminished levels of serotonin in the central nervous system. Post mortem findings also indicate low levels of serotonin and some non-specific changes in the noradrenergic system of suicide victims.
4. Genetic: Suicidal behaviours may run in families. A positive family history of suicide increases the risk both for attempted and completed suicide.
5. Medical: Chronic and debilitating physical illnesses may increase the risk for suicide. Mental disorders also belong to this category and constitute the most important associated factors in suicide. Examples include depression (associated with over 90% of cases), alcohol abuse, personality disorders, and schizophrenia.

Completed suicide is more common in males; however suicide attempts and deliberate self-harm (DSH) are commoner among females and include acts of poisoning, cutting, and burning. Suicide is hardly ever the consequence of a single reason, but may rather ensue as a result of a multiple factors acting in concert to bring about such an act. These risk factors have been classified into individual, socio-cultural and situational factors, as depicted in Table 1.[1]

Table 1:
Risk factors for suicide*

INDIVIDUAL	SOCIO-CULTURAL	SITUATIONAL
Mental disorder	Stigmatization of health-seeking behavior	Financial difficulties
Alcohol or drug abuse	Lack of access to healthcare services, including mental health	Social losses and breakdown of significant emotional relationships
Hopelessness	Cultural and religious beliefs glorifying suicide as a noble outlet in the face of personal difficulties	Ready access to lethal means
Previous suicide attempt	Exposure to suicidal behaviors, through the media and the influence of others who have died by suicide	Stressful life events
Isolation and lack of social support		
Aggressive tendencies		
Impulsivity		
History of trauma or abuse		
Acute emotional distress		
Major physical or chronic illnesses		
Family history of suicide		

*Modified from the WHO publication, "Public health action for the prevention of suicide: a framework, WHO; 2012".

GLOBAL SITUATION AND TRENDS

Suicide rates have increased by 60% worldwide, in the last 45 years, with an estimated global incidence rate of 16 per 100,000.[7] This trend is occurring despite the improvements in the recognition and management of depression and other mental disorders, and the increased availability of newer medications with better and more tolerable side effects.

The incidence of suicide is usually reported as a rate per

100,000 on a country basis. Countries such as Sri Lanka, Lithuania, Russia and Belarus which record 30 or more deaths per 100,000 are classified as high rate countries. Countries with numbers ranging from 10 to 29 per 100,000 such as Japan, Hungary, and China have middle rates; while those countries with fewer than 10 suicide deaths per 100,000 (e.g. Syria, Jamaica, Egypt) are classified as low rate countries.[7]

However, these rates may actually be misleading as they do not convey the true extent of the problem. For example, China has a suicide rate of about 25/100,000, which places it in the middle range but it accounts for the largest number of human deaths from suicide annually, with 287,000 reported suicide deaths; thus accounting for nearly a third of the global mortality from suicide in a year.[8] Similarly, India's rate of 10/100,000 places it marginally ahead of countries with low rates, but India is second to China in the number of suicide deaths recorded per year, with reported figures of about 110,000 suicide deaths.[9] Khan, illustrated the misleading nature of relying entirely on these rates, without putting them in the larger context of the country's population. He utilized comparative analysis using the available figures, and showed that four countries with high suicide rates: Lithuania, Russia, Estonia and Latvia have a combined total number of suicide deaths that is less than the total number of suicide deaths from India alone, which is barely above a low rate country.[10]

Unfortunately, similar country-wide data is not uniformly available across the globe. Indeed, several countries, including Nigeria, do not routinely collect death records and have no reporting systems to document the causes of death. These non-reporting countries exceed 50, and include nations with populations numbering over 100 million people such as Indonesia, Pakistan and Bangladesh.[11]

There is a paucity of research on suicide from developing countries. Very little is known about suicides in many African countries, including Nigeria.[12] Mental illness is rarely mentioned or is implicated in only a small number of suicides. The majority of available reports in developing countries are based on hospital autopsy reports or police data, neither of which would ordinarily document psychological factors involved in suicides. Suicide is no longer a criminal offence in any developed country but continues to be criminalized in many developing countries, including Nigeria.

Religious and social factors also continue to influence the diagnosis and registering of suicides. Families do not disclose the true nature of the act, for fear of harassment by police and the resultant social stigma that would accrue from such disclosures. Instead they are more likely to declare the death an accident or in some cases, a homicide.[13]

THE NIGERIAN CONTEXT

There is paucity of information about the epidemiology of suicide in Nigeria. Suicides are generally reported to be rare in less developed countries. This is partly attributable to the routinely poor records of death and its causes. In a study that evaluated coroners' reports over a four-year period (1957-60) in the Western Region (now broken down into several states) of Nigeria, Asuni concluded that the suicide rate in Western Nigeria was very low. He reported higher rates of suicide in the rural areas compared to urban regions.[14]

Some important hospital-based studies have also provided useful insight into this problem. A review of reported cases of attempted suicide from the three largest hospitals in Benin City (Specialist, Uselu Psychiatric Hospital and the University Teaching Hospital) indicated that the incidence had not increased over the four-year period spanning 1978 to 1981, during which the average crude suicide attempt rate was 7 per 100,000. The commonest age group was among teenagers aged 15-19 years (39.4%), while nearly nine out of ten attempters (87%) were aged 30 years and below. The most important predisposing factors reported were mental illness (32%) and parental conflict (24%). There was no significant gender difference.[15]

In a six-month prospective study of thirty-nine cases of deliberate self harm reported in the three major hospitals in Ibadan, Nigeria; Odejide et al., found that nearly eight in ten (76.9%) were under the age of 30 years; and just over half (51.3%) were students, while 25.6% were manual workers. The commonest methods used were ingestion of chemicals and psychotropic drugs.[16]

Nwosu and Odesanmi, in a study carried out in the Teaching Hospital, Ile-Ife, Nigeria, that was based on medico-legal autopsy reports, reported the suicide rate as 0.4 per 100,000 populations, with nearly four times as many males committing suicide when compared to females (ratio of 3.6:1). The majority of the suicides were committed by the ingestion of Gammalin 20 and use of the local dane gun.[17]

Large-scale epidemiological studies have been recently conducted among adults. A nationally representative epidemiological study, covering 21 out of the 36 states in Nigeria was conducted by Gureje et al., among 6752 adults, to evaluate for suicide related outcomes, and their association with mental disorders and a history of childhood adversity. They reported prevalence of suicidal ideation, plan and attempts were 3.2%, 1% and 0.7% respectively. The presence of mental disorders, especially mood problems significantly correlated with suicide outcomes, while a history of early childhood adversity was identified as a risk factor for lifetime suicide attempt.[18]

Uwakwe and Gureje also examined the relationship between comorbid mental and substance use disorders with suicidal behaviours in the Nigerian survey of mental health and wellbeing. They found that persons with lifetime suicide attempts were more likely than those without attempts to have experienced lifetime DSM-IV disorders. Lifetime attempters were also more likely to have comorbid conditions. Eleven percent of persons with a lifetime history of suicidal attempt had three or more co-occurring disorders, as compared with only 0.4% of persons with no history of lifetime attempts. Controlling for the effects of comorbid conditions suggests that while mood disorders may be independently associated with suicidal outcomes, comorbidity partly explains the association of anxiety disorders and almost fully accounts for the association of substance use disorders with suicidal outcomes. The authors therefore concluded that comorbidity is an important factor in the association of mental and substance use disorders with suicidal behavior in this environment.[19]

Furthermore, Oladeji and Gureje, also established a relationship between parental mental disorders and suicidal behaviour in their offspring. The presence of panic disorder and substance abuse in the parents were found to be associated with suicidal ideation in the offspring, but only parental panic disorder was found to be related to suicidal attempts. The suggestion therefore, is that disorders of anxiety and impulse control may play some role in the observed pattern of inherited

suicidal behaviours in their offspring.[20]

Large scale studies have also been conducted among young people in Nigeria. Omigbodun et al., conducted a study to establish the prevalence and associated psychosocial correlates of suicidal ideation and attempts among young Nigerians, which revealed that, of the 1,429 youths who were assessed, over 20% reported suicidal ideation and approximately 12% reported that they had attempted suicide in the preceding year. The study reported the rates of both suicidal ideation and attempts as tending towards the upper limits of acceptable rates for youths.[21] The second study evaluated the presentation and psychosocial issues associated with preadolescent suicidal attempts using the 'hanging' method in Nigeria, and reported the existence of the following mental health problems: depression, conduct problems, oppositional defiant disorder and impulse control problems. Other factors found to be associated with these suicidal behaviours included stressful life events such as family disruption, physical abuse, and bullying at school.[22]

The pattern of attempted suicide in the Nigerian military context has also been studied by Okulate. He described the characteristics of patients who attempted suicide and examined the differences between the suicide attempters and a group of non-suicidal, affective disorder patients at the Department of Psychiatry, Military Hospital, Yaba, Nigeria. The study revealed that suicidal attempt .patients constituted 0.37% of all admissions during a five-year period, and 60.8% of them were under the age of 30 years. The numbers of male and female patients were approximately the same. Depression and acute stress reaction were the commonly associated diagnoses. While military dependents frequently ingested substances in their suicide attempts, military personnel used more violent methods such as hanging and self-stabbing, but none used firearms. Compared with non suicidal patients, suicide attempters were more likely to be unmarried and to have a family history of mental disorder.[23]

The highest risks for transition from suicidal ideation to planning, and from planning to attempted suicide usually occurs within the first year of having either the ideation or plan. Other risk factors for a lifetime suicidal attempt include dysfunctional family backgrounds; such as protracted separation from biological parents, high levels of domestic conflicts, childhood adversity, physical abuse and being nurtured by a woman with a history of depression, anxiety or suicidal attempt.[18]

Concerning the risk and methods of suicide employed in Nigeria, new patterns appear to have emerged. HIV/AIDS has emerged as an additional risk of suicide.[24,25] Other emerging risks include the internet and social media as well as terrorism and suicide bombing which though alien to Nigerian society, appears to have come to stay. Burning with kerosene[26], cutting one's throat[27] and inflicting penetrating abdominal stab injury on oneself[25] are also new but disturbing methods of attempting and completing suicide in Nigeria.

PREVENTION STRATEGIES

Suicide prevention is receiving increased attention in many developed countries, but remains largely ignored in developing countries like Nigeria. There are no easy solutions to the problem of suicide in developing countries, given the serious lack of resources and low priority given to mental health. There is also the additional problem of limited research on suicide in developing countries, making it imperative to rely on prevention strategies that have been proven to work elsewhere but not in developing countries. Furthermore, due to the unfavourable attitude towards suicide and mental illness, as well as the punitive legal requirements for suicidal behaviour, suicide continues to be under reported in developing countries, making it difficult to conduct research or develop and test prevention strategies.

The World Health Organization has identified suicide as an increasingly important area of public health and has issued guidelines to member states in order to develop and implement co-ordinated and comprehensive national and international strategies. It has also included suicide as one of the nine priority conditions in the recently launched mhGAP Intervention manual for scaling up services for mental and neurological conditions globally. The mhGAP manual is designed to serve as a training manual for non-specialists in the identification and provision of intervention for priority mental health conditions, as a way of reducing the huge treatment gap in several parts of the world.[28]

There is evidence for the effectiveness of two major strategies for preventing suicide.[29] These include restriction of access to lethal means and training programmes for primary care doctors to enhance early recognition and treatment of depression with or without suicidal ideation. Both approaches should be useful in our setting, but the latter approach to enhance the ability of general practitioners, primary health care workers and all other cadres of health professionals to recognize and offer interventions for depressive disorders is of crucial importance.

Suicidal behaviours are also strongly associated with the presence of mental disorders. In a developing country like Nigeria an important step towards suicide prevention will be to reduce the stigma associated with mental health problems.

A review of the country's Mental Health Policy and Legislation, to comprehensively address the current challenges of mental disorders, and their complications, including suicide and suicidal behaviours is long overdue. These efforts should also aim for the decriminalization of suicidal behaviours in our laws.

These steps will be meaningless, if our health records and reporting systems are not reformed to include mortality rates and the documentation of the causes of deaths. This should help in ascertaining the suicide rates in the country, and provide a platform for useful planning and the implementation of suicide prevention strategies. Focused research in this area should be promoted, especially with respect to identifying risk factors, coping mechanisms, protective factors and possible interventions to minimize the tragedy of suicide and suicidal behaviours in this environment

CONCLUSION

In this work, the authors have demonstrated that suicide and suicidal behaviour are a public health issue, just like in other countries of the world. Like in other parts of the developing world only a modest volume of research has been conducted on the subject in Nigeria, reflecting the lack of interest of clinicians, researchers, policy makers and, perhaps, research grant providers on the subject. For better suicide research which should result in better prevention strategies, it is imperative that suicide be decriminalized. Cultural and religious factors preventing people from reporting and stigmatizing suicide should also be addressed through public enlightenment campaigns. An improvement in the mortality records, that also specifies the causes of death should be ensured at all levels of

care. It might also be helpful if the WHO could leverage on member countries to collect and provide annual suicide rates in their jurisdictions. Finally, suicide is a public health problem that requires a multidisciplinary effort at enquiry, prevention and management. The earlier this is realized in the Nigerian context, the better for our emerging mental health care.

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HYPERTENSIVE CRISES: A REVIEW

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A B S T R A C T

Hypertensive crises though just a minute aspect of the large spectrum of hypertension results in an immediate life threatening danger to those affected. They account for about 28% of all medical emergencies presenting to the emergency room and affect between 1-5% of hypertensive patients. They can occur with/without a previous history of high blood pressure and could result from any disorder that can give rise to hypertension although previously normotensive individuals are more likely to develop hypertensive crises at lower blood pressures. Differentiating between hypertensive emergencies and urgencies is critical to deciding the line of management. The administration of the appropriate antihypertensive therapy has dramatic lifesaving potentials and prevents end organ damage.

Keywords: *Hypertension, Hypertensive emergency, Hypertensive urgency*

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INTRODUCTION

The World Health Organization (WHO) defines arterial hypertension as the level of systolic blood pressure of 140 mmHg or higher and/or diastolic blood pressure of 90 mmHg or higher in people not taking antihypertensive therapy.[1]

Hypertension is the most common condition seen in primary care and remains one of the most important preventable contributors to disease and death if not detected early and treated appropriately.

Blood pressure is a continuously distributed variable and its detrimental effects increase continuously as the pressure increases with no rigidly defined threshold level to distinguish risk from safety.[2]

Hypertensive crises are defined as hypertensive emergencies and hypertensive urgencies, depending on either presence or absence of acute end-organ dysfunction, respectively.[3]

DEFINITION

A hypertensive emergency is defined as a situation that requires immediate blood-pressure reduction (not necessarily to normal values) to prevent or limit target organ damage, and a hypertensive urgency is defined as a situation in which blood pressure should be lowered within a few hours.[4] There are usually no set blood pressure cut off anddiagnosis is made based on the clinical state of the patient. Differentiating between hypertensive emergencies and urgencies is critical as this would dictate line of management.

Hypertensive emergencies include hypertensive encephalopathy, hypertensive acute left ventricular relaxation associated with acute myocardial infarction or unstable angina, aortic dissection, subarachnoid hemorrhage, ischemic stroke, and severe pre-eclampsia or eclampsia. [5]Although hypertensive crises represent just a small portion of the spectrum of hypertension, they have lethal consequences; but prompt intervention proves that they are also great evidences of life saving effect of parenteral therapy.[6]

EPIDEMIOLOGY

Hypertension is said to be present in about a billion of the world population and causes the death of an average of 7.1 million individuals annually. [7]

Prevalence of hypertension increases with age as well as the vulnerability to its complications, especially in black populations all over the world including those in the diaspora. [2] About 20–30 % of adults in the more developed countries have hypertension.[8]

Hypertensive crisis accounts for as many as 27.5% of all medical emergencies presenting to the emergency room and may affect as many as between 1-5% of hypertensive patients [2, 9, 10.]

PATHOPHYSIOLOGY

There is currently an improved understanding of the molecular pathways that regulate blood pressure but the exact mechanism of hypertension in most individuals is largely unknown.These groups of individuals are said to have "essential" (a term that is a misnomer due to the erroneous belief that because blood pressure increases with age, it is indeed essential for cardiovascular functions) or primary-hypertension with multiple factors being associated. [2]Any disorder that can give rise to hypertension can invariably cause hypertensive crisis. [8]The most important factor in hypertensive crisis is severe and frequently rapid elevation of blood pressure with the rate of change in blood pressure determining the likelihood that an acute hypertensive syndrome will develop.[11]

Long standing chronic hypertension may lower the probability of an hypertensive crisis through adaptive changes that protect end organs from acute rise in blood pressure, but individuals with no history of pre-existing hypertension (e.g. pre-

existing hypertension (e.g. pre-eclampsia) are more likely to develop crisis at a much lower blood pressure.[8]

The vascular endothelium plays a major role in blood pressure regulation. Normal vascular tone is a reflection of a normal interplay between the humoralvasoconstrictors (angiotensin II, catecholamines and endothelin) and the vasodilators which are the moderators of vascular tone (nitric oxide, kinins and prostaglandins). They, especially nitric oxide (NO), are largely secreted by the endothelium.[7] Under homeostatic conditions, the endothelium is protected from increased blood pressure by the blood vessel's vasoconstrictive ability. Nitric oxide is released under theinfluence of endothelial agonists such as acetylcholine, norepinephrine, and substance P, and this could also be released by the endothelium in response to mechanical forces such as shear stress.[13] With severe and persistent injury from hypertension, persistent vasoconstriction and a compensatory release of vasodilators, the autoregulatory mechanism that protects vascular endothelium fails, resulting in vasodilation and transfer of blood pressure elevation to the vascular endothelium leading to damage and endothelial permeability.[9] The renin-angiotensin pathway is also activated. It has been found that the potent vasoconstrictor, angiotensin II has a direct cytotoxic effect on the vascular wall.[13] The vascular sequelae and target-organ damage seen in hypertensive crises may therefore be due to the injurious effects of angiotensin II on the blood vessel wall. Ultimately, these molecular events may inhibit local endothelial fibrinolytic activity, and activate the coagulation cascade. Platelet aggregation and degranulation on damaged endothelium may promote further inflammation, thrombosis, and vasoconstriction resulting in a vicious cycle.

A summary is illustrated in figure 1 below.

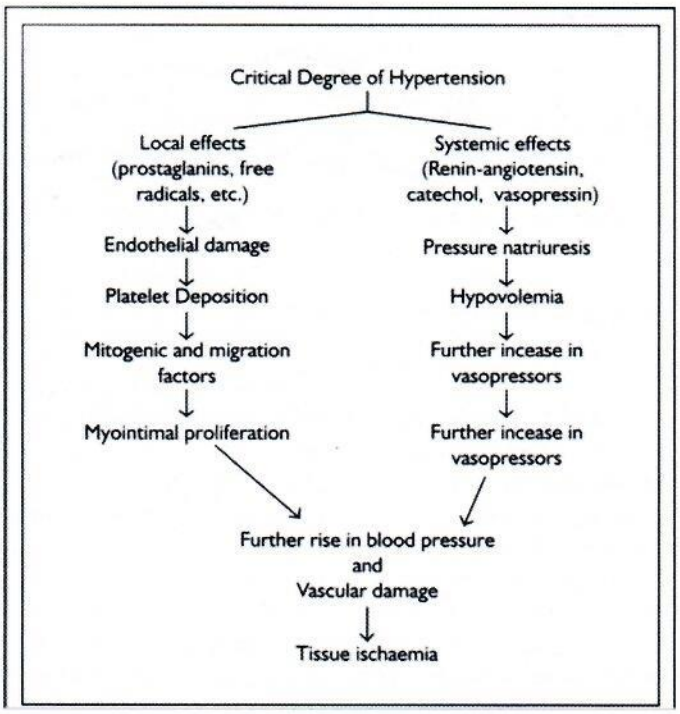

Figure 1: Scheme of Progression of Events Following a Rapid Rise in Blood Pressure. Adapted from Kaplan's Clinical Hypertension, 10th Edition, Lippincott Williams & Wilkins, 2010.

HYPERTENSIVE ENCEPHALOPATHY

This is a hypertensive emergency characterized by high blood pressure and neurological symptoms which include transient disturbances of speech or vision, paraesthesiae, disorientation, fits and loss of consciousness which are reversible if the hypertension is promptly and properly treated.[17]

It is an organic brain syndrome which occurs as a result of failure of the upper limit of cerebral vascular autoregulation (autoregulation breakthrough). Changes in blood pressure causes cerebral vessels to dilate or constrict to maintain a relatively constant level of cerebral blood flow (CBF), and this process of autoregulation is regulated by sympathetic nervous system. In normotensive individuals, cerebral blood flow remains the same between mean arterial pressures of 60 mm Hg and 120 mm Hg. With increasing mean arterial pressure, compensatory cerebral vasoconstriction limitscerebral hyperperfusion and at a mean arterial pressure ofabout 180 mm Hg this autoregulatory mechanism is overwhelmed resulting incerebral vasodilation and cerebral oedema.[6, 8, 18]

Individuals with previously normal blood pressures whose blood pressure rises rapidly e.g. during pregnancy can develop signsof encephalopathy at blood pressures as low as160/100 mm Hg, whereas individuals with long-standinghypertension may not do so until the blood pressure rises to220/110 mm Hg or greater.[8] This is shown in figure 2 below.

Clinically, encephalopathy can occur with or without proteinuria and hypertensive retinopathy. Seizures may be the presenting manifestation. Papilloedema is also common.[8, 17, 19]

It is associated with untreated or undertreated hypertension and other known causes and associations of severe hypertension such as renal disease, immunosuppressive therapy, erythropoietin use, and thrombotic thrombocytopenic purpura; it may also occur in unique circumstances without a previous history of hypertension such as in pre-eclampsia and eclampsia.[8, 20, 21, 22]

A cranial computed tomography scan shows haemorrhage in and around the basal ganglia and magnetic resonance neuroimaging shows a characteristic posterior leucoencephalopathy (Figure 3) that predominantly (but not

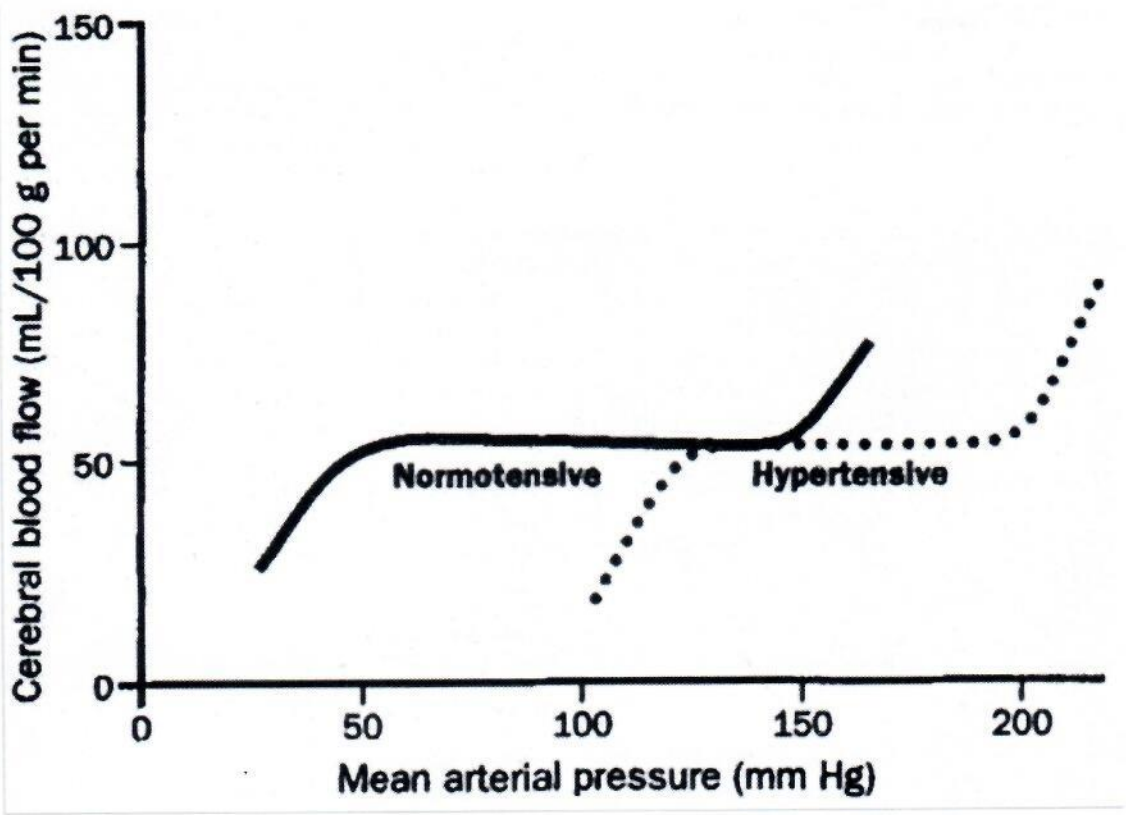

FIGURE 2: Idealized curves of CBF at varying levels of systemic BP in normotensive and hypertensive subjects. Rightward shift in autoregulation is shown with chronic hypertension. (Adapted from Strandgaard S, Olesen J, Skinhøj E, et al. Autoregulation of brain circulation in severe arterial hypertension. Br Med J 1973;1: 507-510.)

exclusively) affects the white matter of the parieto-occipital regions often the cerebellum and brainstem .[17, 23, 24]

Many other conditions could present the same way as hypertensive encephalopathy and the attending physician must also be on the lookout for them. They include acute left ventricular failure, end-stage renal disease, cerebrovascular accident, subarachnoid hemorrhage, brain tumor, head injury, reversible cerebral vasoconstriction syndromes, epilepsy (postictal), and collagen diseases, particularly systemic lupus with cerebral vasculitis amongst others.[6]

MALIGNANT HYPERTENSION

This is a type of hypertensive urgency. It is a rare condition and is characterized by accelerated microvascular damage with necrosis of the walls of small arteries and arterioles and by intravascular thrombosis. The characteristic pathologic changes of malignant hypertension are endothelial injury, arteriolar involvement, and glomerular ischemia (It occurs in 1% of hypertensive patients and can develop in people with pre-existing hypertension or those who are previously normotensive. It affects more males than females; male to female ratio being 2:1 [6, 9, 17, 25, 26]

Diagnosis of malignant hypertension is based on evidence of high blood pressure, and rapidly progressive end organ damage like presence of Keith-Wagener grade IV retinopathy, (Figure 4) renal dysfunction etc. It is important to diagnose malignant hypertension because if untreated, it carries a very poor prognosis with a 5-year survival rate of 1%but effective treatment improves survival with the prognosis at 5 years being reported to be between 60% and 75% in developed countries. [27, 28, 29] In developing countries like Nigeria, the prognosis appears to be considerably worse with 1-year survival rates of only 40%. [30]

Kadiri et al also observed that the patients with malignant hypertension were more likely to be from lower socio-economic groups, with higher stress exposure and lack of adequate antihypertensive therapy prior to presentation. [31] Sesoko et al also investigated the histories of 39 patients with malignant hypertension and noted that insuffcient sleep, overwork and mental burden were prominent factors in a significant number of these patients. [32] These support the possibility that the sympathetic nervous system may have an important role in the course of the disease.

Macroscopically, in the absence of any underlying renal pathology, the kidneys are often normal-sized and show cortical and subcapsular hemorrhages with the medulla being hyperemic due to capillary engorgement, resulting in streaks running parallel with the tubules. With light microscopy,

proliferative endarteritis in small arteries and arterioles, arteriolar necrosis, and mucoid changes are characteristically seen. The arterioles typically show fibrinoid necrosis and hyaline thrombi formation. Markedintimal hyperplasia is accompanied by concentric layers of collagen, resulting in changes often referred to as "onion skin" which can result in occlusion of the arterial lumen and produce ischemia. Larger renal arteries are usually normal or show onlychanges of chronic hypertension. Similar vascular lesions of proliferative endarteritis and focal necrosis are seen in other organs, including the pancreas, heart, adrenalglands, intestine, liver, and brain. [2,9]

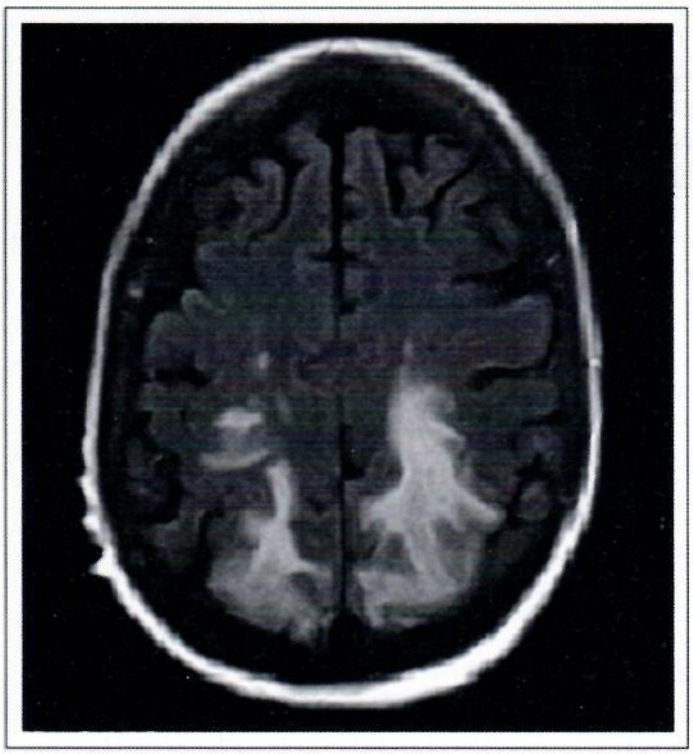

Figure 3: Cranial CT showing Posterior Leucoencephalopathy; jco.ascopubs.org, accessed October 12, 2014; 10:55am.

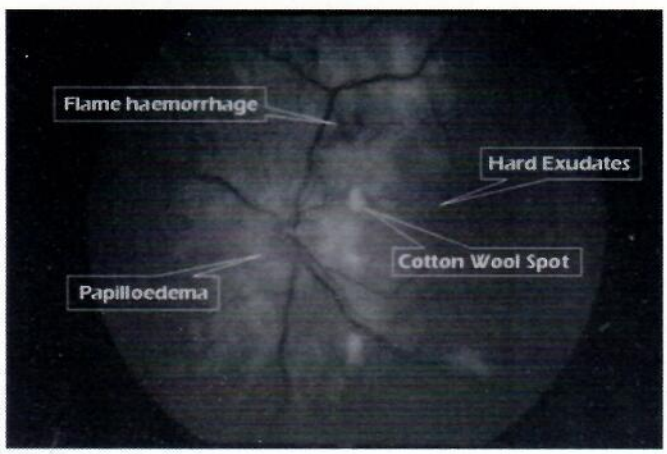

Figure 4: Keith- Wagener Grade IV Retinopathy; karenchantek.files.wordpress.com; accessed November 02, 2014; 01:10am.

PRE-ECLAMPSIA/ECLAMPSIA

Eclampsia and pre-eclampsia are part of a spectrum of conditions associated with raised blood pressure during pregnancy, known as the hypertensive disorders of pregnancy. They are both hypertensive emergencies with fatal consequences on mother and child.

Pre-eclampsia is a life-threatening multisystem disorder of unknown aetiology, which includes the development of hypertension [raised blood pressure] and proteinuria, and associated abnormalities of the coagulation system, altered liver function, renal failure and cerebral ischaemia[33]. It complicates an estimated 2–8% of pregnancies and is one of the most

common causes of premature delivery, maternal and perinatal morbidity, and mortality in low and middle income countries [34]

Hypertension during pregnancy is generally defined as systolic pressure ⩾ 140 mmHg and/or diastolic pressure ⩾ 90 mmHg, and proteinuria as >300 mg/24 h or ⩾ 30 mg/mmol in a single specimen and the diagnosis of pre-eclampsia is strengthened if there is further indication of multisystem involvement, such as raised serum creatinine or liver enzymes, lowered platelets, or neurological symptoms (hyperreflexia, severe frontal headache, or visual disturbance).[35]

Eclampsia,a serious and life-threatening condition, is the occurrence of one or more convulsions superimposed on the syndrome of pre-eclampsia.It occurs less commonly, complicating 1 in 100–1700 pregnancies in the developing world and about 1 in 2000 pregnancies in Europe and other developed countries. Compared to pre-eclampsia, it carries a much higher risk of death and serious morbidity for the woman and her baby. In the UK, for example, 1 in 50 of the women who have eclampsiadie.[36, 37]

Globally, approximately 63,000 women die each year of pre-eclampsia or eclampsia which accounts for an estimated 9% of maternal deaths in Asia and Africa and about one-quarter of maternal deaths in Latin America and the Caribbean. [38, 39, 40, 41]

Risk factors attributed to the development of preeclampsia include nulliparity, multifetal gestations, previous history of pre-eclampsia, obesity, diabetes mellitus, vascular and connective tissue disorders like systemic lupus erythematosus and antiphospholipid antibodies, age >35 years at first pregnancy, smoking, and African American race. Among primiparous women, there is a disparity among ethnic groups as the risk in African American women is twice that of Caucasian women, and the risk is also very high in women of Indian and Pakistani origin suggesting that genetic factors play a strong role in the pathogenesis of pre-eclampsia.[42]

Most theories on the etiology of pre-eclampsia/eclampsia suggest that the disease is a cascade triggered by combination of abnormal maternal inflammatory response, endothelial cell activation/damage with deranged hemodynamic milieu, and deranged immunity. The precise trigger that unifies the deranged vascular, immune and inflammatory responses remains to be elucidated.[43,44]

MANAGEMENT

History, Examination and Investigation [8, 9, 14, 15, 16]

The clinical presentations of hypertensive crises is a clear reflection of the devastating effects of high blood pressure on target organs, and depend on the rate of change of blood pressure, level of the blood pressure and other coexisting conditions. The effects would be more marked on people with an acute rise in blood pressure without any prior hypertensive history.

History and subsequent evaluation would determine the line of management either as an urgency or emergency.

History of duration, severity and treatment of pre-existing hypertension should be obtained. Care should be taken to check for any sign of end organ damage especially in the cardiac, renal and nervous systems by doing a detailed general and systemic clinical examination. A few key points are discussed here.

Blood pressure should be accurately measured with the appropriate cuff. It should be measured with the patient in both supine and standing positions (if possible) to assess whether there is volume depletion. It should also be measured in both arms: a significant difference should raise the suspicion of aortic dissection.Al-Bannay and Husain, in a cohort study which examined the clinical presentation and comorbidities of hypertensive crises, demonstrated that 154 patients had systolic and diastolic blood pressure >179 mm Hg and >119 mm Hg respectively.

A funduscopic examination should be carried out to differentiate between an hypertensive emergency and hypertensive urgency (the presence of new haemorrhages, exudates, or papilloedema indicate hypertensive emergency).

In a study carried out in Tulsa on Clinical Presentation of Hypertensive Crises in Emergency Medical Services, by Salkic et al, it was found that over the six month period of investigating a total of 180 patients: [72 men (40%) and 108 women (60%)], more cases of hypertensive urgencies were seen as compared to emergencies: 71 (83.53%) vs. 14 (16.47%). Most of the subjects belonged to the age group of 60-69 years (28.23%), in the total number of subjects of all ages the most common accompanying symptoms were headache (75%) and vertigo (44.44%). Their results also indicated that acute coronary syndrome and acute left ventricular relaxation were the two main clinical manifestations of hypertensive emergency.

In another one-year study by Zampaglione et al results showed that out of 14,209 patients that presented to the Internal Medicine Emergency Unit, 1634 (11.5%) were classified as hypertensive crisis, 76% of whom had hypertensive urgency and 24 % hypertensive emergency. It was also found that 23% of patients who checked in did notknow that they were suffering from hypertension, clearly indicating that hypertensive crises might be the first time a patient would present with any sign of hypertension. They also reported that the most common accompanying symptoms in the hypertensive urgency group were headache (22%), epistaxis (17%) and psychomotoragitation (10%); while in the hypertensive emergency group the most common symptoms were chest pain (27%), shortness of breath (22%) and hypertensive encephalopathy (16%).

Investigations required include urine analysis, measurement of concentrations of urea, electrolytes, and serum creatinine, a full blood count (including a peripheral blood smear for evidence of haemolysis indicated by the presence of schistocytes), an electrocardiogram and chest radiography.

Treatment

Generally, blood pressure is required to be lowered rapidly in hypertensive emergencies hence the need for parenteral therapies. The patient should be immediately admitted to an intensive care unit, have an intravenous access set up; and frequent monitoring of the blood pressure with an intraarterial line, commenced. The initial blood and urine samples should be obtained, and antihypertensive therapy should begin immediately. Drugs of choice include urapidil, nitroprusside, captopril, clonidine, labetalol,nitroglycerin, fenoldopam andnicardipinealthough urapidil is said tohave the most desirable number needed to treat. The choice of therapy is based on rapidity of action, ease of administration, and propensity for side effects although nitroprusside has been most widely used. Abrupt falls in pressure should be avoided, and the goal of immediate therapy should be to lower the diastolic pressure only to approximately 110 mm Hg. [6, 45] Sublingual

nifedipine is generally avoided now because of this.

Hypertensive urgencies are usually managed with oral therapy and virtually all available antihypertensive drugs with short duration of action have been found to be effective in blood pressure control. The most commonly used drugs include captopril, clonidine, fenoldopam, labetalol, and furosemide.

Manifestations of severe pre-eclampsia should be treated in accordance with World Health Organization recommendations for treatment of pre-eclampsia and eclampsiawhich includes vigilant monitoring of the woman and fetus, management of acute hypertension and prevention of seizures in women with pre-eclampsia, and prevention of recurrent seizures in women with eclampsia. The definitive treatment of pre-eclampsia/eclampsia is delivery of the fetus.[46]

Magnesium sulfate is the drug of choice for prevention of seizures in the pre-eclamptic woman, or prevention of recurrence of seizures in the eclamptic woman, as demonstrated in two large clinical studies. In 1995, the Eclampsia Trial Collaborative Group reported that when magnesium sulfate was used for treatment the risk of recurrent convulsions in women with eclampsia was reduced by 52% when compared with diazepam, and by 67% when compared with phenytoin. [47] In 2002, the Magpie trial reported that women with severe pre-eclampsia given magnesium sulfate had a 58% lower risk of developing eclampsia compared to the placebo group. [48] Findings from a recent Cochrane review also support the use of magnesium sulfate as the drug of choice.[49]

Magnesium sulfate is associated with several minor side effects such as a feeling of warmth, flushing, nausea and vomiting, muscle weakness, somnolence, dizziness, and irritation at the injection site. More serious side effects are rare but include the loss of the patellar reflex (typically occurring at a serum concentration of 8 - 10mEq/L) and respiratory depression (> 13 mEq/L).[50, 51]

CONCLUSION

Hypertensive crises are common presentation inthe emergency room. They can occur with or without a previous background of existing hypertension. Careful history and examination findings are needed to decide if it is an emergency or urgency; which is needed to dictate the line of therapy.

At the time of writing, authors were final year clinical students of the University of Ibadan.

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METABOLIC AND MOLECULAR INTERELATIONSHIPS AMONG MICRONUTRIENTS: RELEVANCE IN CLINICAL PRACTICE

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A B S T R A C T

The term micronutrient strictly embraces the vitamins and essential trace elements or microminerals. They function as cofactors and coenzyme in the synthesis of purine and pyrimidine bases such DNA and RNA polymerases, as components of hormones, as transcription factors such as the zinc fingers (DNA binding proteins), or as antioxidants and others as immune modulators. Though the importance of the micronutrients in health and disease is well recognized, the clinical significance of the molecular and metabolic interrelationships is still ill defined and understood. Clinical interest in micronutrient largely centres on deficiency states (particularly in the developing countries), though with the increasing practice of fortifying foods and increasing consumption of supplements the risk of micronutrient toxicity may increase. Micronutrient deficiencies have a range of varied effects owing to their diverse roles in metabolism and molecular processes. During development for instance, DNA is transcribed to RNA, which in turn translates to proteins that produce the enzymes and other cellular components driving molecular and metabolic activities. Ascorbic acid, a well known micronutrient can recycle tocopheryl radical generated from α -tocopherol after playing a role in antioxidant defence including protection against DNA damage to the biologically functional tocopherol. Ascorbic acid also enhances Fe (II) absorption and plays an important role in preserving the metabolic integrity of folate through prevention of oxidation of active folate (tetrahydrofolate, THF, TH4), a key player in biological methylation, in turn important in many molecular events including genomic stability. Folate itself has an important role in B12 metabolism through one-carbon metabolism where methionine synthetase, a zinc dependent enzyme, plays a major role in the detoxification or remethylation of homocysteine to methionine and the requirement of B12 again for generating an important metabolic intermediate of folate (methyl-THF). Vitamin B12 deficiency leads to folate trap, making folate unavailable and precipitating the clinical state of megaloblastic anaemia. Copper is required for the conversion of Fe (II) to Fe (III), the form bound by transferrin, a deficiency of which may manifest as refractory irony deficiency (Fe resistant) anaemia. The copper and zinc containing potent antioxidant, copper-zinc superoxide dismutase (Cu-ZnSOD) may protect against the DNA damaging pro-oxidant effects of Fe (through Fenton reaction). Zinc plays a vital role in the metabolic interconversion of vitamin A through its effect on hepatic synthesis of retinol binding protein (RBP). Vitamin A, a derivative of ß-carotene is in turn a stimulant in the transcription of retinoic acid receptors RAR and RXR; significant in many key molecular events including signalling. These metabolic and molecular interrelationships may determine prepathologic features such as DNA damage and mutagenic events across populations. Responses to therapy may be dependent on micronutrient interrelationships giving insight into differential disease susceptibility, important in risk assessment and indeed the classical clinical manifestations of micronutrient deficiency disorders (MDDs).

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INTRODUCTION

Growing evidence continues to increase our understanding of the micronutrients; nutrients required in small amounts to drive vital molecular and metabolic pathways that sustain life and health. Micronutrients have no caloric values, unlike the macronutrients but required for the metabolism of the macronutrients. This is because micronutrients are components of enzymes and hormones or cofactors needed for most molecular and metabolic reactions. The importance of micronutrients is revealed by the diversity of metabolic processes they participate in regulating. The metabolic relationship may be governed by the Mertz model proposed over three decades ago that the dose –response relationship between essential nutrients and biological processes was U-shaped [1] According to this model, a region of optimal nutrient status lies between two sub-optimal (low and high) regions and the extreme values of deficiency and toxicity. This is elegantly exhibited by selenium and was recently confirmed by Walters et. al.[2] in a canine model of prostate cancer. Though micronutrients do not have caloric values they are very important for the proper metabolism of the caloric macronutrients and the detoxification of the toxic intermediates (free radicals) generated during intermediary metabolism of the macronutrients. While the concept of marginal deficiency is not accepted by some, evidence exists that intermediate stages of depletion (prepathologic states) can have decided effects on

health.

While over 800 million people are classified undernourished worldwide, the number of people affected by micronutrient deficiency disorders (MDDs) (hidden hunger) is two-and- a half (2 ½; 2.5) times this magnitude [3] An important aspect of MDDs is that they affect those who may appear to get enough to eat but actually lack micronutrients, like iron, iodine, selenium or zinc. This may partly explain the often unrecognized clinical manifestations such as cardiovascular disease, cognitive dysfunction, dementia, and osteoporosis and vulnerability to cancer.

Thus the symptoms of these often unrecognized MDDs broadly include:

- Listlessness
- Poor vision
- Impaired cognitive and physical development
- Increased susceptibility to disease (frequent bouts of illness) including increased risk of cancer.

These non specific symptoms largely reflect derangements in the molecular and metabolic functions of micronutrients which can be accentuated or modulated by the interrelationships among these entities. Thus understanding of these relationships ensures proper evaluation of their status. For us in the developing countries this is very important, in that while MDDs have been eradicated in the economically advanced countries, they still remain a major source of health problems in the developing countries albeit mainly in subclinical form. Micronutrient deficiency disorders affect over 40% per cent of the world population with the developing countries bearing a disproportionate fraction of this burden. This is what has driven scientists in Brazil with the support of their national government to come up the with 'super foods', crops fortified with the micronutrients, Fe, ß-carotene, vitamin A and Zn.[4] This is a commendable step by a government to combat the problem of MDDs head on in a country with a large population afflicted by this problem. It is envisaged that in less than ten years consumers throughout Brazil will have access to eight biofortified food items enriched with key micronutrients. This project (crop biofortification), uses a combination of conventional plant breeding methods to raise the concentration of micronutrients in food crops utilizing the combined techniques of laboratory and agricultural techniques and apparently in part bearing the key players in the interrelationship concept in mind.

The project has as the driving force to combat micronutrient deficiencies known to cause severe health problems; anaemia, blindness, impaired immune response and developmental delays [4] It is very gladdening that Zn which has a number of biochemical and molecular roles in key physiological processes vital for health and with direct and indirect metabolic and molecular regulatory links with other micronutrients is included. Deficiency of zinc was reported in 2002 by the joint committee of FAO/WHO to be among top 10 killers in the developing countries accounting for over 800000 deaths annually [5]. This brief review largely attempts to bring to focus the poorly recognized metabolic and molecular interrelationships among micronutrients and their clinical relevance in understanding differential susceptibility to disease and therapeutic responses.

IINTERRELATIONSHIPS AMONG MICRONUTRIENTS

The interrelationship among micronutrients though important is often disregarded. This will be illustrated with the key micronutrients.Selenium, together with other micronutrients, zinc, iron and copper are required for production of many of the enzymes needed for functional cell defence system (antioxidant) interaction. Micronutrients intake has been correlated with increased antioxidant biomarker in plasma and altered regulation of cellular defense genes involved in DNA repair and metabolic pathways [6].Despite the potential for a beneficial effect of increased DNA repair and reduced DNA damage indicated by many studies, other reports have implicated consumption of some micronutrients; flavonoids with DNA strand breaks [7]

Zinc and vitamin E, two very important micronutrients have several common functions. These include:

- Membrane stability
- Antioxidant function
- Modulation of prostaglandin metabolism

Reports indicate that vitamin E malabsorption occurs during Zn depletion and appear that there is interaction between both micronutrients. Vitamin E deficiency is associated with Zn deficiency, increased cell fragility and significantly reduced plasma Zn level [8] Thus vitamin E deficiency leads to zinc deficiency and vice versa. Vitamin E and zinc have been found to interact in their effects in the protection of skin lipids [9] Supplementation of Zn deficient chicks with vitamin E was demonstrated to decrease the severity of zinc deficiency, thus suggesting or corroborating the antioxidant properties of zinc. Alternatively, it may just imply an interactive effect between Zinc and vitamin E.

In clinical practice deficiency states attract more attention than toxicity states or excess (particularly in the developing countries), although the latter can be very important for some of the fat soluble vitamins. Toxicity states may become increasingly important with the increasing practice of fortifying foods and increased intake of supplements with increasing risk of micronutrient toxicity. Micronutrient deficiencies demonstrate a range of effects owing to the diverse roles they play in molecular events and metabolism. During development for instance, which involves increase in cell growth, DNA is transcribed to RNA which in turn translates to protein synthesis including enzymes and other cellular components important in molecular and metabolic activities. At different points in the development process, micronutrient are essential, either as signals (retinoic acid), or structural (Zn in transcription factors) or catalytic (e.g. copper) micronutrients. A discussion of some micronutrients and functional activities illustrating interrelationships including molecular and metabolic connections follows.

VITAMIN B12

Vitamin B12 is required by only two enzymes in human metabolism: methionine synthetase which is zinc- dependent and l- methylmalonyl-CoA mutase. Methionine synthetase has an absolute requirement for methylcobalamin and catalyses the conversion of homocysteine to methionine. During this reaction 5-methyltetrahydrofolate (5-methyl- THF) is converted to tetrahydrofolate (THF). This vitamin B12 dependent reaction is the only way by which THF can be regenerated from 5-methyltetrahydrofolate in human subjects. Consequently, in vitamin B12 deficiency, folate may become "trapped" (unreleased) in the 5-methyltetrahydrofolate form and THF is then unavailable for conversion to other coenzyme forms needed for purine, pyrimidine, and amino acid syntheses.

Expectedly, all folate-dependent reactions are impaired in B12 deficiency, culminating in similar pathohaematological disorders in deficiencies of both micronutrients (B12& Folate). The interaction or role of zinc as the coenzyme for methionine synthetase should be recognised in the close relationship between B12 and folate thus zinc deficiency may also precipitate folate trap indirectly. It should be recalled that folate and normal activity of 1-carbon metabolic pathway are central to nucleotide synthesis, methylation and maintenance of genomic integrity as well as protection from DNA damage (Figure 1). Thus the intricate metabolic and molecular interaction of micronutrients deserves proper understanding for application in clinical situations. Zinc though often poorly recognised has a pivotal role in this.

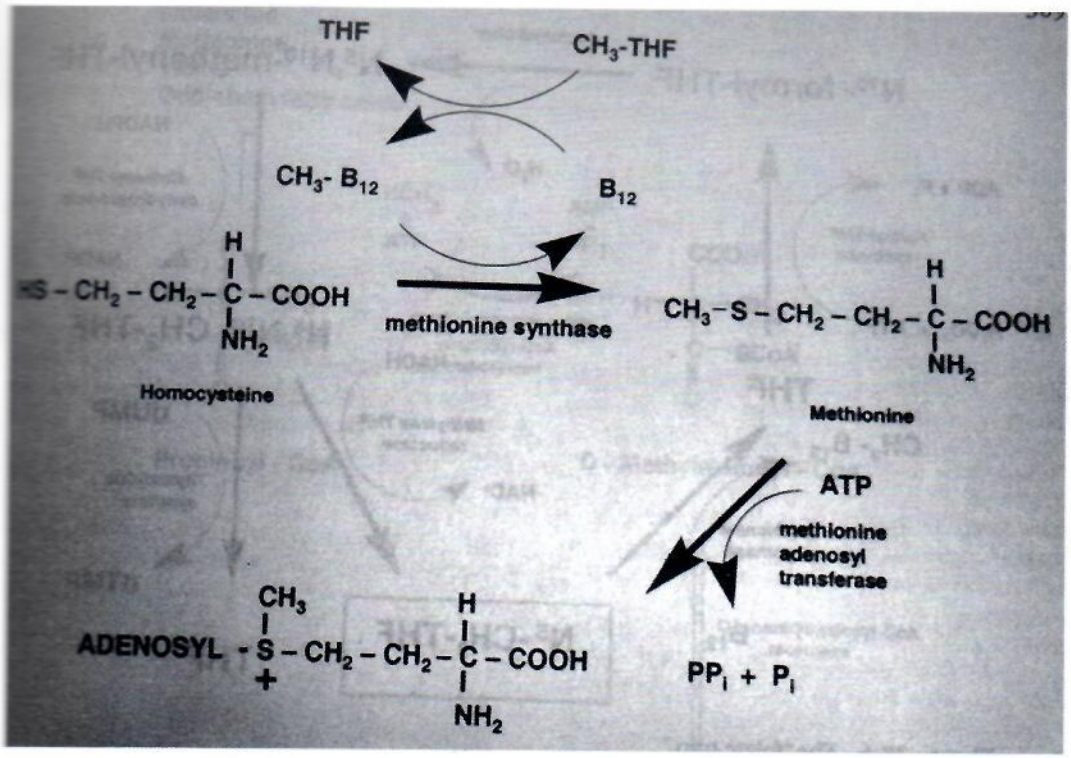

Figure 1. Interrelationship of THF, MTHF, homocysteine and methionine and methionine synthase- Zn dependent enzyme (After Glew, RH and Rosenthal, M D, 29)

ZINC FINGERS

The role of zinc in molecular processes is critical, stemming from the number of transcription factors and enzymes involved in DNA and RNA metabolism in which it participates. In many cases, specific DNA binding proteins contain zinc thus they are called zinc fingers (Figure 2). Zinc forms a bond with certain base sequences therefore these zinc fingers are very important for transcription. Most genes are turned on or off by zinc fingers. Gene expression is regulated by the formation of these zinc fingers, but only as a part not in total control of the process. Vitamin A receptor (RAR or RXR) is an elegant example of a protein that contains several zinc fingers without which retinoic acid will be non-functional as a transcription factor. Another zinc dependent protein that has important molecular roles is specific protein-1 (SP1). It is a zinc- finger transition factor originally defined in the promoter of simian virus SV40 by Albright and Tjian** . This zinc –protein plays a vital role in eukaryotic gene expression, maintenance of homeostasis, cell cycle control, terminal differentiation and apoptosis. The SP1 binding mortif has also been observed to be existent in other gene promoters embracing those that are highly modulated by cadmium such as human metallothioneins IIA.

COPPER/ SELENIUM INTERACTION

The interactions that exist among many micronutrients are often ignored in clinical states of MDDs. An important interaction is exhibited by copper for instance. Copper-deficient rats and mice have been shown to have reduced glutathione peroxidase (GPx) activity [10] Deficiency of Cu increases oxidative stress (a term first used by Sies 1 1 to describe the imbalance between the rate of ROS production and capability of the antioxidant system) and oxidative stress has a suppressing effect on all enzymes involved in free radical scavenging. Though GPx does not contain Cu, the expression of the genes for the enzyme and catalase is reduced in copper-deficient models [9,10] Other micronutrients are also involved through their involvement in SOD. Copper, zinc, magnesium (Mg is a cofactor for SOD), and manganese are part of the antioxidant defence system as well as NADPH and NAD (niacin-dependent coenzymes). As is well known vitamin E is an antioxidant which reacts with and neutralizes lipid radicals and hydroperoxides, in the process transforming to a free radical which is handled as indicated below. The function of vitamin E is however shared with ß-carotene, ascorbic acid, selenium dependent GPX and the copper-manganese – and magnesium dependent superoxide dismutases [9] Selenium and alpha-tocopherol have synergistic relationship; zinc is thus important in mutually enhancing the antioxidant potential of each of vitamin E and selenium. An antagonistic relationship exists between cooper and zinc; this relationship has been therapeutically exploited in the clinical management of Wilson's disease (Hepatolenticular degeneration of the cord). It therefor appears critically important to bear interrelations in mind when attributing clinical significance to micronutrient status; in

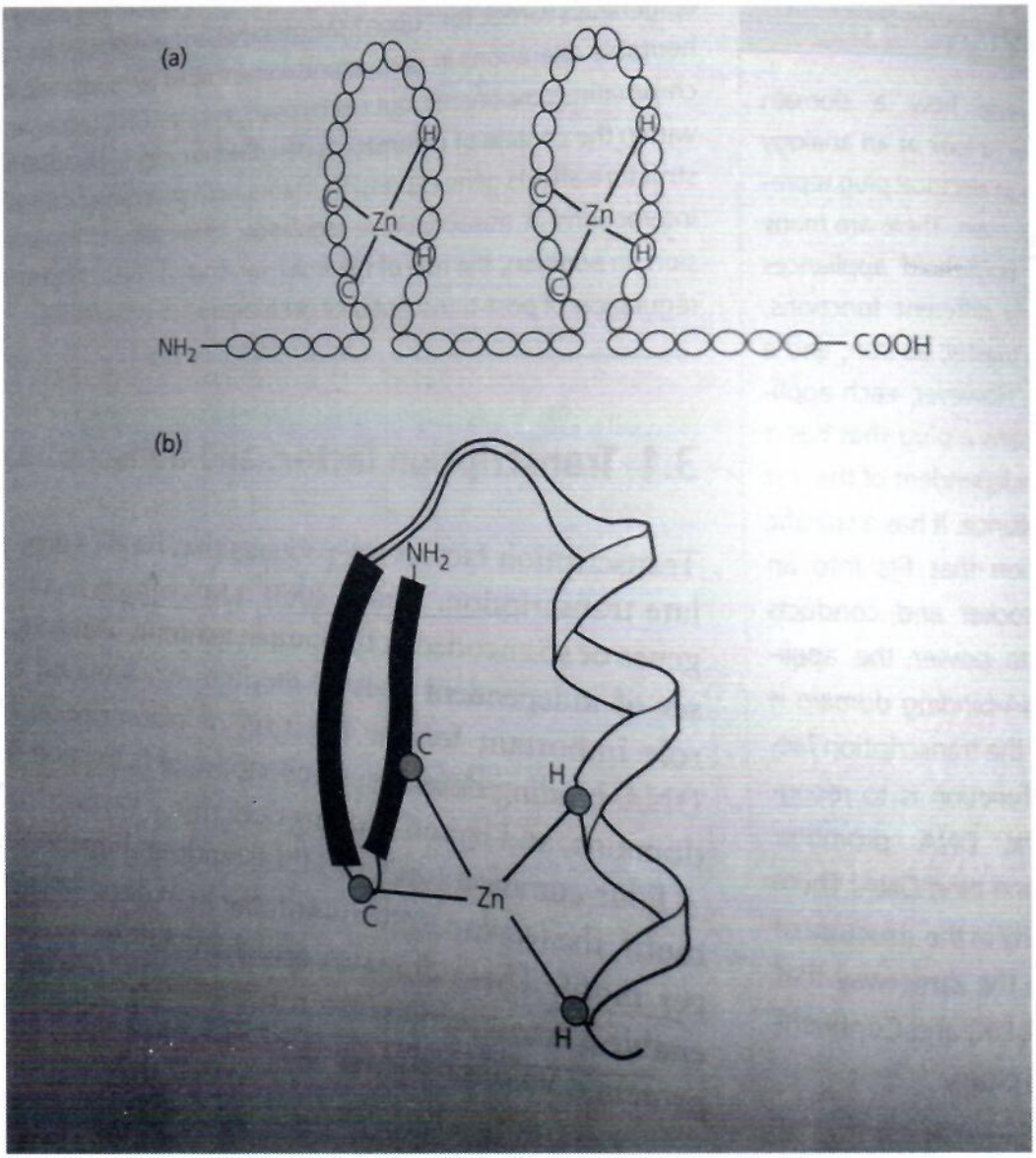

Figure 2. Showing zinc fingers (a) and how it coordinates binding (b) (After Pecorino L, 13)

deficient and states of excess but particularly in deficient states in our environment.

Alpha-tocopherol (vitamin E) potentiates peroxidase action by acting as a free radical scavenger suppressing hydroperoxide generation. These relationships illustrate clearly that numerous nutrient interactions occur at several levels to ensure maintenance of optimal (functional) micronutrient status important for ensuring optimal redox state in the case of antioxidant micronutrients. This is important in proper risk assessment and in attributing significance in demonstrated micronutrient status and probably partly explains the observation by Gey 12 that consuming optimal levels of antioxidant rich foods reduces the risk of death from cardiovascular disease and cancer. But that consuming antioxidant micronutrients at 25-30% below optimal levels doubles the risk of cancer or CVD. Gey 12 further observed that antioxidants (vitamins A, C, or E, and beta- carotene) have greater health benefits when there are optimal amounts of all the antioxidant micronutrients and that the absence of one or more in the diet can increase the risk of CVA. This again stresses the importance of interrelationships among the micronutrients and their clinical implications.

CLINICAL MANIFESTATIONS OF MICRONUTRIENT DEFICIENCY DISORDERS

The clinical manifestations of some key micronutrient deficiency disorders are presented briefly:

Vitamin A deficiency could present as skin lesions, or follicular hyperkeratosis; rough texture on the legs and arms, especially at the back of the upper arm. This is distinct from generalized dermatitis which may arise from inadequate fatty acids, zinc and B –vitamins. Very many bruises may indicate ascorbate or vitamin K deficiencies. Observation of a shiny smooth tongue, bleeding gums and cheilosis may suggest riboflavin deficiency or overlap with ascorbate deficiency. A well-known sign of MDD is that of an enlarged thyroid gland which would suggest iodine deficiency. But it should be noted that this may indeed be secondary to the absence of the required interaction with selenium which catalyses 51'deiodinase required to convert thyroxin (T4) to the metabolically active triiodothyronine (T3). Bone malformation, typically rickets or osteomalacia in adults may suggest vitamin D deficiency (vitamin D will be given further attention subsequently, owing to the growing prominence in molecular mechanisms operant in cancer prevention). Bone malformation may also arise from ascorbate deficiency due to the role the micronutrient plays in the

synthesis of the connective tissue protein, collagen. Ascorbic acid is required for the hydroxylation of proline to form hydroxyproline, a key constituent of collagen. The failure of the metabolic interconversion may also precipitate dental problems such as swollen and bleeding gums and loose teeth.

Neurologic manifestations such as tetany may be suggestive of pyridoxine (due to role in GABA synthesis); thiamine or niacin deficiencies particularly when associated with foot or hand reflexive responses, though commonly due to either calcium or magnesium deficiency. Disorientation or dementia may also arise from some of these micronutrients that are important in ensuring adequate neurological function. These clinical manifestations again seem to underscore the importance of recognising the molecular or metabolic interactions operative among micronutrients and that reversal of these symptoms will be better scientifically addressed when considered in this light.

SPECIFIC DISORDERS:

Vitamin A deficiency is a common micronutrient deficiency disorder in developing countries involving mostly children. Though its role in vision or blindness is better appreciated, it also plays a very important role in growth and normal development and differentiation of tissues. This is the role that has earned it a place in chemoprevention and as a possible contributor to the carcinogenic process in deficiency states. This vitamin also plays a very important direct role in gene expression and post transcriptional modification of a number of proteins. Its interaction with two other micronutrients, beta-carotene, its precursor and zinc as earlier indicated should be noted. Rarely, ingestion of large quantities of the vitamin may cause increased intracranial pressure in acute cases or bone and liver diseases in chronic conditions. Retinol excess in particular is teratogenic and calls for caution in prescribing supplements of this fat soluble micronutrient for pregnant women.

VITAMIN D

Vitamin D like vitamin A is a fat soluble vitamin implicated in bone deforming disorders as previously discussed above. It may also involve the teeth. It was one of the early classical micronutrient deficiencies described many decades ago. Recent epidemiological studies demonstrate that an increased risk of several cancers such as prostate, colon and breast may exist in deficiency states [13]. The cells making up tissues of the prostate, colon and breast contain the enzyme 1-α -hydroxylase needed to produce active vitamin D; 1-25-dihydroxycholecalciferol (calcitriol) [14, 15]. Vitamin D deficiency has been proposed as an underlying factor. An experimental model examined the growth of colon cancer cells in human cells implanted behind immunodeficient mice (xenografts) that are vitamin D- deficient compared to vitamin D- replete mice [16]. The study revealed tumours 80% larger on average in mice deficient in vitamin D compared with control. Currently, the combination of epidemiological and in vivo studies suggests a link between vitamin D deficiency and elevated cancer risk [13]. An interesting observation again highlighting the interaction among micronutrients at the molecular and metabolic levels is that the link between nutrients and gene expression became obvious when it was discovered that the receptors for vitamins A and D are both members of the steroid hormone receptor super family. Zinc-dependent enzymes play important roles here through their Zn-finger motifs involved in steroidogenesis.

The proposed molecular mechanism is that calcitriol serves as a ligand for the cytoplasmic vitamin D receptor, which is a member of the steroid hormone receptor super family. It is believed that this receptor recognizes vitamin D response element in the gene promoter regions and regulates transcription of the target genes.

Recent evidence suggests that vitamin D is a member of the class of chemopreventive agents which inhibits growth and induces differentiation and apoptosis via a number of molecular targets. Some of the modes by which vitamin D accomplishes this include:

·Acting as a dominant negative ligand for epidermal growth factor receptor (EGF-R), wherein vitamin D binds to the ligand –binding domain of EGF-R instead of the epithelial growth factor (EGF) thus preventing EGF from reaching EGF-R. In the process vitamin D inhibits growth. An interesting point to note is that there is a relationship between vitamin D and the prime micronutrient zinc; vitamin D enhances Zn uptake probably due to an effect on the synthesis of metallothioneins [9]. There may also be a remote relationship between vitamin D and Zn through the vitamin D binding protein (VDP) that its synthesis is enhanced by Zn.

·Another approach is that when vitamin D binds to the receptor, the active metabolite, calcitriol activates some specific tumour suppressor genes like BRCA1 and p21 (an inhibitor of cyclins-dependent kinase thus inducing cell cycle arrest). Vitamin D also promotes apoptosis through mitochondrial signaling without the aid of caspase, by inducing redistribution of pro-apoptotic or apoptotic promoting proteins BAK and BAX. At the same time Bcl-2 and IAPs that inhibit apoptosis are repressed or down regulated. It is perhaps important to recall that apoptosis is an exquisitely regulated process of cell death which not only plays a role in developmental morphogenesis but additionally controls cell numbers and eliminates damage cells. By this way apoptosis plays an important role in tumour suppression. Apoptosis is a very important endogenous tumour suppressor mechanism by which it eliminates cells that have extensive DNA damage and potential pathway to cancer.

VITAMIN E

Vitamin E as previously considered is the major antioxidant of the lipid rich constituents of the body. Most of the symptoms of deficiency such as haemolysis, neurologic disorders and infertility are all largely due to failure of this function. Toxicity as a result of excess intake is rare unlike vitamin A, although both are fat soluble. Its interaction with other micronutrients particularly selenium as seen previously is well established.

VITAMIN C (ASCORBIC ACID)

Vitamin C is an important aqueous antioxidant in the body just as α - tocopherol is for lipid constituents that is what ascorbate is to the aqueous system. Its interaction or relationship with other micronutrients has been previously discussed above. Its best characterised role as in the post- translational conversion of proline to hydroxyproline cannot be overlooked, a disorder of which in deficiency states leads to impaired collagen synthesis, the biochemical basis of scurvy. This may manifest clinically in addition to scurvy as perifollicular haemorrhages, bleeding gums, and failure of hair follicle eruption, poor wound healing and anaemia (secondary to Fe and THF unavailability; folate trap earlier discussed). The elegant role of interrelationship should not be ignored. What is particularly striking here is the

interaction with several other micronutrients and the common clinical manifestations as earlier seen. This may in part explain the variability in the clinical manifestations of micronutrient deficiency disorders. This concept may be relevant in the education in micronutrient approach first proposed by Anetor and Agbedana [17].

IRON

What this micronutrient is most widely recognized for is its association with microcytic hypochromic anaemia arising from its deficiency. Iron deficiency anaemia as we have seen may also develop through the interrelationship pathway with other micronutrients. Iron excess either from non-discretional consumption or from hereditary hemochromatosis (HH; disorder of HFE gene) can be toxic or damaging to body tissues. As is well known the chemical properties of iron makes it potentially a hazard in the organism. This is because the Fe(II) state in particular in non-protein bound (free) state can catalyse the generation of free radicals, which in turn can lead to peroxidation and radical chain reactions with attendant molecular damage (pro-oxidant effect). The well recognised Fenton reaction illustrates this: H2O2 + Fe(II) OH. + OH- + Fe(III) (the hydroxy radical (OH.) is the most damaging free radical to DNA and other biological constituents; Fenton reaction is inhibited by caeruloplasmin rich in Cu or the antioxidant enzyme Cu-ZnSOD)

This is the molecular pathway of the implication of Fe in carcinogenesis. In an environment where Fe preparations are readily available over the counter (an OTC drug) and the prevailing MDDs with associated oxidative stress there is need to exercise caution.

ZINC: MOLECULAR AND CLINICAL LINKS

Zinc may indeed be described as a prime micronutrient interacting with or regulating the activities of many other micronutrients owing to the very critical roles it plays in fundamental molecular and metabolic events, especially those bothering on protein synthesis, cellular replication and collagen synthesis. Zinc is required in the genetic makeup of every cell and is an absolute requirement for all biological reproduction. Zinc is needed in all DNA and RNA syntheses and is required at every step of the cell cycle. Thus it is not surprising that among the wide ranging deficiency disorders are, dermatitis and hair loss, growth retardation and poor wound healing. The latter of which it shares with ascorbate deficiency. Zinc deficiency in humans also inactivates other zinc containing proteins such as the tumour suppressor protein, p53 (guardian of the genome) and DNA base excision repair (BER) enzyme, apurinic endonuclease, with a resulting synergistic effect on genetic damage [18, 19]. Collectively, these observations illustrate the vital significance of micronutrient interrelationships. Ames 20has observed that deficiency in each of the micronutrients, Fe, Mg, (Mg, strictly not a micronutrient), Zn, and the vitamins B6, C, folic acid and biotin that have been examined resulted in increased DNA damage in rodents, primary human cells in culture or humans.

INCREASED DNA DAMAGE, MITOCHONDRIA DECAY OR MUTAGENIC OXIDANT RELEASE:INSIDIOUS CONSEQUENCES OF MICRONUTRIENT DEFICIENCY DISORDERS

Ames [20] from data in the above experiments consequently asserted that optimizing micronutrients intake will in turn optimize metabolism resulting in decreased DNA damage and less cancer as well as other degenerative diseases of aging. Ames [20] has rightly warned that there is little societal concern about MDDs because no overt pathologies have been associated with marginal to moderate levels of deficiency. Prepathologic features do exist as early markers of MDDs. The triage theory of Ames [21] predicts that the pathology of MDDs is insidious, but measurable. The triage theory posits that modest to moderate micronutrient deficiencies common in many populations, particularly in the developing countries accelerates molecular aging, including DNA damage and mitochondrial decay [22]. Ames and his colleagues hypothesize that two of the many insidious, but measurable consequences of moderate micronutrient deficiency disorders are increased DNA damage (future cancer) and mitochondrial decay (mutagenic oxidant release, future cancer, and cognitive dysfunction) as aspects of the triage response. Sensitive assays aimed at these end points have been suggested to have a high likelihood of detecting changes in individuals with moderate micronutrient deficiencies which may be better or more easily detected by examining interrelationships preferably at the molecular and metabolic levels (Figure 3) Previous and under listed examples will further drive this point home.

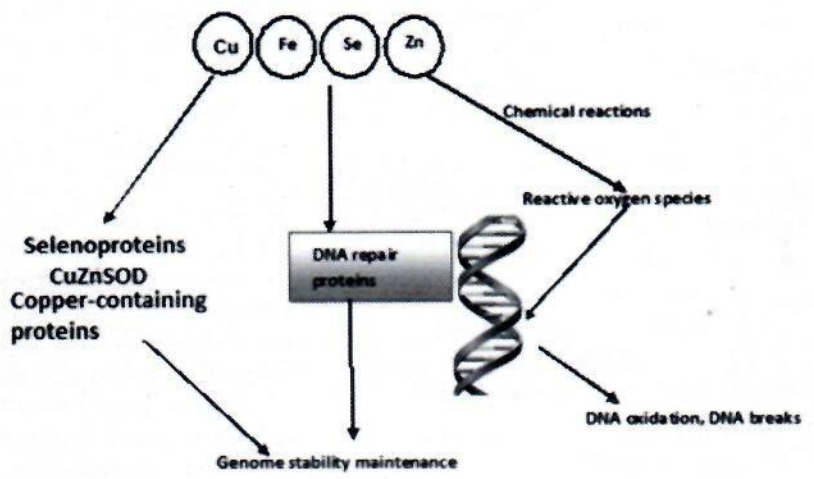

Figure 3. Shows the interrelationships of key trace elements in genomicstability: derangement the concentrations either due to nutritional deficiency or oxidative stress leads to genomic instability (After Cheng W-H. Impact of inorganic nutrients on genomic stability and maintenance, 2009; Environmental and Molecular Mutagenesis 50: 349-360)

COPPER: BIOCHEMICAL AND HAEMATOLOGICAL INDICES OF DEFICIENCY

Copper like Zn is also an important micronutrient well known for its role in electron transport chain via cytochrome c oxidase. In addition to its interaction with Fe, [23] and its antioxidant roles earlier considered, Cu, is also important in the synthesis of elastin and collagen cross linking which requires Cu-dependent amine oxidase as well as in the synthesis of neurotransmitters through its role dopamine-ß- hydroxylase and ascorbic acid in ascorbate oxidase.A well-known inherited deficiency disorder of this micronutrient is Wilson's disease previously mentioned. This may lead to precipitation of Cu in the basal ganglia (Parkinson's syndrome), in the cornea (Kayserfleicher's rings) and in the liver leading to cirrhosis which could also be a pathway to cancer of this site. Interestingly one of the ways of managing the condition is employing the antagonistic interaction between copper and zinc as earlier indicated. (not considered, see refs for details). Suggestive biochemical indices of the condition include, low plasma Cu, low caeruloplasmin, increased urinary Cu and demonstration of raised copper deposit in the liver (liver biopsy shows a lot of Cu). Leucopoenia, especially neutropenia are common haematological manifestations of Cu deficiency states. This isagain an elegant illustration of a metabolic derangement manifesting as haematological disorder that may require several differential diagnoses.

SELENIUM IN METABOLIC INTEGRATION OF NUTRIENTS

Selenium is another micronutrient of growing biological and medical importance. Its chemopreventive role now appears well established. It is more widely known for its role in the important antioxidant enzyme glutathione peroxidase (GPx). Its synergistic interaction with Cu and α -tocopherol (vitamin E) as alluded to above, as well as its role in thyroid metabolism are less well appreciated [24] Thus selenium integrates the metabolism of vitamin E and iodine important in thyroid physiology. Its earlier recognition in the cardiomyopathy, Keshan's disease first recognized in China is also very well established. This is one micronutrient, where extreme levels are very important because of the deficient and toxic effects respectively. Selenium is a prominent member of the chemopreventive agents and it is perhaps currently better recognised for this.

MANGANESE

Manganese is an important micronutrient or specifically a micromineral which helps to keep down oxidant release, thus mitochondrial decay and associated degenerative disorders. Owing to its role in the potent antioxidant, mitochondrial superoxide dismutase (MnSOD), manganese mops up most of the toxic oxygen intermediates released during respiratory burst in the mitochondrion. This role is more efficiently fulfilled when the other antioxidant, vitamin E in the mitochondrial membrane is in optimum level. It is possible that Fe excess may adversely affect this vital antioxidant function, as both micronutrients share a common transporter, transferrin.

ASSESSMENT/ CLINICAL SIGNIFICANCE: ROLEOF INTERRELATIONSHIPS

Briefly, it is important to note that the assessment of the micronutrient status of populations or individual patients should always take cognisance of the concept of interrelationships preferably at the molecular and metabolic levels. For instance both B12 and folate are required for erythrocyte replication and development. Thus both micronutrients are characterized by megaloblastic anaemia. The deficiency of the former may present as a neurological disorder, subacute combined degeneration of the cord (SCDC) with such signs as peripheral neuritis, degeneration of the dorsal column and cortico-spinal tract involvement. This is one reason why it is important to clearly differentiate the deficiency of one from the other as treatment with folate may mask the potentially serious neurological consequence of B12 deficiency. Pyridoxine deficiency may culminate in microcytic anaemia. Serum iron level may be raised in this condition; pyridoxine supplementation is required for the excess Fe to be incorporated into protoporphyrin-IX to form haem and finally Hb, thus restoring proper erythropoiesis. Microcytic hypochromic anaemia may also arise from both Fe and Cu inadequacy. Under this condition serum Fe level may be less than the reference value of ~13.40 μmol/l. In contrast to the previous case plasma Fe level is reduced. In the same vain Zn deficiency can also adversely affect erythropoiesis and associated Hb production, Zn is not commonly associated with microcytic hypochromic anaemia. But it does, and this is traceable to its interrelationships; casting our minds back to molecular and metabolic events will clarify this. This effect of Zn is indirect, arising from its role in gene expression, protein synthesis (Thymidine kinase, RNA & DNA polymerases are Zn dependent). Zinc is also present in the active site of the second enzyme in the haem biosynthetic pathway, delta-aminolaevulinate dehydratase (d-ALA-D), an enzyme exquisitely sensitive to lead exposure, hence the pathway for a long time served as a biomarker of effect for lead poisoning and haematolopathologic effect of lead. The impaired incorporation of Fe into protoporphyrin-IX due to lead's inhibition of ferochelatase leads to Zn substituting for Fe forming zinc-protoporphyrin (ZPP) used as a biomarker of both lead toxicity and detection of Fe deficiency depending on the clinical state (Figure 4- Haem biosynthetic pathway).Thus zinc deficiency among the well known clinical manifestations (briefly discussed above) may mimic in part Fe deficiency. It is a common mistake in the laboratory investigations for anaemia as well as other nutritionally related disorders to assume that the deficiency condition is a simple one or mononutrient deficiency disorder. This occurs rarely. Rather the disorder may develop as a molecular or metabolic response interactive or clustering effect. Assessment of iron status may be inadequate just looking at the traditional indices of Fe homeostasis alone; serum Fe, Ferritin, transferrin levels, per cent saturation, transferrin receptors etc. This will be more effectively done, if other indices such as ascorbate, Zn, B6 and even caeruloplasmin are included. The later will in addition give information about acute phase response which can spuriously raise ferritin levels. Just as from the metabolic point of view in assessing rickets the ascorbate status will be useful.

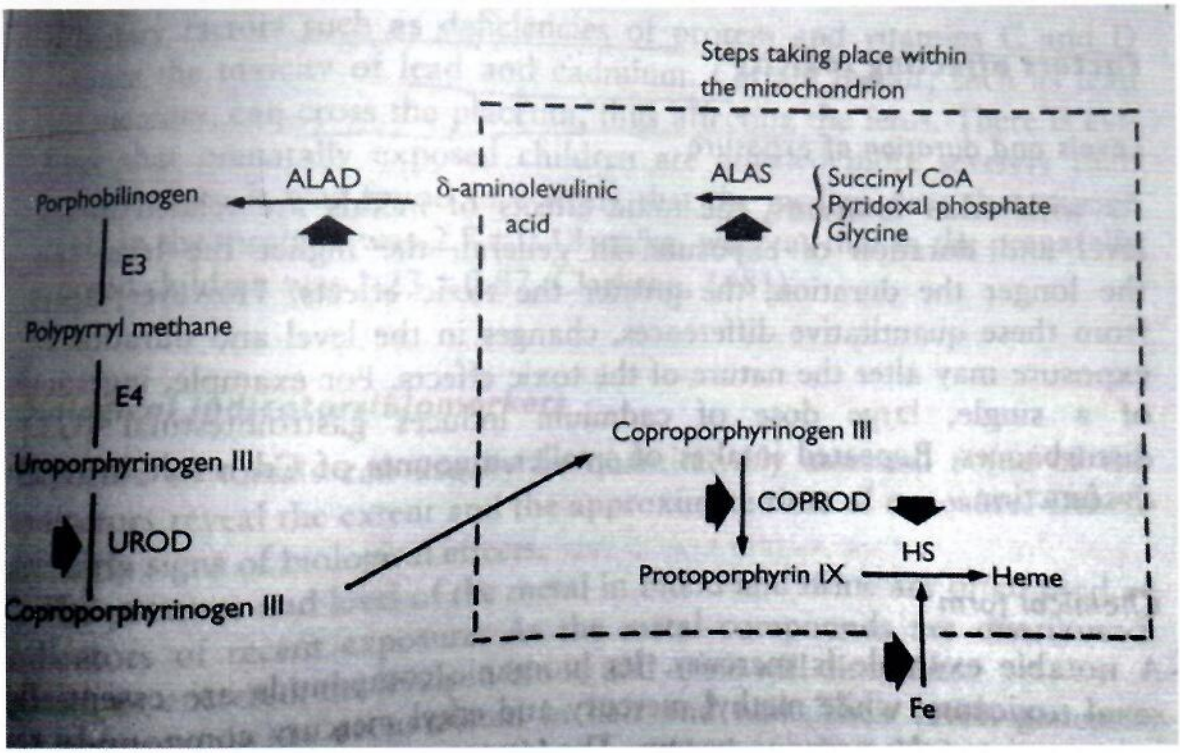

Figure 4. The Haem Biosynthetic Pathway. Thick arrows show point of lead (Pb) interference; ALAD is Zn dependent (After Lu F and Kacew S, Lu's Basic Toxicology: Fundamentals, Targets Organs and Risk Assessment, 2003, Taylor and Francis, Bristol)

The clinical value of the micronutrients continues to gain recognition. This is evident from the recent randomized controlled study by the team of Smith et. al. [25] from the United Kingdom, who found that high doses of the of B-vitamins; folate, vitamin B12 and vitamin B6 in elderly subjects with mild cognitive impairment can reduce the pace or slow down the atrophy of brain tissue, a wasting process associated with Alzheimer's disease. The subjects in this study wereconsideredto have high risk of dementia. These investigators demonstrated that the brains of subjects administered B – vitamins shrunk less during the two-year duration of the study compared to individuals given placebo. The B- vitamins supplemented group also exhibited less atrophy of grey matter regions, a region very vulnerable to Alzheimer's disease. The investigators suggested that data from their study may indicate need to pay attention to non-genetic aspect of the disorder and that it has potentials for better treatment option. Though not explicitly stated, one clear operative mechanism here may be the joint relationship of these vitamins in dissimilating homocysteine, a metabolite from methionine demethylation. These vitamins cooperatively either remethylated homocysteine to methionine an action involving B12& folate through the intermediary of methyl synthetase an enzyme dependent on zinc or the breakdown of homocysteine via cystathionine ß- synthase, an enzyme requiring pyridoxine or B6. The important message here is the metabolic and molecular relationships of these micronutrients in bringing about an improved clinical state.

The relationship between vitamin A and Zn in part accounts for both micronutrients being molecular targets in the treatment of cancer. Zinc as previously indicated is necessary for the production of retinol binding protein, both RBP and vitamin levels can be reduced in cancer patients. Without adequate RBP, the mobilization of vitamin A from the liver may be impaired [26, 27] Vitamin A is vitally important; acts to regulate gene expression through interactions with its specific ligand-dependent transcription factors also known as nuclear receptors [28] Aside from transcription regulation, vitamin A is required for normal cell proliferation and differentiation of both leukocytes and intestinal epithelium. This may in part explain the diarrhoea that characterizes Zn deficiency, particularly in children. The increased morbidity and mortality arises mainly from G.I.T and respiratory infections traceable to compromised vitamin A deficiency needed to mount optimum immune response at these sites [29] An important lesson for this region of the world is that vitamin A deficiency is a common MDD which will ultimately result in death if not detected early and treated due to impaired immunity and infection. But it is perhaps more important to recognise the vital interrelationship with Zn whose deficiency may serve as a prepathologic marker. In other words an appropriate assessment for vitamin A status will be better conducted if both RBP and Zn levels are simultaneously evaluated. The wide spread zinc deficiency5 and interrelationship with other antioxidant micronutrients probably aptly justifies Tolonen's 30 argument over two decades ago for micronutrient analysis and therapy. More recently, other investigators have directly or indirectly supported this principle as a means of protecting the population against degenerative diseases of old age particularly cancer and cardiovascular disease and with increasing industrialization in the developing countries the toxic states may be included [31, 32, 33] Therecent review of Hughes et. al. [34] provides a breath of fresh air to emerging issues in micronutrients particularly as it concerns vitamin B12 and how metabolic interrelationship is vital in assessments of micronutrients status function and clinical manifestations of disorders. Another very recent report,

incidentally from a developing country, India again elegantly illustrates the role of intricate metabolic relationships in a number of pathologic states such as vascular and ocular pathologies commonly occurring in Eale's disease (an idiopathic retinal vascular disorder)[35]. Though hyperhomocysteinaemia was identified as a major factor, this can arise from both folate and B12 biounavailability in turn leading to copper deficiency [36] leading to lysyl oxidase decreased activity, a copper dependent enzyme required for the synthesis of crosslinks in collagen and elastin [37] in part explaining the vascular pathology in this condition. Aside from this, it appears important to note that the metabolism of homocysteine, a metabolic intermediate and Cu are intimately linked and can cause Cu deficiency which would additionally imply weakened antioxidant defence of the two enzymes superoxide dismutase (Cu-ZnSOD) and caeruloplasmin [38, 39] This pathway also has implications for the ferroxidase activity of caeruloplasmin whichscavenges Fe (II) countering the Fenton and Haber-Weiss reactions reducing oxidative stress. In this condition (Eales'disease) this will be accentuated. This condition and many others clearly illustrate the central role micronutrients play in metabolism and tissue function which in the final analysis rests on molecular mechanisms.The review of Alan Shenkin [40] has elegantly illustrated and emphasised this, alluding to interrelationships through intricate fluxes.

CONCLUSION

The micronutrients play key significant roles in the molecular and metabolic processes of life. Consequently many systems exist in the living organism ensuring that the micronutrients strictly, vitamins and trace elements such as vitamins, A C, D, E, folate, cyanocobalamin and the trace elements; Cu, Fe, Mn, Se and Zn are appropriately channelled into cellular and Subcellular compartments where they exert their molecular and metabolic functions. The micronutrients exhibit intricate metabolic and molecular interrelationships which appear to govern the manifestations of their disorders. It is critically important to recognise this. Thus the prepathologic and clinical manifestations of disorders affecting these nutrients are markedly modulated by their interrelationships. These relationships largely define the true biological state of micronutrients thus the molecular and metabolic interrelationships deserve greater understanding and attention in clinical practice.

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A REVIEW OF CHILDHOOD HYPERTENSION IN NIGERIA

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A B S T R A C T

Hypertension is a chronic medical condition whereby the arterial blood pressure is elevated. Normally blood pressure is usually within a continuous range, so cut-off levels are defined according to their effect on patients. In children, this cut-off has been defined for age, sex and height. Though commonly seen in adults, its prevalence is gradually increasing in children and more of this burden in Africa. The knowledge, early diagnosis and proper management of this disease have greatly improved the quality of life even into adulthood.

Keywords: *hypertension, children, Africa (Nigeria).*

INTRODUCTION

Hypertension is one of the commonest non-communicable diseases affecting both males and females of all races and it is a leading cause of morbidity and mortality. [1] The prevalence of childhood hypertension and the rate at which it is diagnosed seem to be increasing because of increase in the rate of childhood obesity as well as the awareness of this disease. Hypertension is commoner in adults but children could also be affected. [2]

Defining childhood hypertension is based on the normal distribution of blood pressure in normotensive children. Normal Blood Pressure is defined as Systolic Blood Pressure and Diastolic Blood Pressure that is less than the 90th percentile for sex, age and height. Hypertension is defined as an average Systolic BP or Diastolic BP that is greater than or equal to the 95th percentile for sex, age, and height on at least three different occasions. [3] There is an evidence that hypertension in children can progress into adulthood thus increasing morbidity and mortality in adults. [4]

Childhood hypertension can either be essential (primary) or secondary.
Essential hypertension is associated with a positive family history of hypertension and other cardiovascular diseases. There is a relationship between obesity and essential hypertension and it often coexist with other risk factors such as diabetes mellitus, therefore children with essential hypertension in the presence of other co morbidities have an increase risk of cardiovascular disease and an adverse effect on their health indices. Secondary hypertension is usually due to an underlying cause, more commonly seen in children than in adults, so when hypertension affects children; it is more likely to be secondary. [5]

Children tend to develop hypertensive cardiovascular complications more than adults leading to decrease in life expectancy if left untreated. [6, 7]

PREVALENCE OF CHILDHOOD HYPERTENSION IN NIGERIA

In children, blood pressure tends to increase with age and height. The prevalence of childhood pre-hypertension and hypertension globally is 3.4% and 3.6% in a recent study by Hansen et al. [8] the prevalence was found to be 0.5% in Caucasian girls while that of African American girls was 1-2%. [9] Globally, the prevalence of childhood hypertension is increasing gradually but more of the burden lies in developing countries. This increase is due to urbanization and the rising prevalence of obesity. [10]

In Nigeria there are few studies on the epidemiology of childhood hypertension and the prevalence of childhood hypertension among children 5 years and below was 1.9%. [11] Among adolescents, the prevalence of hypertension ranges from 0.5 % in South West Nigeria, to 22% in the middle belt and 17.3% in Eastern Nigeria. The prevalence of childhood hypertension in both children and adolescent however has ranged from 0.1% in South West Nigeria to 4.6% in the middle belt and 3.2 -5.4% in Eastern Nigeria. Childhood hypertension in children and adolescents is usually associated with childhood obesity. [12, 13, 14, 15]
In a review of 138 children who attended University College Hospital Ibadan, during a 9 year period, Aderele W.I., Seriki O. reported that out of the 138 cases reviewed, 73 had various complaints such as convulsions, hemiplegia and features of heart failure and anemia, 36 presented with hypertension associated with acute glomerulonephritis, 30 presented with uraemia and 20 with severe anaemia. Most of the patients who had uraemia were found to be anaemic. 19 were in heart

failure, 9 patients had hypertensive encephalopathy and 2 out of these had papiloedema. The remaining 5 patients presented in various other ways; Leukaemia, hydronephrosis, haemolytic-uraemic syndrome, nephroblastoma, haematuria. [16]

AETIOLOGY

Childhood hypertension can either be primary/essential or secondary.

Primary childhood hypertension also known as essential hypertension has been seen in children and adolescents without an obvious underlying cause. There has been evidence that childhood obesity is a risk factor and is associated with positive family history of hypertension. Other risk factors include race and sex. [5]

Secondary hypertension is more common in children than in adults. For all age groups, renal parenchymal or renovascular causes together account for ~60-90% of secondary causes. [17]

Increase in blood pressure can be transient i.e. short lived hypertension which may rarely become sustained hypertension. This can be caused by acute renal disease (nephritis), lead poisoning, hypercalcemia, familial dysautonomia, drug therapy (steroids) or overdose, excess administration of blood. Hypertension can also be reactive in nature; this can be due to resposne to pain, hypovolemia, change in emotion, or time of the day. [18]

The table below shows the aetiological diagnosis in the 138 children who attended university college hospital Ibadan during a 9 year duration; a retrospective review by Aderele, W. I., and Seriki, 0. [16]

Table 1:

The aetiological diagnosis in the 138 children who attended university college hospital Ibadan during a 9 year duration; a retrospective review by Aderele, W. I., and Seriki, 0. [16]

	MALE	FEMALE	TOTAL	% OF TOTAL
Acute glomerulonephritis	18	18	36	26.0
Subacute and chronic glomerulonephritis	13	14	27	20.0
Nephrotic syndrome	8	16	24	17.0
Nephrotic syndrome treated with steroids	16	20	36	26.0
Renovascular	1	2	3	2.2
Pyelonephritis	1	1	2	1.5
Undetermined	5	1	6	4.4
Miscellaneous – hydronephrosis, steroid therapy only, haemolytic-uraemic syndrome, nephroblastoma	3	1	4	2.9
	65	73	138	100.0

STAGING OF CHILDHOOD HYPERTENSION

Normal BP is systolic BP or diastolic BP < 90th percentile for age and height.

Pre-hypertension is systolic BP or diastolic BP of 90th -95th percentile for age or BP that exceeds 120/80 even if below 90th percentile up to 95th percentile.

Stage I hypertension is systolic or diastolic BP of 95th-99th for age plus 5mmHg.

Stage2 hypertension is systolic or diastolic >99th percentile for age plus 5mmHg. [5, 17]

CLINICAL EVALUATION

Generally, hypertension is asymptomatic in most people; however the clinical presentation varies in children who are hypertensive. A good detailed history, physical examination and laboratory investigations are important in evaluating a child with hypertension.

The history should include history of headaches, dizziness, symptoms of underlying renal disease (gross hematuria, enuesis, fatigue, and oedema), heart disease (chest pain, exertional dyspnoea, and palpitations). The past medical history including recent and chronic illnesses, previous hospitalization, and recurrent urinary tract infections and obstruction. A family history of hypertension, renal disease, and diabetes mellitus should be elicited.

The physical examination should include determination of patient's height and weight percentiles to know whether or not the child is normally grown as this gives clue to presence of an underlying chronic illness such as chronic renal disease. Vital signs should be done, a high pulse rate will suggest hyperthyroidism, phaechromocytoma, essential hypertension. A significant difference between the BP reading of upper and lower extremities may suggest coarctation of the aorta. Moon facies, Elfin facies, webbed neck and thyromegaly will suggest cushing's syndrome, Williams syndrome, Turner syndrome and hyperthyroidism or hypothyridism respectively.

The following laboratory investigations should be carried out to

Table 2:

Drugs Of Choice For Pediatric Hypertension. [20]

CLASS	DRUG	DOSAGE	COMMENTS
Angiotensin-converting enzyme (ACE) inhibitor	Benazepril	0.2 mg/kg/day up to 10 mg/day (qd)	Dry cough and hyperkalemia may occur, it is therefore contradicated in pregnancy, hyperkalemia, and bilateral renal artery stenosis. Use in high plasma rennin activity, renovascular disease, renal parenchymal disease, proteinria, chronic heart failure, diabetes mellitus, hyperlipidaemia, and reactive airway disease
	Captopril	Infant:0.02-0.5mg/kg/d (bid-tid) Child:0.15-1.5mg/kg/d (bid-tid) Adolescent:25-100mg/d up to 450mg/d	
	Enalapril	0.08 mg/kg/day up to 5 mg (qid-bid)	
	Fosinopril	0.1mg/kg/d upto 10mg (qd)	
	Lisinopril	0.07 mg/kg/day up to 5 mg/day	
	Quinapril	5-10mg/d (qd)	
	Ramipril	2-5mg/d (qd)	
Angiotensin-receptor blocker	Candesartan	Ages1-6y: 0.2mg/kg/d(qd) Ages >6y: 4-8mg/d (qd) Weight >50kg: 8-16mg/d (qd)	They are used less commonly than ACE inhibitors although concomitant therapy may further reduce proteinuria. Cough and hyperkalemia may occur..
	Irbesartan	75-150mg/d(qd)	
	Losartan	0.7mg/kg/d upto 50mg (qd)	
	Valsartan	1.3mg/kg up to 40mg/d(qd)	
α- βblocker	Labetalol	1-3mg/kg/d up to 1200mg/d (bid)	Used in the management of chronic heart failure.
	Carvedilol	0.2mg/kg/d up to 12.5mg(bid)	
B-adrenergic antagonists	Atenolol	0.5-1mg/kg/d(qd-bid)	They are the drug of choice in coarctation of the aorta but should be avoided in athletes and patients with diabetes.
	Bisoprolol	0.04mg/kg/d up to 2.5/6.25mg/d(qd)	
	Propranolol	1mg/kg/d(bid-tid)	
Calcium channel blockers	Amlodipine	0.06mg/kg/d up to 5mg(qd)	They can be used in patients with hyperlipidemia, asthma, renal disease, diabetes mellitus. Adverse effects include flushing, nausea/vomiting, headache and edema.
	Nifedipine XR	0.2-0.50mg/kg/d(qd-bid)	
	Felodipine	2.5mg/d up to 10mg/d(qd)	
Central α agonists	Clonidine	5-10mcg/kg/d(bid-tid)	May cause transient sedation initially and should not be stopped abruptly.
	Methyldopa	5mg/kg/d(bid-qid)	
Diuretics	Amiloride	5-10mg/d(qd)	Use in fluid overload and chronic heart failure.
	Chlorothiazide	10mg/kg/d(bid)	
	Furosemide	0.5-2.0mg/kg/d up to 100mg/d(qd-bid)	
	Spironolactone	1mg/kg/d(qd-bid)	
Peripheral α antagonist	Doxazosin	1mg/d up to 4mg/d(qd)	Higher risk of hypotension and syncope.
Vasodilators	Hydralazine	0.75-1mg/kg/d up to 200mg/d(bid-qid)	Hydralazine causes systemic lupus erythematous-like syndrome. Use mioxidil in resistant hypertension, contraindicated in chronic heart failure.
	Minoxidil	0.1-0.2mg/kg/d(qd-bid)	

determine the cause of the hypertension and presence or absence of end organ damage and other co-morbidities; urinalysis and culture, electrolytes, urea and creatinine, lipid profile, electrocardiogram, echocardiogram, renal ultrasound, etc. [19]

MEASUREMENT OF BLOOD PRESSURE IN CHILDREN

Children over the age of 3 years should have their Blood pressure measured during hospital visits. This is done by using a cuff that is appropriate to the size of the child's upper arm, using the auscultation method which is the most preferred method. Blood pressure greater than 90th percentile obtained by oscillometric devices should be repeated using auscultation method: also elevated BP must be repeated on several occasions before confirming the diagnosis of hypertension.
Instances where children less than three years should have their blood pressure measured include:

- History of prematurity, very low birth weight, or other neonatal complication requiring intensive care.
- Congenital heart disease (repaired or non-repaired).
- Recurrent urinary tract infections, hematuria, or proteinuria.
- Known renal disease or urologic malformations.
- Family history of congenital renal disease.
- Solid-organ transplant.
- Malignancy or bone marrow transplant.
- Treatment with drugs known to raise BP.
- Other systemic illnesses associated with hypertension (Neurofibromatosis, tuberous sclerosis, etc).
- Evidence of elevated intracranial pressure. [5]

MANAGEMENT

This can be; Non pharmacologic therapy
Pharmacologic therapy

Non-pharmacologic therapy
Lifestyle modification is an important therapy for hypertension associated with obesity through weight reduction and subsequently preventing excess weight gain. Regular physical activities (exercise), avoiding sedentary lifestyles, reduction of alcohol intake and ceasation of cigarette smoking will all contribute to improved blood pressure control.

Dietary modification such as reduction in salt intake, increase dietary potassium should be strongly encouraged in children and adolescents who have BP levels in the pre-hypertensive range as well as in those with hypertension. Family-based intervention has been shown to improve outcomes.

Pharmacologic therapy
Indications for anti-hypertensive drugs.

- Symptomatic hypertension.
- Secondary hypertension.
- Hypertensive target-organ damage.
- Diabetes (types 1 and 2).
- Persistent hypertension despite non-pharmacologic measures. [5]

In the study carried out by Aderele, W. I., and Seriki, O., specific antihypertensive drugs (methyldopa, hydrallazine, guanethidine) were used on 68 patients with either nephrotic syndrome or chronic renal failure. Reserpine was used patients with acute glomerulonephritis. In addition to the specific antihypertensive drugs, all patients with encephalopathy received magnesium sulphate. Remission of the hypertension followed nephrectomy in 1 patient who had nephroblastoma. The prognosis in the 138 patients was 28% died, 59% had normal blood pressure when last seen, 4% were still attending hypertension clinic, 9% were still hypertensive when lost to follow-up. [16] Most of these drugs used are no longer first line antihypertensives according to several current guidelines on management of hypertension.

CONCLUSION

Childhood hypertension is a determinant of adult morbidity and mortality and can only be diagnosed with the knowledge of the normal range of blood pressure for the age, height and sex of that individual. Considering the gradual increase in its prevalence globally and much more in Africa even though it is less common than that of adults, there is need for early diagnosis and proper evaluation in order to reduce the negative impact of the disease.

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ROLE OF RADIOLOGY IN PSYCHIATRY

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A B S T R A C T

Objective: Interest in neuroimaging of psychiatric disorders has increased in the last decade. Apart from the use of structural imaging modalities like Computed Tomography (CT) to exclude physical disease mimicking psychiatric illnesses, recent advances have been made in the use of neuroimaging to study the neurobiological changes in psychiatric disorders. There will be an increase in the clinical use of neuroimaging modalities in the near future hence clinicians need to be aware of the potential applications.

Method: An electronic search of published literature between 1990 and 2012 was conducted via MEDLINE, PubMED and Google Scholar using a variety of search terms to find relevant articles. Bibliographies of retrieved papers were further examined for publications of interest. Articles that reported clinically significant findings and research reports conducted using applicable neuroimaging modalities were reviewed in detail.

Results: The review suggests that there are exciting neuroimaging advances that have relevance to psychiatry. New neuroimaging modalities and applications with potential clinical utility are emerging and the use of these technologies will increase in coming years. Although most of the neuroimaging applications are still under research, clinically meaningful findings have begun to emerge in mood disorders, post-traumatic stress disorder, schizophrenia and dementia.

Conclusion: Neuroimaging has a well recognized role in the diagnosis of various psychiatric disorders and clinicians should understand the benefits and limitations. The integrated use of neuroimaging in conjunction with clinical assessments promises to improve clinical care and markedly alter psychiatric practice.

Keywords: *radiology, psychiatry*

INRODUCTION

Radiology is the medical specialty that utilizes medical imaging technologies for diagnosing and treatment intervention. Psychiatry on the other hand, is a medical specialty that is concerned with the prevention, diagnosis and treatment of mental illness.

While several imaging modalities can be useful in the evaluation of a psychiatric patient, the focus of this review will be on neuroimaging.

Neuroimaging is a powerful tool for the study of the neurobiological changes in psychiatric disorders. In recent years, the research of brain structure and function has increased exponentially[1]. In psychiatric practice, the focus of aetiopathological basis of mental illness has shifted from the mind to the brain. Before now, psychiatrists routinely explain behavioural dysfunctions solely in terms of psychological concepts; however, they are beginning to explain these disorders with reference to the structure and function of the brain[1].

With the recent advance in technology, biomedical engineering and computing have increased our ability to better understand the neurobiology of the brain. In this review, an overview of the available neuroimaging modalities and highlights of significant findings across a select number of psychiatric disorders will be discussed. Certain disorders are amenable to investigation using neuroimaging and significant numbers of studies have been conducted to examine these disorders. They include: Post-traumatic stress disorder (PTSD), mood disorders, schizophrenia, and Alzheimer's disease (AD)[1].

Neuroimaging can also be used to rule out organic brain diseases which sometimes cause psychiatric-like symptoms[1]. These include brain tumors, intracranial infections and stoke.

The possible neuroimaging modalities available now are classified into structural and functional modalities. The structural types include Plain radiography, Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI).

Functional imaging modalities however include Positron Emission Tomography (PET), Single photon Emission CT (SPECT), functional MRI (fMRI), Magnetic Resonance Spectroscopy (MRS), Magnetic Resonance Morphometry, Diffusion – Tensor Imaging (DTI)[2].

CLINICAL NEUROIMAGING IN PSYCHIATRY

1. Organic Brain Disease

This is a nearly obsolete term in psychiatry referring to many

physical disorders that cause impaired mental function. This includes disorders such as brain abscesses and tumours (figs 1 & 2), traumatic head injury (figs 3), stroke (fig 4) and intracranial infections. It usually does not include psychiatric disorders. It is important to exclude physical disorders since management of these differ from that of psychiatric illnesses. Some of these conditions are amenable to surgical or medical treatment once a diagnosis is made. Excision of an intracranial tumor for example, might result in improvement in symptoms. Intracranial toxoplasmosis can be treated medically with resultant resolution in patient's symptoms.

In patients with organic brain disorders, plain radiograph of the skull may show intracerebral calcifications, intracranial infections or bone destruction in lesions such as metastasis (fig.5).

CT and MRI are cross-sectional imaging modalities that are more sensitive than plain radiograph in neuroimaging. They show adequate soft tissue resolution without craniectomy. CT is cheaper and more readily available than MRI in a low income country like Nigeria. MRI though with a better soft tissue resolution and multiplanar capability, is still not readily accessible by a majority of patients.

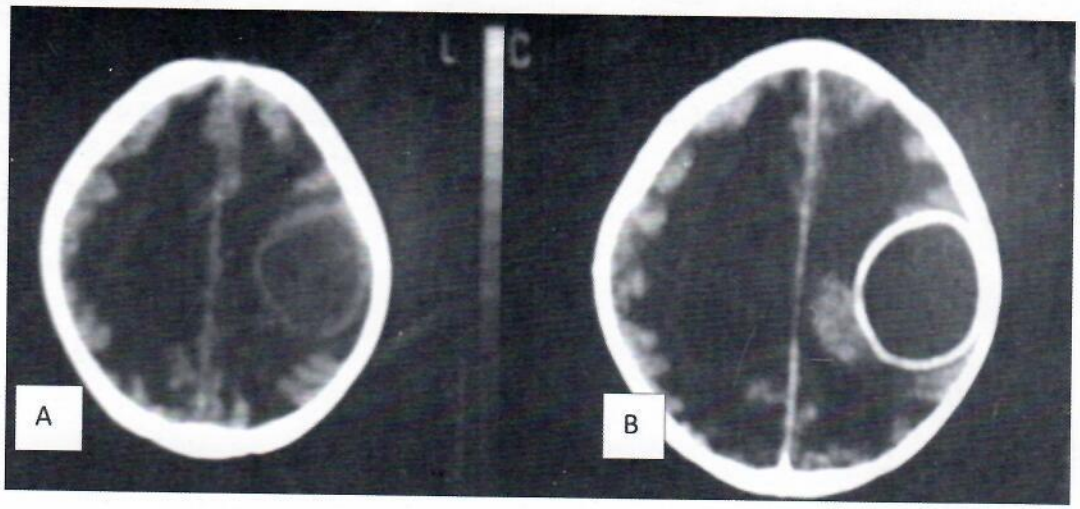

Fig. 1 Axial non-enhanced cranial CT showing a roundish hypodense mass with slightly hyperdense rim in the left parietal lobe. The mass shows avid ring enhancement post contrast injection (B) consistent with an intracranial abscess.

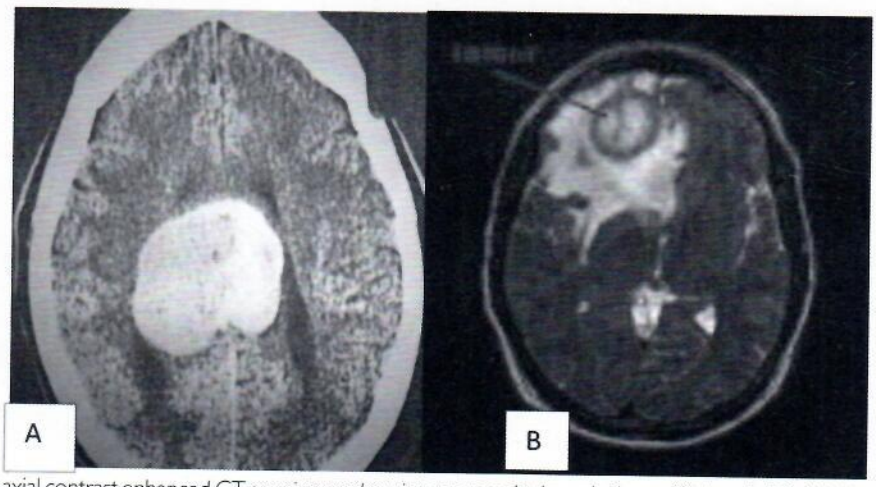

Fig. 2 (A) An axial contrast enhanced CT scan image showing a parasagittal meningioma. (B) An axial T2-Weighted cranial MRI showing a roundish tumour of mixed signal intensity with extensive surrounding hyperintensity consistent with perilesional oedema.

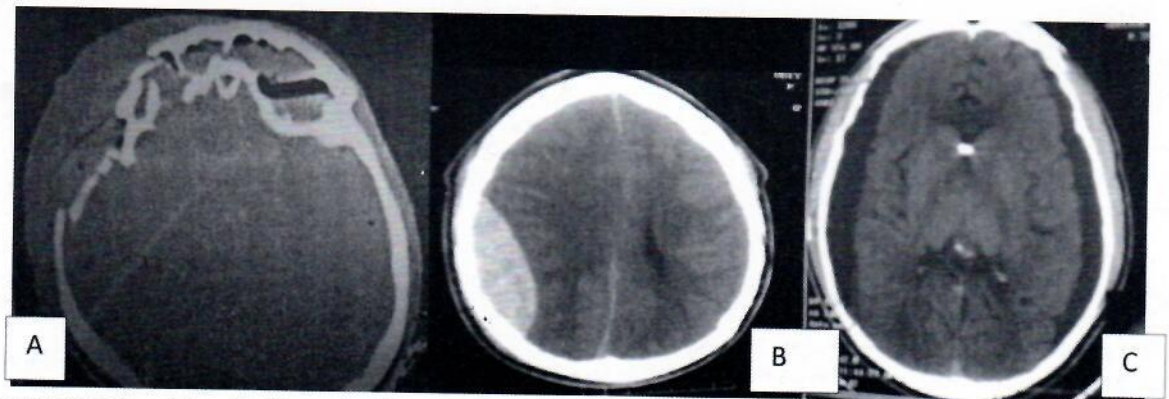

Fig. 3 (A) Bone window of an axial cranial CT scan showing comminuted right frontal depressed fractures with associated intracavitoryhaematoma in the frontal sinuses and overlying soft tissue swelling. (B) A non-enhanced axial cranial CT scan image showing a biconvex hyperdensity in the

right parieto-occipital convexity consistent with an acute epidural haematoma. There is associated compression of the ipsilateral lateral ventricle, and generalized effacement of the cerebral sulci. (C)A non-enhanced axial CT scan showing bilateral cresentic shaped hypodensity in the fronto-parietal-occipital convexity consistent with chronic subdural haematoma.

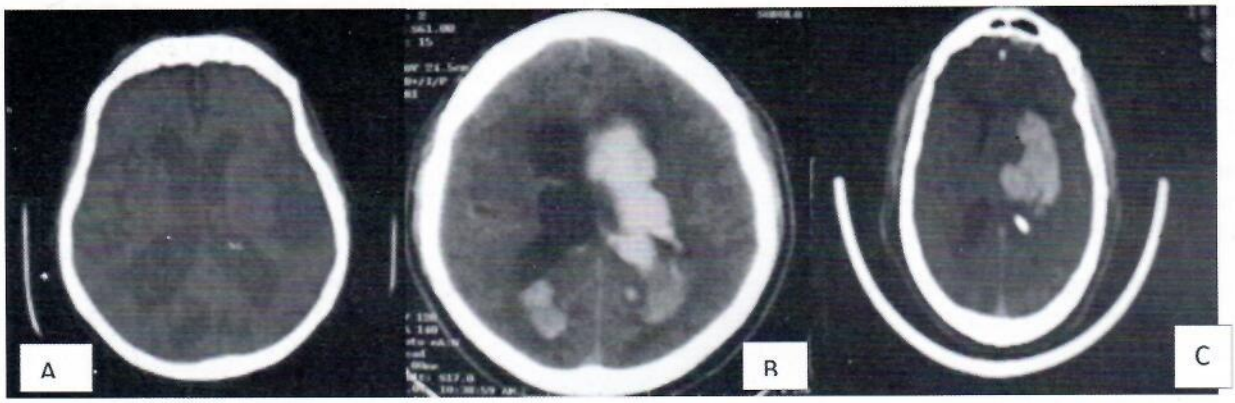

Fig. 4 (A) Axial non-enhanced cranial CT scan showing prominence of the cerebral sulci and ventricles in keeping with cerebral atrophy. A triangular shaped hypodensity is seen in the left parietal lobe consistent with a typical watershed cerebral infarct. (B) Axial non-enhanced cranial CT scan showing extensive intraventricular hemorrhage from a large putaminal hemorrhage (C) in a patient with hemorrhagic cerebrovascular accident.

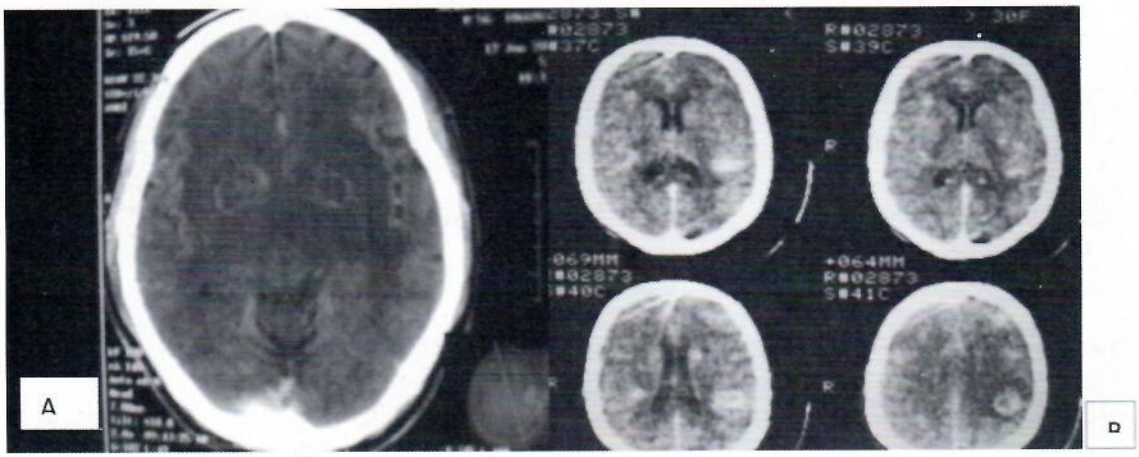

Fig. 5 (A) An axial contrast enhanced CT scan showing multiple ring enhancing lesions in the basal ganglia region bilaterally in keeping with intracranial toxoplasmosis. (B) Another contrast enhanced CT scan of a patient with left parietal tuberculoma.

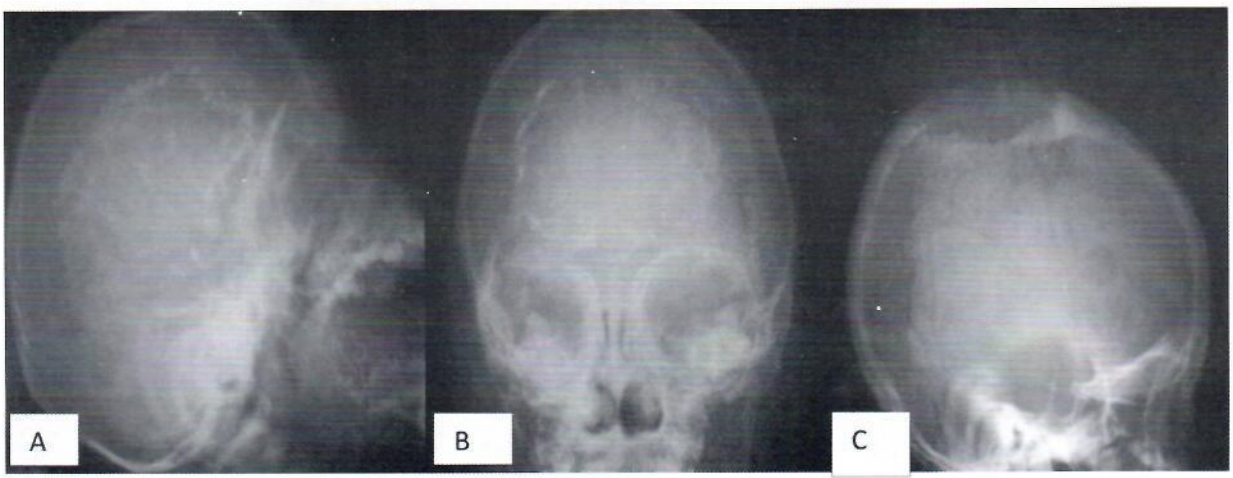

Fig.5. Plain radiograph of the skull showing intracranial calcifications (A&B). A Lateral plain radiograph of the skull showing destruction of the parietal bone at the vertex consistent with a metastatic bone lesion ©.

1. Post- traumatic Stress Disorder (PTSD)

Structural changes involving the anterior cingulated cortex and hippocampus have been identified in Post Traumatic Stress Disorder (PTSD) patients. The hippocampus is noted to be reduced in size by different types of trauma including physical and sexual abuse[3,4]. Functional neuroimaging such as Positron Emission Tomography (PET) and Single Photon Emission CT (SPECT) in PTSD suggest that metabolic activity in the medial pre-frontal cortex – amygdale circuit is significantly altered. The most consistent findings have been those of increased amygdale

and decreased medial pre-frontal cortex activation[5].

2. Mood Disorders

The mood disorders include major depression and bipolar disorder. The most consistent MRI structural neuroimaging finding in studies of patients with mood disorders is that of increased white matter hyperintensities (WMH) especially in unipolar patients[6]. A similar finding is seen in bipolar disorders especially in the subcortical grey, periventricular and deep white matter[7]. However, signal hyperintensities lack anatomical and diagnostic specificity. They occur in aging and are found in a variety of neuropsychiatric disorders including schizophrenia and dementia[8].

Studies in unipolar depressed patients suggest reduction in prefrontal cortical volume compared with healthy subjects while amygdala enlargement is a consistent finding in bipolar disorder[1]. Hippocampus is reduced in size in unipolar depressed patients but largely unaltered in patients with bipolar disorder[1].These neuroimaging are best demonstrated with Magnetic Resonance Imaging (MRI), which may be responsible for the poor imaging diagnosis in our setting where MRI are few and far between.

Functional imaging- Using cerebral blood flow studies (PET and SPECT) in patients with depression, a consistent finding is that of decreased anterior paralimbic, midbrain and cortical activity (figs. 6 & 7). In patients with major depression, this finding of diminished blood flow reverses with successful treatment of the illness[1]. Unfortunately, this imaging modality is not yet available in a developing country like ours.

Proton spectroscopy studies like the PET and SPECT are also not available in Nigeria. However in depressed patients, they show modest increase in concentration of basal ganglia and anterior cingulated Choline. Dorsolateral pre-frontal N- acetyl aspartate (NAA) and creatinine (CR) as well as basal ganglia NAA are also reported to be diminished in patients with bipolar disorders[9,10]. Functional Magnetic Resonance Imaging (fMRI) has been used to suggest that the right prefrontal cortex is an important destination for limbic projections and that it may play a role in modulating mood states[11]. The amygdala is also a region of interest as it has been noted that sad and happy affect can produce amygdala activation[12].

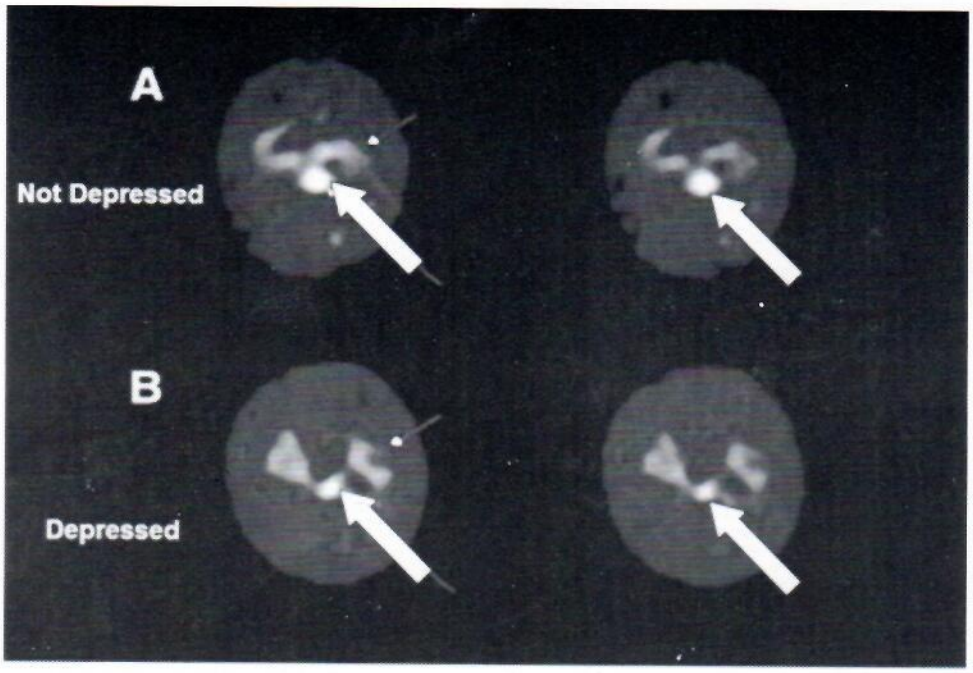

Fig. 6 Axial SPECT functional images showing a control subject (A) and a depressed subject (B). Long arrows point to midbrain uptake, which is markedly less in depressed subject than in control subject.

Fig. 7 Axial PET functional images comparing fludeoxyglucose 18 (FDG) uptake in a normal individual (right) and a patient with depression (left). There is generalized reduction in the cortical uptake in the patient with depression.

1. Schizophrenia

It is now known that Schizophrenia is a neurodevelopmental disorder with neuropathological evidence from macroscopic and histological studies of the brain[1]. On Magnetic Resonance imaging, the Schizophrenic shows white matter hyperintensities (WMH) which are usually common later in life (fig 8)[13]. Recently, it has been found that there are focal decreases in brain parenchyma in specific brain regions and nuclei, such as the putamen, thalamus and superior temporal gyrus in this same category of patients[14]

PET and SPECT studies demonstrate increase dopamine release in Schizophrenia[15]. Magnetic Resonance Spectroscopy (MRS) studies reported a reduction in frontal and temporal cortex NAA concentrations suggesting neuronal loss that is in keeping with localized reduction of grey matter[1].

A consistent finding on functional Magnetic Resonance Imaging (fMRI) of patients with Schizophrenia is hypofrontality (fig. 9), that is, inability to generate a frontal cerebral response to certain tasks[16].

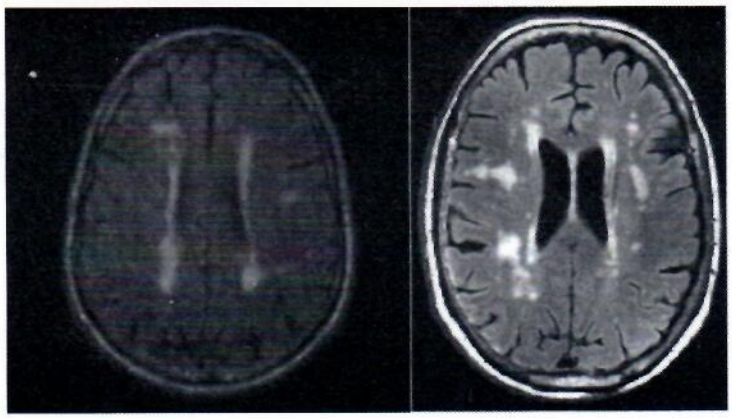

Fig. 8 Axial Fluid Attenuated Inversion Recovery (FLAIR) MR images of the brain showing periventricular and deep white matter hyperintensities .

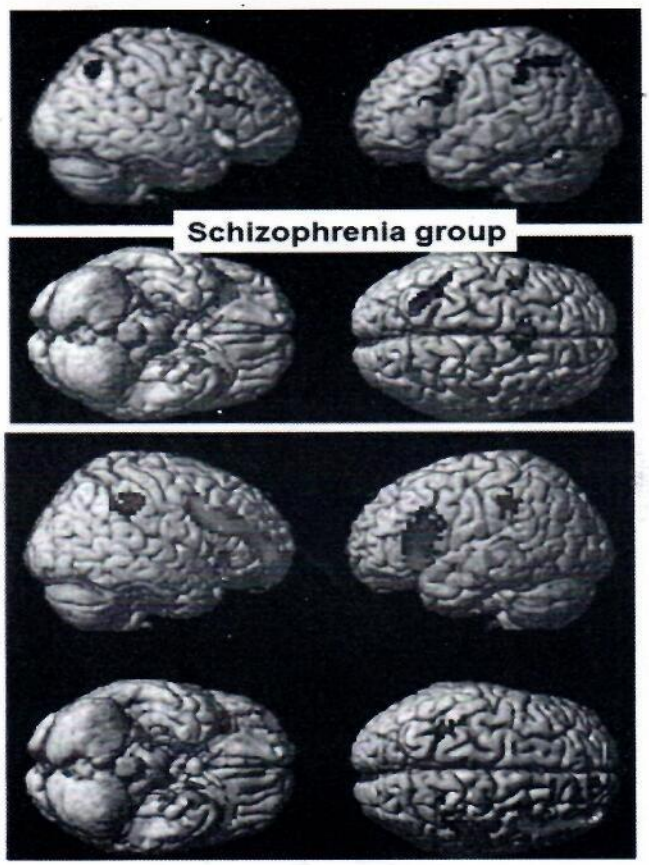

Fig 9. Functional Magnetic Resonance Imaging (fMRI) showing hypofunctionality in patients with Schizophrenia (A) compared with healthy controls (B).

1. Alzheimer's Disease (AD)

Clinical neuroimaging is of increasing importance in the diagnosis and management of dementia. Apart from cerebral atrophy and white matter hyperintensity demonstrated on structural MRI imaging of these patients, their functional MRI (fMRI) show entorhinal and hippocampal atrophy and reduced activation[17].

CONCLUSION

Recent advances in neuroimaging are well recognized in their diagnostic role in the management of various psychiatric disorders. They also have a further role in elucidating the

underlying neurobiological components of the majo functional illnesses. Unfortunately, the developing countries like Nigeria are yet to benefit from these advances. Hopefully with the emergence of more MRIs and advent of PET and SPECT in the tertiary hospitals, there will be an increase in the clinical use of neuroimaging modalities to the benefit of patients.

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PREVENTION OF MOTHER – TO – CHILD TRANSMISSION OF HIV; CHALLENGES AND PROGRESS IN SUB-SAHARA AFRICA

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A B S T R A C T

By the end of 2012, over 35.3 million people were living with HIV/AIDS, including 17.7 million women and 3.3 million children below the age of 15 years. Also in 2012, over 260,000 children younger than 15 years were newly infected with HIV. A large proportion of the infection occurs in resource-limited countries, notably in sub-Saharan Africa. Majority of HIV infections in children < 15 years are due to vertical (mother-to-child) transmission, either during pregnancy, at delivery or during breastfeeding. Whereas significant successes are being recorded in some African countries towards maximising the effectiveness of PMTCT programmes and elimination of new paediatric HIV infection, gaps still exist in several countries of sub-Saharan Africa as the level of implementation falls short of reaching the 2015 global plan target. The falloff in the rate of new infection has been slow and PMTCT service integration is still low as majority are centralised outside where most women receive MNCH services. This review aims to assess the progress towards the effective implementation of PMTCT programmes in resource-limited countries in response to the 2015 target for elimination of new HIV infections in children along with the various barriers and challenges forestalling the realisation of these aims.

Keywords: *HIV, PMTCT, Gaps, Progress.*

INTRODUCTION

By the end of 2012, the World Health Organisation estimated that over 3.3 million children younger than 15 years were living with HIV, majority of who resides in low and middle income countries, particularly in sub-Saharan Africa. [1] Paediatric HIV-1 infection is a known cause of childhood mortality in Africa [2] and over 90 per cent of the infection occurs in countries of sub-Saharan Africa, [3] largely due to vertical (mother-to-child) transmission. Mother-to-Child transmission of HIV occurs either in utero, intra partum or during breastfeeding. In the absence of any intervention, the risk of the mother transmitting the infection to her baby is 20-45 per cent. [4] Correspondingly, without antiretroviral therapy, more than 50 per cent of infected children die before the age of 2 years [5] while children born to women with advanced disease – class C disease, low CD4+ lymphocyte count and high HIV viral RNA copies – rapidly progress to AIDS or death before the first birthday. [6]

In 2002, the United Nations adopted a comprehensive approach to the prevention of mother-to-child transmission of HIV, addressing various aspects of prevention, care, support and treatment of HIV positive pregnant women, mothers and children. The four-pronged comprehensive approach includes; the primary prevention of HIV among persons of reproductive age group, preventing unintended pregnancy among women living with HIV, provision of specific interventions to reduce HIV transmission from HIV-infected women to their infants and the provision of appropriate treatment, care and support to women living with HIV, their children and families. [4]

Between 2001 and 2012, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported improved service coverage of PMTCT, with a 52 per cent reduction in new HIV infections among children. [7] While this may be the case, especially in some African countries with significant success like Botswana, Namibia, South Africa and Swaziland, gaps still exist in several African countries, as the rate of decline in the number of new paediatric infections has been slow. In Nigeria, which contributes the largest to the number of new infections, the rate has been stalling while in fact that of Angola is still rising. [8, 9] Importantly, most efforts aimed at increasing implementation of PMTCT services have centred largely on the provision of specific intervention to reduce HIV transmission from HIV-infected women to their infants, [10] despite the fact that more could be achieved by emphasising the comprehensive PMTCT approach.

Furthermore, women are particularly more vulnerable to HIV infection in sub Saharan Africa, constituting more than half of the infected population. [12] A vast range of social factors such as gender inequality, lack of education, poverty, sexual violence, and the increased prevalence of sexually transmitted infection further increases the vulnerability of women to HIV infection in this region. [11,12] Taking these into consideration, effective implementation of the comprehensive PMTCT measures and more efforts at integration with other maternal, newborn and child health services is therefore essential in this pursuit of the 2015 global plan's target. The global plan's recommendation on the scale up in PMTCT services as well as service integration, particularly in the 22 priority countries should be intensified as a strategy towards achieving zero new HIV infection. This will go a long way towards the realisation of the 2015 global target for elimination of new HIV infection in children and keeping their

elimination of new HIV infection in children and keeping their mothers alive and as well intensify progress towards the realisation of the UN Millennium Development Goals targets by 2015, [13] (MDG 4 – Reduce by two thirds the mortality rate among children under five, MDG 5 – Reduce by three quarters the maternal mortality ratio, and MDG 6 – Halt and begin to reverse the spread of HIV/AIDS).

MOTHER-TO-CHILD TRANSMISSION OF HIV

Mother-to-Child transmission of HIV occurs either in utero, intra partum or during breastfeeding. Evidence for in utero transmission of HIV derives from studies performed by analyses of foetal tissues obtained from second trimester abortuses for the presence of HIV nucleic acid sequences using polymerase chain reaction. [14] These studies revealed a risk of transmission from mother to developing foetus in about 30% of pregnancies. High maternal baseline HIV-1 viral load and delayed initiation of maternal ARV prophylaxis are among risk factors strongly associated with in utero transmission. [15] Similarly, the risk of in utero HIV transmission is more likely in women who developed their primary HIV infection during pregnancy contrasted with women who acquire the infection prior to conception. [16] About two-thirds of HIV/AIDS infections in children occur during delivery. [14] Estimates based on hypothetical cohort studies of 100 children born to HIV positive mothers aimed at determining time of HIV transmission suggest that 50 per cent of infants' HIV infections occur at the very end of pregnancy, i.e. near the time of labour in the non-breastfeeding populations while the postnatal period accounts for significant number of infants' infection in the breastfeeding populations. [17]

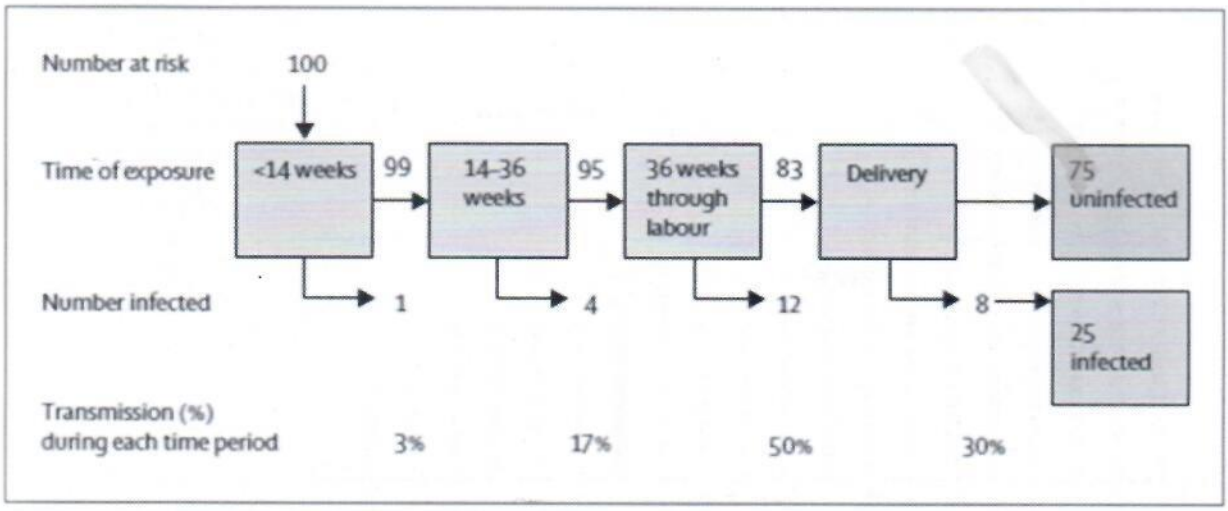


Figure 1: Estimation of timing of mother-to-child transmission of HIV-1 in a non-breastfeeding population based on a hypothetical cohort of 100 children born to HIV-infected women without any interventions. Source; Ref. [17]

The mode of delivery and specific circumstances during delivery which extend the period of infant's exposure to maternal blood and secretions at delivery are key factors which affect the risk of intra partum infection. [18]

Postnatal transmission is strongly determined by the pattern or choice of infant feeding. [19] In most developed countries where replacement feeding is safe, affordable and culturally acceptable, [20] mother-to-child transmission of HIV has been significantly lowered. However, in developing countries where breastfeeding still ranks as the preferred choice of infant feeding as safe replacement feeding is usually not possible, [21] mother-to-child transmission of HIV through breastfeeding contribute a significant percentage to the number of infections in these regions. [20,21]

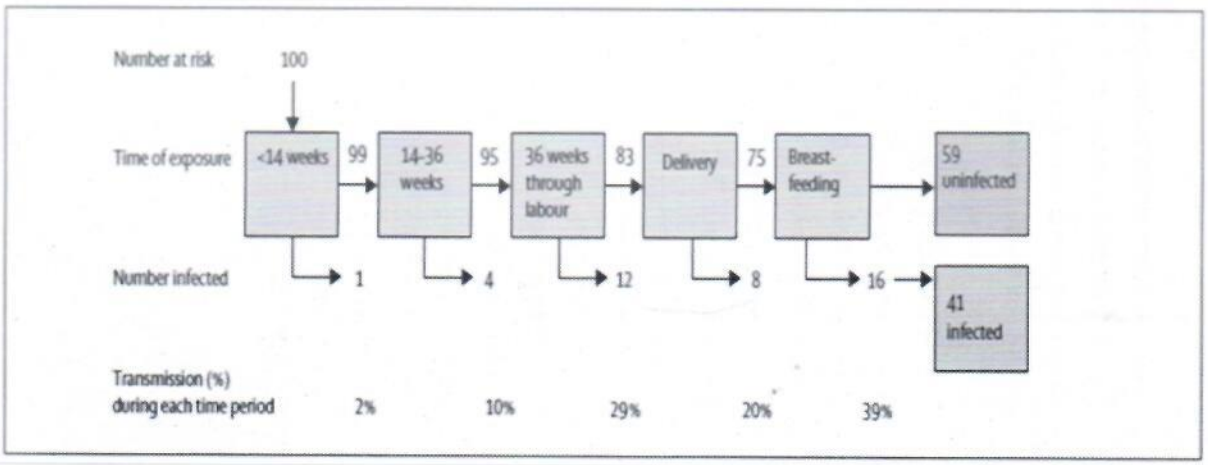


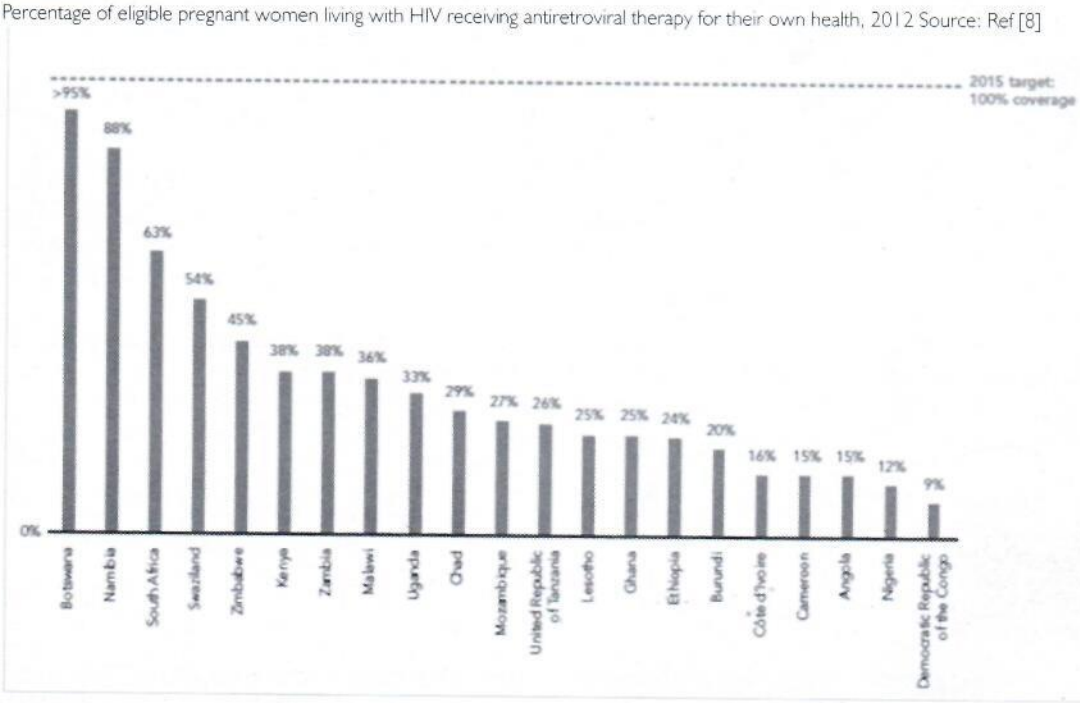
Figure 2: Estimation of timing of mother-to-child transmission of HIV-1 in a population that practises prolonged breastfeeding of 18–24 months based on a hypothetical cohort of 100 children born to HIV-infected women without any interventions. Source; Ref. [17]

PROGRESS IN THE IMPLEMENTATION OF PMTCT

Over the years, significant progress has been recorded in reducing the incidence of HIV among children in sub Saharan Africa, reflecting the fewer number of children who acquire the infection and deaths from AIDS. The estimated 230,000 new paediatric HIV infection in 2012 is 48 per cent lower than in 2001 while fewer children, 190,000, died from AIDS in 2012, compared to estimated 320,000 in 2005. [7, 22] Sequel to the commitment of the global community towards the elimination of new paediatric HIV infections by 2015, the field of PMTCT has witnessed rapid changes and developments both in the care of HIV positive pregnant women and preventing the infections of infants. As at 2006, 71 countries worldwide were already implementing national PMTCT programmes with defined country-specific policies and strategies. In most of the 22 Global Plan priority countries of sub-Saharan Africa, the number of new paediatric HIV infection has reduced significantly between 2009 and 2012 with Botswana taking the lead in the provision of PMTCT services. Other countries like Ethiopia, Malawi, Namibia, Zambia and Zimbabwe have also made significant headway. [8]

Pertaining to antiretroviral therapy coverage, only four of the priority countries – Botswana, Ghana, Namibia and Zambia – have achieved the goal of providing ARV drugs to 90 per cent of the eligible women to prevent mother – to – child transmission of HIV. [8] As a result, Botswana has recorded a steady decrease in the proportion of infants born to HIV positive mothers (from 20.7 per cent in 2003 to 3.8 per cent in 2007). [8, 24] Comparably, though the percentage of children receiving ARV has increased, access in most countries still remains unacceptably low, as only 3 of 10 eligible children receive HIV treatment. Also, in most of the priority countries, access to early infant diagnosis is less than 20 per cent. [8, 9] Hence the persistent high rates of mother – to – child transmission and mortality.

Percentage of eligible pregnant women living with HIV receiving antiretroviral therapy for their own health, 2012 Source: Ref [8]



Percentage of eligible children (0–14 years old) receiving antiretroviral therapy, 2012

In countries like Botswana where great success has been recorded in the implementation of PMTCT services, some of the key factors associated with this achievement have been the high level of political commitment and national financing of HIV prevention, care and treatment services. The programme provides increased access to testing for mothers and infants (at 6 weeks and followed up to 18-24 months for HIV-free survival) and provision of eligible HIV positive pregnant women with ARV prophylaxis and supply of formula feeds to HIV exposed infants, making adequate provision for universal access to clean water and patients education. Counselling was considered to play a critical role in PMTCT programmes. Male participation in PMTCT was successfully scaled up and adequate programme monitoring and evaluation and research to identify gaps in the system were ensured in order to provide information for programme improvement and expansion.[23,24]
Similar approaches were also identified in Thailand, a resource-limited country that has successfully implemented PMTCT programmes. Counselling was also considered to play crucial role in PMTCT programmes. In Botswana, lay counsellors were introduced into the programme and trained to counsel pregnant women about HIV testing and prevention. This helped to provide pregnant women with information about HIV testing and prevention, assisting HIV-infected women to adjust to their diagnosis, thereby reducing transmission to their child as well as reducing the burden on health professionals from the time consuming demands of counselling. Data obtained from research, surveillance, monitoring and evaluation were employed to advocate development, expansion and improvement of PMTCT programmes.[25]

BARRIERS TO IMPLEMETATION OF PMTCT

Major barriers to maintaining high coverage of PMTCT in most developing countries include low availability of facility-based PMTCT services and low utilisation of antenatal care services and facility-based deliveries.[26] While antenatal care coverage has increased substantially in most developing countries, service uptake and utilisation are still low. While majority of pregnant women (78 per cent) have at least one visit, coverage of the recommended at least four visit is less than 50 per cent.[39] Women presenting for ANC tend to wait until the second trimester and quite a sizable proportion present only in third trimester[27,28] Factors responsible for low uptake of ANC services in these settings resonate around. the misalignment of ANC service delivery with the local contexts and settings. Pregnancy is generally perceived as a healthy state in most of these settings with no increased risk to well being, as such many find no reason for specialized care. Direct and indirect costs of ANC also pose significant barrier such that even when services are free, the cost of transport, medications and the loss of earnings associated with the visit often deter women from attending.[45]The low uptake of ANC has important implication on PMTCT services delivery as it leads to missed opportunities and failure to effectively maximize the opportunities offered by repeated visits.[26]

Another major contributing factor is the low contraceptive prevalence and access to family planning services in sub Saharan Africa. West and Central Africa particularly constitute the region with the greatest need for family planning with an average of 29.3 per cent married women age 15-24 in the unmet need category (14.7 % in Niger and 45.7% in Ghana) and an average total demand of family planning of 34.7 per cent (23.9% and 27.5% in Niger and Nigeria respectively, and 69.6% and 77.55% in Congo Brazzaville and Sao Tome and Principe respectively).[38] Insufficient information about contraceptive methods, concerns about side effects and health implications and social barriers opposing their use are prominent reasons responsible for the high unmet need in these settings.[46] Providing family planning services for HIV positive women of reproductive age, particularly in the face of high prevalence of HIV in sub Saharan Africa, and implementation of strategies to increase uptake will help to prevent unintended pregnancies in this population and thereby reduce the frequency of HIV positive births.

According to a systematic review conducted in sub-Saharan Africa between January 2000 and September 2012 aimed at investigating reasons for low access, initiation and adherence to antiretroviral drugs by mothers and exposed infants for prevention of mother-to-child transmission in sub-Saharan Africa, the factors identified were broadly classified under individual, community and health system levels (Fig. 1). Poor knowledge of HIV, ARV and vertical transmission, low maternal education and psychosocial issues following HIV diagnosis were key factors identified at the individual level. Factors at the community level range from stigma and fear of status disclosure to partners, family or community members and reduced partner and community support, while major barriers identified at the health sector level include poor staff-client relationships, staff shortages, low service accessibility and non-facility deliveries.[29]

Results from other studies also identified similar factors. For example, studies from Kenya identified the challenges of uptake and scale up of PMTCT services to stem from late presentation for care (all the women studied presented at 20 weeks of gestation or later), less than four ante-natal clinic visits, poor contraception coverage, lack of partner support, stigma and discrimination, and low disclosure rates. Inadequate staffing and lack of specialized training were also identified as barriers to PMTCT service integration.[30,31,32]
A study from Uganda identified the level of knowledge of MTCT and preference for rapid HIV testing to be equal in both rural and urban settings; however, it was observed that women in rural areas had a higher tendency to think that they should consult their husband before testing. This bolsters the effect of the male partner in PMTCT. Low level of health facility based deliveries was also a limiting factor especially in the rural settings.[33]

In Nigeria, other major challenges with the implementation of PMTCT programmes have been related to inadequate service uptake by pregnant women, minimal male involvement and poor community participation in PMTCT and inadequate number of early infant diagnosis in the country. As at 2013, only 30.1 per cent of HIV positive pregnant women receive antiretroviral drugs to reduce the risk of mother to child transmission of HIV, although an appreciable rise compared to 15.9 per cent in 2011 and 25.9 per cent in 2012. Also in 2013, only 3.9 per cent of infants born to HIV positive mothers receive virological test for HIV within two months of birth. This corroborates the low rates of early infant diagnosis in majority of the global plan priority countries.[8,9]

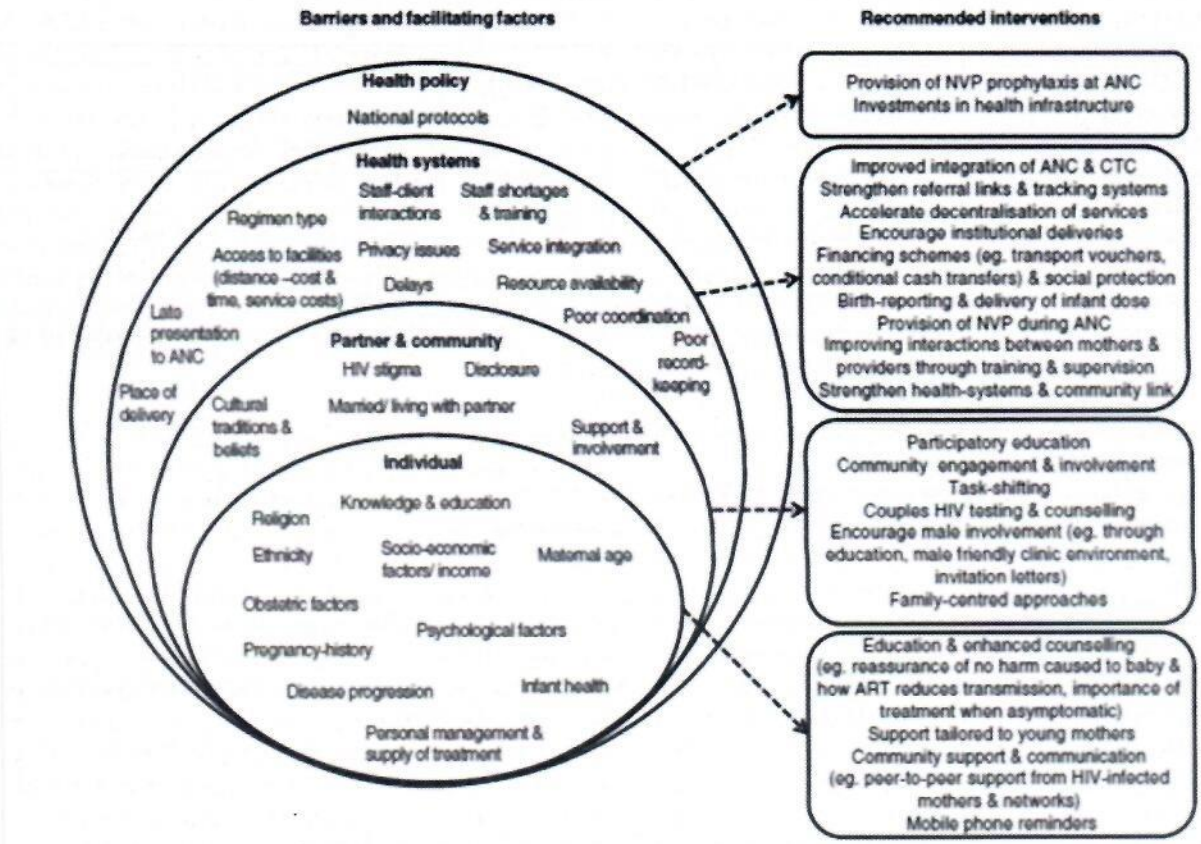


Figure 3: A socioecological model illustrating the interplay of the barriers at each level and possible interventions and policy recommendations addressing these barriers. Source: Ref [29]

CURRENT RECOMMENDATIONS ON PMTCT

In light of evidence from the Paediatric AIDS Clinical Trials Group (ACTG) 076 protocol and reports from the European Collaborative Study, administration of combination therapy of Highly Active Antiretroviral Drugs combined with elective caesarean section and not breastfeeding reduce the risk of mother – to – child transmission to approximately 0.5 – 1 per cent. [34, 35, 36] In 2001, the world health organization issued the first recommendation for the use of antiretroviral drugs in relation to infant feeding for the prevention of mother – to – child transmission of HIV. This guideline was revised in 2004 and updated in 2006 and 2010, in alignment with the global commitment to universal access.

The 2013 guidelines on prevention of mother to child transmission recommend [29] testing and counselling be provided during the pregnancy and postpartum period as component of care in all MCH care settings and in view of the risk of acquiring HIV infection during pregnancy, re-testing should carried out later in pregnancy, labour or shortly after delivery. Testing for HIV-exposed infants and children <18 months should be done 4-6 weeks of birth with the definitive diagnosis carried out at the end of breastfeeding period. Children ≥ 18 months and not breastfeeding can be reliably tested using standard HIV serological tests to determine HIV infection status. On the use of antiretroviral therapy, either of two PMTCT options is recommended, depending on CD4 counts or clinical stage, in addition to whether infant is being breastfed or formula-fed (Table 1). Regarding infant feeding options, in settings where mothers choose to breastfeed, ARV intervention should be provided. Exclusive breastfeeding is recommended for the first six months for HIV-positive mother whose infants are HIV-negative or of unknown status. Appropriate complementary foods can then be introduced while continuing breastfeeding for the first 12 months of life.

BRIDGING THE GAP

The gaps in PMTCT programmes in most countries of sub Sahara Africa can be overcome by adopting and implementing interventions to address the barriers forestalling its successful implementation at the different levels. Decentralization of services from the tertiary level of healthcare and expansion of access to the other levels and particularly the rural areas where most women receive MNCH services and among whom high rate of missed opportunities are being reported will help to improve service coverage and uptake of PMTCT. [40] In the same vein, accelerating efforts at integrating PMTCT services into other MNCH services will afford the opportunity for more entry points of HIV positive mothers and HIV exposed infants into the PMTCT cascade. Most women and babies at risk of MTCT of HIV may belong to any of the risk categories for HIV/AIDS and may have accessed services such as antenatal care, delivery, family planning and well child clinic at different levels. [41] It is therefore important that these opportunities be maximized by integrating PMTCT into existing MNCH programmes. This will also translate to improved service accessibility and uptake by bringing these services closer to the people and available in one location. Strengthening the weak health systems which exist in most of the countries of sub-Saharan Africa through provision of human resources and necessary infrastructure will also help improve service performance. This also has particular implication for PMTCT integration in lieu of the possibility of overwhelming the weak

<table>
<tr><td>NATIONAL PMTCT PROGRAMME OPTIONS</td><td colspan="2">PREGNANT AND BREASTFEEDING WOMEN WITH HIV</td><td colspan="2">HIV-EXPOSED INFANT</td></tr>
<tr><td>Use lifelong ART for all pregnant and breastfeeding women ("Option B+")</td><td colspan="2">Regardless of WHO clinical stage or CD4 count.</td><td>Breastfeeding</td><td>Replacement feeding</td></tr>
<tr><td rowspan="3">Use lifelong ART only for pregnant and breastfeeding women eligible for treatment ("Option B")</td><td colspan="2">Initiate ART and maintain after delivery and cessation of breastfeeding</td><td rowspan="3">6 weeks of infant prophylaxis with once-daily NVP</td><td rowspan="3">4–6 weeks of infant prophylaxis with once-daily NVP (or twice-daily AZT)</td></tr>
<tr><td>Eligible for Treatment[a]</td><td>Not eligible for Treatment[a]</td></tr>
<tr><td>Initiate ART and maintain after delivery and cessation of breastfeeding[b]</td><td>Initiate ART and stop after delivery and cessation of breastfeeding[b,c]</td></tr>
<tr><td colspan="5">a. CD4 count ? 500 cells/mm3 or clinical stage 3 or 4 disease at the time of ART initiation or in accordance with national guidelines.
b. Patients who develop clinical or laboratory criteria indicating failure during pregnancy or the breastfeeding period should be assessed for second-line therapy.
c. In the case of breastfeeding stop ART one week after breastfeeding ends. In the case of replacement feeding stop ART after delivery.</td></tr>
</table>

Table 1: Options for Prevention of Mother-to-Child Transmission of Human Immunodeficiency Virus. Source: Ref. [37]

health systems in these settings.

Over the years, little progress has been achieved in addressing fundamental issues including health system infrastructures such as staffing and accessibility. This suggests lack of commitment on the part of international donors to invest in health infrastructure, while giving preference to funding of antiretroviral drugs. [29] Therefore, high level of political will and commitment, country–driven and –funded PMTCT programmes as highlighted in the case of countries like Botswana are necessary for successful implementation and integration of fully functional PMTCT programmes. These will foster the adaptation of PMTCT service provision to fit individual local contexts and address challenges peculiar to different settings.

The provision of enabling social environment for women through interventions such as female education and economic empowerment aimed at addressing social issues such as gender norms, reducing HIV-related stigma, promoting maternal health through community mobilization and provision of social support for pregnant and postpartum women are key to effective PMTCT programmes. These have been found to positively influence policy, demand and delivery of PMTCT and maternal health services in various settings. [42] Male partner involvement in PMTCT intervention has been demonstrated to enhance uptake in various settings in view of the fact that men are the key decision makers in many societies and families of African settings. Several strategies employed in increasing male participation include sending of invitation letters to men to participate in PMTCT programmes, extending clinic hours to accommodate men with busy schedule and introduction of male and couple friendly clinic. [43] Whereas several studies have suggested involvement of men in PMTCT to improve uptake and performance in terms of communication, disclosure and support, further evaluation is required to validate effectiveness of male involvement in PMTCT services as enough evidence is currently lacking. [29, 43, 44]

CONCLUSION

The considerable progress being recorded in most of the global plan priority countries towards bridging the gap in effective implementation of PMTCT programme is promising. However, the various barriers limiting scale up in each setting should be proactively addressed if the 2015 global plan target for elimination of new HIV infection among children is to be achieved. High level of political commitment and primary prevention of HIV infection in the general population are very crucial while the different aspects of women health, especially those which increase their vulnerability to HIV infection should be equally addressed.

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CORD CLAMPING: A NEGLECTED COMPONENT OF THE ACTIVE MANAGEMENT OF THE THIRD STAGE OF LABOUR

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A B S T R A C T

The third stage of labour is the period following the delivery of the newborn until the completed delivery of the placenta. Management of the third stage of labour has typically focused on women and prevention of postpartum haemorrhage and has been the thrust of most papers in the management of third stage of labour neglecting the issue of cord clamping that also contributes to the outcome of pregnancy. Less attention is given to this in most publications probably due to its simplicity and not considering the importance of exploring the long term effects on health of cord clamping on the baby. In view of this, a review of the new trends in the management of the third stage of labour is discussed in this article; a very important perspective considered in this article is the issue of early and delayed cord clamping.

Keywords: *cord clamping, active management, third stage, labour*

INTRODUCTION

The third stage of labour commences with the delivery of the fetus and ends with the completed delivery of the placenta and its attached membranes [1]. It is a continuum that begins immediately the fetus is delivered followed by cord clamping and cutting to the delivery of the placenta and its membranes. This stage of labour can be managed physiologically or actively but most centers engage the active management because it is associated with less complication like post-partum hemorrhage [2].

Management of the third stage of labour has typically focused on women and prevention of postpartum hemorrhage.The definition of active management of the third stage of labour varies. According to a systematic review on the prevention of post-partum hemorrhage and prolonged third stage of labour which was published in 2009 by WHO , the definitions included use of a uterotonic drug immediately following delivery of the fetus, controlled cord traction and early cord clamping and cutting. This is also in keeping with the Federation of Gynaecology and Obstetrics/ International Confederation of Midwives(FIGO–ICM) definition that includes use of a uterotonic immediately following delivery of the fetus, controlled cord traction and fundal massage immediately after delivery of the placenta, followed by palpation of the uterus every 15 minutes for 2 hours to assess the continued need for massage however cord clamping is excluded based on some research indicating that delayed clamping benefits preterm (and probably term) infants. The above is also in tandem with the Cochrane reviews in 2013 that delayed cord clamping increases early haemoglobin concentrations and iron stores[3]. For this reason, early clamping was accepted into obstetric practice without much reservation[4]. Management of the third stage of labour has typically focused on women and prevention of postpartum haemorrhage and this has been the thrust of most papers in the management of third stage of labour neglecting the issue of cord clamping that is also a very important aspect of the third stage of labour. Less attention is given to this in most publications probably due to its simplicity and not considering the importance of exploring the long term effects on health of cord clamping on the baby. In view of this, a review of the new trends in the management of the third stage of labour is discussed in this article; a very important perspective considered in this article is the concept of delayed cord clamping.

PHYSIOLOGY[6]

In-utero, the baby is connected to the placenta by the umbilical cord. The placenta is an organ that attaches to the wall of the uterus and allows oxygen and nutrients to pass from mother to fetus via the umbilical cord. The blood from the fetus circulates through the umbilical cord to and from the placenta for this purpose. After birth, the baby's lungs expand with the first breaths causing larger volumes of blood to be directed to the baby's lungs to receive oxygen. Red blood cells within the baby's bloodstream transport this oxygen around the baby's body, which stimulates the baby to breathe. Until the baby starts breathing oxygen is provided from the mother to the baby via the umbilical cord.

THE THIRD STAGE OF LABOUR

It is very pertinent that the care-giver is skilled in identifying the signs of this stage of labour and even prepared ahead before labour commences, hence this will reduce the mortality and morbidity that are associated with this stage of labour. Also planning ahead will also aid the decision of whether to manage physiologically or actively. Below is a table that compares the two.

Table 1:

Physiological Versus Active management [1]

	PHYSIOLOGICAL MANAGEMENT	ACTIVE MANAGEMENT
Uterotonic	None or after placenta delivered	With delivery of anterior shoulder and baby
Uterus	Assessment of size and tone	Assessment of size and tone
Cord Contraction	None	Application of controlled cord contraction when when there are signs of placenta separation
Cord Clamping	Variable	Early

The aim of this paper is not to compare and contrast the two but it is worthy of note to state that early cord clamping is a component of the active management of the third stage of labour.

CORD CLAMPING

For centuries, people have been clamping and cutting the umbilical cord at birth. However, the timing of cord clamping continues to vary according to clinical policy and practice, and the optimal timing has not yet been defined.[1]

Early cord clamping is generally carried out in the first 60 seconds after birth, whereas delayed cord clamping is carried out greater than 60 seconds after the birth or when cord pulsation has ceased[1]

In the guidelines issued by the International Confederation of Midwives (ICM) and the International Federation of Gynaecology and Obstetrics (FIGO) , and in those issued by WHO , the word "early" has been left out in relation to the timing of cord clamping and cutting because of evidence suggesting benefits for the baby of delayed cord clamping and cutting. In its guidelines for the prevention of postpartum haemorrahge, WHO recommends delayed cord clamping and cutting as part of the active management of the third stage of labour. The guidelines recommend that the timing of cord clamping and cutting should be determined by observing uterine contractions following the administration of a uterotonic [5,6]

The new guideline by WHO in 2012 in order to provide a foundation for the strategic policy and programme development needed to ensure the sustainable implementation of effective interventions for reducing the global burden of PPH recommended late cord clamping (performed after 1 to 3 minutes afterbirth)for all births while initiating simultaneous essential newborn care although early cord clamping (less than 1 minute after birth) is recommended if the neonate is asphyxiated and needs to be moved immediately for resuscitation.[7]

DELAYED CORD CLAMPING

In the past most active management protocols include early clamping of the cord. However, of the 3 active management components, this practice seems the least important in conferring the observed benefits. Early cord clamping may be indicated in order to facilitate newborn assessment or resuscitation. Barring these indications, rushing to clamp the cord is unnecessary because traction cannot be applied until the uterus is well contracted.

Delayed cord clamping is the clamping of the cord after 60 seconds of delivery or the clamping of the cord when the pulsation in the cord ceases. [6] If the umbilical cord is left unclamped after birth, the blood in the placenta will travel back to the baby's body increasing the baby's blood volume.The umbilical cord pulsation (beating like a heartbeat) would be noticed. Eventually the pulsation in the umbilical cord will cease as blood stops travelling from the placenta to the baby's body. The time it takes for cord pulsation to cease is different for every neonate. For many neonates it takes around 3 minutes, if the neonate is level with the maternal introitus, however for some neonates it can take between 1 and 10 minutes. The effect of this is that it results in higher hemoglobin and hematocrit values in the newborn and, possibly, lower levels of early childhood anemia and greater iron stores. These effects are probably more profound in preterm infants and may result in fewer transfusions in the neonatal period and lower rates of neonatal intraventricular hemorrhage and sepsis. This may also be particularly relevant for infants living in low-resource settings with less access to iron-rich foods. [6] It also decreases the incidence of intracranial haemorrhage in preterm infants [7,8]

However concerns exist regarding adopting delayed umbilical cord clamping. It is said that delay in umbilical cord clamping may jeopardize timely resuscitation efforts, if needed, especially in preterm infants[9] . This might not be necessarily true as the placenta continues to perform gas exchange after delivery. Sick and preterm infants are likely to benefit most from additional blood volume derived from a delay in umbilical cord clamping. Another issue that has been raised is that delay in umbilical cord clamping increases the potential for excessive placental transfusion, which can lead to neonatal polycythemia thereby leading to increase neonatal jaundice, especially in the presence of risk factors for fetal polycythemia, such as maternal diabetes, severe intrauterine growth restriction, and high altitude [9, 10].Another issue is that delayed umbilical cord clamping might interfere with attempts to collect cord blood for banking. However, the routine practice of umbilical cord clamping should not be altered for the collection of umbilical cord blood

for banking.[11]

CONCLUSION

The issues surrounding the timing of cord clamping have not been extensively studied with respect to the neonatal outcome, and the practice of delayed cord clamping is not based on strong evidence especially with respect to neonatal outcomes. It therefore suffices to say that practices that will promote the health of both the mother and the newborn during delivery should be encouraged and each component of the active management of the third stage of labour should be given the same attention.

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AN UPDATE ON PITUITARY ADENOMA

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A B S T R A C T

Background: The pituitary gland produces hormones that have wide ranging effects on the physiology of the human body. As such tumours of this organ can also be the cause of many pathological conditions. Pituitary adenomas have been shown by many studies to be the third most common intracranial neoplasm. Recently the classification of pituitary adenomas has involved the use of not only the clinical history and histology alone but also radiology, immunohistochemistry, electron microscopy and molecular studies. This review is an update on the recent classification and molecular pathology of pituitary adenomas.

Materials and methods: An online search of published works and a review of literature were done.

Results: Pituitary adenomas can present as functional or silent types and also show varying degrees of aggressiveness. Although most are benign a significant number are atypical adenomas with increased recurrence rates. The aggressiveness of a tumour is often reflected in the subtype of the tumour. The silent adenomas may require molecular techniques to determine the particular class of the adenoma. This is done by the use of genetic markers expressed by the different types of cells found in the normal pituitary gland.

Most pituitary adenomas are sporadic but familial cases are also seen in the setting of some syndromes such as MEN1. The mutated genes in these inherited cases are sometimes also seen in sporadic cases. Other mutations often seen in pituitary adenomas are highlighted in this review.

Keywords: *pituitary, adenoma, classification, genetics*

INTRODUCTION

The pituitary gland, often referred to as "the conductor of the orchestra", is the main endocrine gland responsible for the control of the other principal endocrine glands in the body and also a few visceral organs. The small size of the pituitary, usually weighing about 5g, often allows pathological processes in the gland to be overlooked. Pituitary adenomas are by far the commonest tumours to arise in the gland and are also the third commonest intracranial tumours. Due to the different endocrine products of the pituitary, the presence of a tumour can have far reaching effects on the body. This brief review attempts to give an update on the pituitary adenomas with particular reference to the current WHO classification of 2004.

The pituitary gland is a small ovoid structure residing in the hypophyseal fossa, a part of the sella turcica, which is found in the body of the sphenoid bone. The aperture of the fossa is covered by dura mater known as the diaphragm sellae above which the optic chiasm passes. The fossa is bounded bilaterally by the cavernous sinus, the internal carotid arteries, the third, fourth, ophthalmic part of the fifth and the sixth cranial nerves. The diapragma sellae is pierced in the midline by the infundibulum which connects the pituitary gland to the hypothalamus[1,2,3,4,5].

The pituitary gland is composed of two parts with separate embryological origin and function. The anterior pituitary (adenohypophysis) is the larger of the two parts and arises as a cranial evagination of the stomodeum known as Rathke's pouch while the posterior pituitary (neurohypophysis) is a downward extension of the hypothalamus. The neurohypophysis consists of the nerve endings of the neurons from the supraoptic and paraventricular nuclei in the hypothalamus, which secrete vasopressin and oxytocin into the vascular plexus in the lobe. The adenohypohysis is composed of several different epithelial cell types which secrete six main hormones and some other peptide[1,2,3,4,5]. The hormones include growth hormone produced by somatotrophs, prolactin by mammotrophs, adrenocorticotrophic hormone by the corticotrophs, thyroid stimulating hormone by the thyrotrophs and the two gonadal hormones, luteinizing hormone and gonadotropin releasing hormone, by the gonadotrophs. The hormone secreting cells of the anterior pituitary are regionally located with the somatotrophs and mammotrophs located in the conical shaped midline area known as the mucoid wedge. The thyrotrophs and corticotrophs are usually clustered in the lateral part of the adenohypophysis while the gonadotrophs are diffusely located amongst the other cell types. Other peptides produced in the pituitary include beta lipotropin, proopimelanocortin, and somatostatin[2,3,5].

Recent studies using molecular techniques have shown that the cells of the anterior pituitary gland have different embryogenesis and are clustered together in families, which have implications in disease conditions. The cells secreting prolactin, growth hormone and thyroid stimulating hormone show expression of a common gene known as the *pit-1* gene [6,7]. The corticotrophs express the *Tpit* gene while the gonadotrophs express the *SF* gene [7,8].

EPIDEMIOLOGY

Pituitary adenomas are the commonest tumours of the sellae region and according to several reported series they are the third most common intracranial neoplasm in adults after gliomas and meningiomas [8,9,10]. They are benign slow growing tumours composed of adenohypophyseal cells. In a meta-analysis of 13 autopsy and radiological studies identified from a MEDLINE search, it was estimated that pituitary adenomas have an overall prevalence of 16.9% [11,12]. Radiological studies have demonstrated the occurrence of clinically silent pituitary adenomas, otherwise called "incidentalomas," in up to 20% of the general population [13]. According to a recent study by Idowu et al the prevalence of pituitary adenoma in this environment is similar to what has been observed in Caucasians [1]. The tumour is more common in adults and occurs more in the middle age group with a male preponderance [10]. It is rare in children with an estimated prevalence of 2.7% [14].

Prolactinomas are the commonest tumour type that was found to occur in both adults and children according to many series [15,16]. However recent studies have shown that gonadotroph adenomas and null cell adenomas are now more common in adults probably because many prolactinomas are treated medically with no surgical biopsy available for characterization [14,15,16,17]. Thyrotroph adenomas are quite rare [17].

PATHOGENESIS

Two main theories have been postulated concerning the aetiology of pituitary adenomas, the hormonal stimulation and the intrinsic cellular defect theory [1,12]. The first theory assumes that the neoplasm arise from continuous stimulation of the gland, either from the hypothalamus or other external source, with a resultant hyperplastic state. The cellular proliferation may generate a genetic accident with a resulting mutation. The genetic progression of the mutation eventually results in a clonal proliferation [8,18]. Although there have been some reports of adenomas seen in association with hyperplasia, most adenomas do not show a hyperpl stic background and this pathway is not so favoured [8,12,18]. The second theory, the monoclonal theory, states that pituitary adenomas arise from genetic mutations that occur in a single cell as a result of an intrinsic genetic defect. The mutated cell proliferates to produce clones of neoplastic cells. Many studies have shown evidence of clonal proliferation of neoplastic cells with identical genetic mutations favouring the monoclonal theory [12,18]. Most authorities at present favour this theory as the most likely pathogenetic pathway for these tumours.

GENETICS

Approximately ninety five per cent of pituitary adenomas are sporadic and only about five per cent are familial [8,19]. Although it is a clonal disease, the common genetic mutations, such as Retinoblastoma and *p53* mutations, often seen in other neoplasms are not associated with pituitary adenomas [19]. Common anomalies seen in these tumours include mutation of *gsp* gene resulting in constitutive activation of *gsa* which produces a stimulatory guanine binding protein that regulates growth hormone releasing hormone effects on somatotrophs [8,19]. Mutations of *p16* are also known to occur commonly in pituitary adenomas although its significance is not yet ascertained [18]. Other mutated genes include the oncogene *PTTG*, a cell division regulator that is thought to contribute to aneuploidy in adenomas [8,18].

Familial syndrome complexes that show increased frequency of pituitary adenomas include multiple endocrine neoplasia (MEN1) which results from a mutation in a tumour suppressor gene located on chromosome 11q13 which controls the promoter region of several endocrine glands. (table 1) Prolactinomas are the commonest type of adenomas seen in this syndrome followed by somatotroph and corticotroph adenomas. The tumours in this syndrome are aggressive and are usually macroadenomas [8,20,21]. Some patients with pituitary adenomas who had similar phenotypic appearance with MEN1 were later found not to have the mutation seen in other patients having this disease. Further studies showed a mutation in chromosome 12 which codes for the *p27* protein. This syndrome has been tagged as MEN4. Other features seen in this syndrome include acromegaly, primary hyperparathyroidism, renal angiomyolipoma, small cell neuroendocrine tumour and Cushing's disease [20,21].

Other familial syndromes include the Carney's complex which tends to have growth hormone adenomas and results from mutations in a tumour suppressor gene in chromosome 17. A small percentage of individuals with this syndrome show mutations in chromosome 2 rather than 17. Familial isolated pituitary adenoma (FIPA) also occurs with mutations in chromosome 11 and the adenoma manifests at a younger age. The affected gene product is a receptor interacting protein which also functions in cellular growth and apoptosis pathways. Prolactinomas occur most commonly in this group of patients [20,21].

CLINICAL MANIFESTATIONS

The clinical manifestations of pituitary adenomas result from their mechanical effects, excessive endocrine secretion or reduced endocrine functions. The mechanical effects include raised intracranial pressure which results in persistent headache and compression of the optic chiasma, classically resulting in bitemporal hemianopia and other visual defects [7,22]. Other effects include cranial nerve palsies, infiltration of the temporal lobe with temporal lobe epilepsy, hydrocephalus and CSF rhinorrhoea in tumours that have infiltrated through the sphenoid sinus and which can result in ascending infections of the CNS [22,23].

In excessive endocrine secretions the resultant manifestation is sometimes dependent on the age and sex. Prolactinomas may cause galactorrhea and amenorrhea in women and cause loss of libido in men. Sommatotroph adenomas cause gigantism in children but manifests as acromegaly in adults [22, 24]. Compression of normal pituitary tissue by the tumour may result in hypopituitarism. Growth hormone is usually the first to show decreased levels followed by gonadotrophins while prolactin levels are the last to drop [25]. In some macroadenomas, particularly the silent adenomas, prolactin levels may be high and the patient may show galactorrhea giving a false impression of a prolactinoma. This phenomenon is called the "stalk effect" and results from compression of the pituitary stalk by the tumour which inhibits the stimulation of the mammotrophs by dopamine, its normal inhibitor, from the hypothalamus. There is thus uninhibited prolactin production [22]. One of the most feared complications that can occur in a pituitary adenoma is an apoplexy which is an infarction of the gland from interruption of the blood supply due

apoplexy which is an infarction of the gland from interruption of the blood supply due to compression [22]

CLASSIFICATION

Pituitary adenomas are classified clinically as functional or non-functional, based on the presence or absence of hormone production [1, 26] Functional adenomas are more common and can elaborate any of the hormones produced in the adenohypophysis, resulting in endocrine over-activity. Non-functional adenomas can result in pan-hypopituitarism or selective endocrine under-activity by compressing normal adenohypophyseal cells [2,24] Surgically pituitary adenomas are classified using the Hardy classification, which is based on their sizes and the degree to which they cause erosion of the sellae. Tumours that are more than 10mm in size using imaging techniques are regarded as macroadenomas while those less than 10mm are classified as microadenomas [18]

Histopathologically the method of classifying pituitary adenomas according to their staining characteristics with haematoxylin and eosin into acidophils, basophils and chromophobes has been discarded. This is because a lot of overlaps were found between different tumour types using these tinctorial characteristics [8,24] Presently pituitary adenomas are classified mainly based on their immunohistochemical staining characteristics. The antibodies used are directed against the different polypeptide products of each tumour type. In 2004 the World Health Organisation (WHO) expert panel recommended that diagnosis of pituitary adenomas should require several modalities which include the clinical history, radiological studies, microscopic morphology, immunohistochemical properties, electron microscopy and in some cases genetic studies [24]

The WHO recognises six main classes of pituitary adenomas based on their immunohistochemical staining properties with further subclassification of the groups (table 2). These groups include: prolactinomas, sommatotroph adenomas, thyrotroph adenomas, corticotroph adenomas, gonadotroph adenomas and null cell adenomas [24] Some of the subclassification can only be done with the use of electron microscopy which is able to recognise ultrastructural properties that further group the tumours. Occasionally some tumour types are only classified with the use of genetic studies that identify molecular properties which are common to certain adenomas such as the *SF* gene that is found in gonadotrophs [17, 24] Many pituitary tumours produce multiple hormones but the truly plurihormonal adenomas as defined by the WHO are those tumours showing derivation from separate unrelated embryogenetic pathways [7, 24, 27] The tumours may consist of a mixture of cells producing different hormones while in some cases the same cell produces more than one hormone [24, 28]

Atypical adenomas are benign tumours that show relatively increased aggressiveness. They have been defined by the WHO as tumours with invasion of neighbouring structures, increased mitosis measured with the MIB index (more than 3%) and expression of the *p53* gene [24, 27]. They usually tend to show increased recurrence rate and carry a poorer prognosis. Pituitary carcinomas are very rare and are diagnosed only in pituitary tumours that metastasize to distant structures. The degree of pleomorphism and nuclear atypia does not qualify a tumour as malignant. These tumours tend to metastasize either to the spinal cord or via the CSF to extraneural organs such as the lungs and liver. They generally have increased ki67 and *p53* expression. They carry a poor prognosis [18, 24, 27]

TREATMENT

Pituitary adenomas are managed either by surgical or drug therapy and occasionally by radiotherapy [23, 28] Inhibitors against the hormonal products are often used to treat the condition. These drugs not only reduce hormonal level but also often cause a reduction in tumour bulk. These drugs include Bromocriptine, Cabergoline and Quinagolide which are used for prolactinomas [28]. Somatostatin and Octreotide is used for sommatotroph adenomas. In corticotroph adenomas, bromocriptine is also sometimes used but other medications include Cyproheptadine and Valproic acid among others [28]

Surgery is often used for macroadenomas as well as gonadotroph and null cell adenomas. The transphenoidal approach is most often used and involves the use of an endoscope to remove the tumour through an opening in the sphenoid sinus via the nasal cavity. Radiotherapy may sometimes be employed with either of the other treatment modalities [28]

CONCLUSION

Pituitary adenomas are relatively common tumours that occur in the intracranial cavity and the prevalence of the tumour in the general population has been found to be higher than earlier thought. The classification of the tumour types with immunohistochemical methods has allowed more targeted therapy for the different tumour types. It is hoped that as more research shows the molecular characteristics of the tumour, better modalities of therapy will start to emerge

Table 1:

Common Genetic Mutations Occuring In Pituitary Adenomas

GENE	FUNCTION	SYNDROME
gsp	Encodes gsa, a guanine binding protein regulating GHRH effects in somatotrophs. Mutation in gsp causes constitutive activation of gsa	Somatotroph adenomas
p16	Mutation of the gene found in 80% of adenomas	
PTTG	Regulate chromatid separation during mitosis	
PtdFGFR4	Induces adenoma in transgenic mice	
GADD45	Growth arrest and DNA damage inducible gene	
MEG3	Inhibits cell growth	
MENIN (11q13)	Tumour suppressor gene	Pituitary adenomas, parathyroid hyperplasia, pancreatic endocrine tumours (MEN1)
CDKN1 (chr12)	coding for p27	Acromegaly, primary hyperparathyroidism, renal angiomyolipoma, small cell neuroendocrine tumour and Cushings disease. (MEN4)
PRKAR1A (chr17q22-24)	Functions in regulating CAMP	Growth hormone adenomas, lentigines, myxomas, Schwann cell tumours, primary pigmented nodular adrenocortical disease (PPNAD), thyroid tumours and nodules, testicular tumours, Leydig cell tumours (Carneys complex)
Aryl hydrocarbon receptor interacting protein (chr11q13.3)	Tumour suppressor gene. Functions in xenobiotics	Prolactinomas and growth hormone adenomas (Familial isolated pituitary adenomas)

Table 2:

Classification of Pituitary Adenomas

ADENOMA SUBTYPES	SUBTYPES	MOLECULAR MARKERS
Prolactinomas	Sparsely granulated Densely granulated Acidophil stem cell	PIT 1
Growth hormone adenomas	Densely granulated Sparsely granulated Mammosomatotroph Mixed lactotroph and somatotroph	PIT 1
Thyrotroph adenomas	Acidophil stem cell	PIT 1 AND GATA 1
Corticotroph adenomas	Sparsely granulated Densely granulated Crooke's cell adenoma Silent adenoma (null cell)	TPIT AND NEURO D1
Gonadotroph adenomas	FSH adenoma LH ADENOMAS FSH and LH adenomas Silent gonadotroph adenomas (null cell)	SF 1
Plurihormonal adenomas	Subtype 1 Subtype 2 Subtype 3	
Atypical adenomas		Ki67 and p53
Pituitary carcinoma		Ki67, p53 and Tp53

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DOKITA NEWS

THE PROFESSOR J. A. ADELEYE NATIONAL INTER-MEDICAL SCHOOL ESSAY COMPETITION

The 6th edition of the biennial Professor J. A. Adeleye National Inter-Medical School Essay Competition held from December 2, 2011 to March 23, 2012.

Topic: The influence of unorthodox medicine on healthcare in Nigeria.
Winner: Mr. Ola Idris Olasumbo (Ladoke Akintola University of Technology)
1st Runner-up: Oladeji Emmanuel (Ladoke Akintola University of Technology)
2nd Runner-up: Ayandele Babajide (Ladoke Akintola University of Technology)

THE 47TH ANNUAL SYMPOSIUM OF DOKITA EDITORIAL BOARD

The symposium held on Thursday, October 11, 2012 under the chairmanship of Mr. Femi Falana, SAN (Human Rights Activist, Femi Falana & Associates). The venue was Paul Hendrickse lecture theatre, University College Hospital (UCH), Ibadan.
Theme: MEDICAL PRACTICE IN NIGERIA: LOOKING OUT FOR THE DOCK
Sub-themes:

1. THE PLACE OF LAW IN MEDICAL PRACTICE
   Speaker: Otunba Kunle Kalejaiye, SAN: Kunle Kalejaiye, SAN & co Legal Practitioners and Consultants
2. MEDICAL LITIGATION: 'AUT PAX AUT BELLUM' (EITHER PEACE OR WAR)
   Speaker: Professor O.O. Adejuyigbe, Chief Medical Director, Obafemi Awolowo University Teaching Hospital, Osun State
3. THE PATIENT'S RIGHT AND THE DOCTOR'S RIGHT
   Speaker: Professor A.O. Malomo, Chairman, Nigerian Medical Association, Oyo State Chapter.

PROFESSOR O.O AKINKUGBE NATIONAL INTER-MEDICAL SCHOOL QUIZ COMPETION

The DOKITA Editorial Board's 7th Biennial Professor O.O. Akinkugbe Quiz competiotion took place at the Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, Ogun State, between 13th – 16th February, 2013. The following schools participated in the event.

- College of Medicine, University of Lagos, Idi Araba, Lagos State
- College of Health Sciences, Obafemi Awolowo University, Ile Ife, Osun State
- College of Health Sciences, Usman Dan Fodiyo University, Sokoto, Sokoto State
- College of Medicine, University of Ibadan, Oyo State
- College of Medicine, University of Ilorin, Kwara State
- College of Medicine, Lagos State University, Ikeja, Lagos State
- Faculty of Medicine, Bayero University, Kano State
- Obafemi Awolowo College of Health Sciences, Sagamu, Olabisi Onabanjo (formerly Ogun State) University, Ago Iwoye, Ogun State
- College of Medical Sciences, University of Benin, Benin-City, Edo State
- College of Health Sciences, Bingham University Karu, Nasarawa State
- College of Medicine, Ladoke Akintola University of Technology, Ogbomoso, Oyo State.
- College of Medicine, Enugu State University of Science and Technology, Enugu State

The closing ceremony held under the chairmanship of Professor Yomi Ogun, Provost, College of Medicine, Olabisi Onabanjo University Teaching Hospital, Sagamu, Ogun State, with the following schools emerging as winners:

- First Position: University of Ilorin
- Second Position: Obafemi Awolowo University
- Third position: Olabisi Onabanjo University

SEMINAR ON RESEARCH AMONG MEDICAL STUDENTS

A seminar was organised by the Board themed: "MEDICAL RESEARCH AND ARTICLE WRITING" on Saturday, 8th March, 2014. This was integrated into the last annual UIMSA health week to enhance active participation and attendance of all medical students, especially clinical students. This took place at the Famewo Common Room, Alexander Brown Hall, University College Hospital, Ibadan. It was anchored by Dr.M.O Owolabi, Consultant Neurologist, University College Hospital, Ibadan. The seminar was aimed at enlightening students on the relevance of research in medical training as well as the rudiments of carrying out research.

ANNUAL GENERAL MEETING

This held on Sunday,25th May, 2014. Executives for the 2013/2014 Board year were elected. They are:

Editor-in-Chief	Ms. Yeka Nmadu
Board Secretary	Ms. Omosalewa Koya
News and Quiz Editor	Mr. Victor Mike-Akinlusi
Production Manager	Mr. Stephen Adeseko
Distributions Manager	Mr. Akinlolu Olawoore
Business Manager	Ms. Oyindamola Ogunwole
Financial Controller (Ag.)	Mr. Ibrahim Olukunle
Publicity Editor (Ag.)	Ms. Omotoyosi Akinbami

ADMISSIONS

The Editor-in-Chief, on behalf of The Board hereby congratulates the following medical students who were offered provisional admission into DOKITA Editorial Board.

May, 2014.

1. Ms. Joy Oluwaniyi
2. Ms Idowu Oladigbo
3. Ms Esther Okoro
4. Mr Ademola Fasanmi

October, 2014.

1. Ms. Saudat Aminu
2. Mr. Babasola Opaneye
3. Ms. Vivian Magboh
4. Ms. Abisola Sumah

Complied by:
Victor Mike-Akinlusi
News and Quiz Editor (2014/2015)
DOKITA Editorial Board.

UIMSA NEWS

The 48th Executive Council, Senate and Congress of University of Ibadan Medical Students' Association (UIMSA) were sworn in a memorable event on Saturday, May 10th, 2014at the Femewo Common Room, Alexander Brown Hall, University College Hospital, Ibadan, with the motto of the executive tenure as *together we can!* The newly inaugurated President, MR. ADENIYI ELEGBEDE, made his inaugural speech laying much emphasis on the need for all *UIMSITES* to continue to support the Executive Council, Senate and Congress towards the progress for the association.
The list of Sworn-in officers is as follows:

EXECUTIVE COUNCIL

Mr. Adeniyi Elegbede	President
Mr. Adedolapo Adejumo	Vice President
Mr. Mas'ud Adewusi	Gen. Sec.
Miss Omolola Owoputi	Asst Gen. Sec.
Miss Omotola Ogunjobi	Financial Sec.
Miss Olayinka Odebunmi	Treasurer
Miss Aishat Olanlege	P. R. O.
Miss Utin Utibeima	Sport Sec.
Mr. Jude Zugu	S.D.O (Clinical)
Mr. Reginald Ononye	S.D.O (Preclinical)

SENATE OFFICERS

Mr. Temiloluwa Oso	Senate Chairman
Miss. Obehi Aimiosior	Dep. Senate Chairman
Mr. Toluwalase Awoyemi	Senate Registrar

CONGRESS OFFICERS

Mr. Afolusho Olayonwa	Congress Chancellor
Mr. Abdulrasheed Adedayo	Dep. Congress Chancellor
Mr. Akande Abbas	Congress Scribe

ACTIVITIES OF THE EXECUTIVE COUNCIL SINCE INCEPTION

Courtesy Visits

The Executive council paid a courtesy visit to Emeritus Prof. O.O. Akinkugbe and Emeritus Prof. Oluwole Akande. Our distinguished Patrons, the current Vice Chancellor of the University of Ibadan, Prof. I. F. Adewole, *FAS* and the Current President of the Nigerian Medical Association (NMA), Dr. Kayode Obembe, were also visited at different times. We were graciously received by allof them. These acts were done in line with the traditions and ideals of the association. It was an exclusive avenue for us to appreciate their various efforts which the association enjoys at all times and also to intimate them on the plans and ideas of the new tenure. Fruitfully, they all promised to continue to support the association in whatever capacity they can.

Congratulatory Messages

The Executive Council sent out congratulatory messages to Dr.KayodeObembe (Christus Specialists' Hospital) as he became the new President of the Nigerian Medical Association (NMA) on May 4th, 2014 and also to one of our staff advisers, Prof. Babatunde Salako, former HOD of Department of Medicine, University of Ibadan as he too became the new Provost of the prestigious College of Medicine, University of Ibadan on May 30th, 2014. These two personalities have been of immense support to our dear association. We further wish them well as they battle new frontiers of knowledge and standards in their various endeavours.

MB;BS Part IV (finals) Examination Members' Welfare Package

In keeping with our great tradition of striving for excellence in all we do, the executive council organised a befitting welfare package for the most senior class in Ibadan medical school writing the final *MB;BS* examinations as medical students. Theclass was grateful for this act and promised to support the association as they were about to draw the curtain as medical students.

Face of Preclinical (FOP)

Although an independent eventof the Preclinical Press of the association, this year's FOP was warmly supported by the Executive council, Senate and the Congress. The event took place at the prestigious University of Ibadan Faculty of Art Lecture Theatre on July 17th, 2014. It event was embroiled with glitz and glamour.

Production of the 2014 Medscion magazine

The production of this year's Medscion magazine is underway and we want to thank all those who have submitted articles and contributed to its production.

Acquisition of the UIMSA Prelim Press Board

It is with joy that I announce to you that, we have finally been able to obtain a board space for the Prelim Press at the CBN lecture hall,University main campus. Arrangements for proper furnishing and locks are all that is left in readiness for the 100 level Press come this year's second semester.

FRESHERS' WELCOME

The current Executive Council with supports from the Senate and the Congress of the association was able to organise a very befitting welcome party for her 100loevel students on August 16th, 2014 at the popular Trans-Amusement Park, Samonda, Ibadan. The event was given much encomium by those present at the event.

FRIENDLY FOOTBALL MATCHES

The University of Ibadan Medical Students' Association (UIMSA) sport team was not left out amidst the wonderful activities of this current tenure.

So far, two wonderful friendly football matches have been played.

The first was an away match with the ObafemiAwolowo University Medical Students' Association. The matched ended 1-1.

The second was also an away match with Association of Medical Students, University of Lagos. The match was an outstanding victory for us as it ended 1-0 in favour of UIMSA.

QUIZ COMPETITION

The University of Ibadan Medical Students' Association (UIMSA) Quiz team contested at the ObafemiAwolowo University medical school intercollegiate quiz competition which was part of their annual health week. UIMSA Quiz team came 2nd behind the host school, OAU MSA.

Although the UIMSA Quiz team has been in a fantastic form, there is room for more improvement.

THE 15TH EDITION OF THE LATE DR. AWOSIKA SYMPOSIUM

This year's edition took place at the prestigious University of Ibadan Trenchard Hall on October 22nd, 2014. The event was well attended by different types of students of the University of Ibadan and also by friends and family of the Awosikas. Seasoned speakers were invited to speak on topical issues bordering on the Ebola Disease Virus, the need to place the health sector at the forefront of political agenda and Development and Health.

UPCOMING EVENTS

- Provost Games
- Restoring of UIMSA Website
- Friendly matches with LASUCOM, BOWEN and ABUAD
- Reviving Prelim Press
- World AIDS Day
- The Annual Late Prof.Osuntokun Inter-level Quiz Competition
- Distinguished Guest Lecture
- Publishing of the Ibadan Medscion Magazine
- Health Week and the 55th Anniversary.

CONCLUSION

It is with great honour and privilege that I convey and conclude this piece of information to you. On behalf of the Executive Council, Senate and Congress, I want to say a big thank you to all *UIMSITES* for their unflinching supports since inception of this tenure. We look forward to more supports in all areas of our activities so that we can collectively move our revered association forward against all odds.

Together we can!

ELEGBEDE, Adeniyi.
President, UIMSA 2013/2014.

COLLEGE NEWS

1. APPOINTMENTS

The new Provost of the College of the Medicine, Professor Babatunde Lawal Salako of the Department of medicine, a consultant physician and Nephrologist, assumed duty on 1 August, 2014.Professor Salako is the tenth elected Provost of the College.

Dr. E.O. Oyewole of the faculty of Public Health was appointed sub-dean (Postgraduate) with retrospective effect from 25 Febuary, 2014 to 31 July, 2014.

Professor O.G.B Nwaorgu of the Department of Oto-Rhino-Laryngology was appointed Chairman of the Board of Health with effect from 1 September, 2013.

Dr. A.A. Adenipekun was appointed acting Head of the Department of Radiotherapy, pending the completion of the process for appointing a substansive Head.

Dr. Juliana O. Taiwo was appointed acting Head of the Department of Peridontology and Community Dentistry with effect from 1 August, 2013 for a period of two years.

Professor A.A. Oni was appointed Head of Medical Microbiology and Parasitology with effect from 1 August, 2013 for a period of four years.

Dr. Eme T. Owoaje of the Department of Community Medicine was appointed Acting Director of Research Management Office (RMO), for a period of two years with effect from 19 May, 2013.

2. PROMOTIONS

At its meeting of Friday, 20 and Monday, 23 December, 2013, the appointments and promotions committee for Academic Staff approved the following:

S/N	NAME	DEPARTMENT	PREVIOUS POSITIONS	POSITION ON PROMOTION	EFFECTIVE DATE OF PROMOTION
1	Dr. A.A. Oni	Medical Microbiology & Parasitology	Reader	Professor	2006
2	Dr. Oyedunni O. Arulogun	Health Promotion and Education	Senior Lecturer	Reader	2009
3	Dr. A.B. Omololu	Surgery	Reader	Professor	2010
4	Dr. Y. Raji	Physiology	Reader	Professor	2010
5	Dr. F.A. Fehintola	Pharmacology & Therapeutics	Senior Lecturer	Professor	2011
6	Dr. Grace T. Fadupin	Human Nutrition	Senior Lecturer	Reader	2011

3. BENEFACTION

Dr. Sheba Gitta, Acting Executive Director, Nigeria Field Epidemiology and Laboratory Training Program (NFELTP), NO. 50. Haile Selassie Street, Asokoro, Abuja, donated the underlisted books to the Department of Epidemiology and Medical Statistics, Faculty of Public Health during a book presentation at the NFELTP Office, Abuja.

NO	Title	Author/ Editor	Quantity
1	Control of Communicable Diseases Manual, 19th Edition.2004	David L. Heyman, MD Editor	10
2	Principles and Practices of public Health Surveillance	Lisa M. Lee, Steven M. Teutsch, Steven B. Thacker and Michael St. Louis	20
3	Field Epidemiology, 3rd Edition, 2008	Michael Cregg	15
4	A Dictionary of Epidemiology, 5th Edition	Miquel Porta, Associate Editors Sander Greenland. Iohn M. Last	10
5	Epidemiology in Medicine (1987)	Lippihcott Williams and Wilkins	20
6	Practical Statistics for Medical Research	Douglas D. Altman	12
7	Molecular Microbiology Diagnostics Principles and Practice, 2nd Edition	David H. Persing, Fred C. Tenover et al	6
8	Food Safety, Old Habit, New Perspective	Phyllis Entis	10
9	Principles of Biostatistics	Marcello Pegun, Kimberlee G.	5
10	Modern Epidemiology, 3rd Edition, 2008	Kenneth J. rothman, Sander Greenland and Timothy L. Iash	10
11	Epidemiology 4th Edition, 2009	Leon Gordis	19
12	Essentials of Epidemiology in Public Health, 2nd Edition (9), 3rd Edition (1)	Ann Aschengrau, George R. Seage	10
13	Manual of Clinical Microbiology, Volume 1 and 2, 10th Edition	James Versalovic, Karen C. Carroll, Guide Funke et al	6
14	Zoonoses infectious Diseases Transmissible from Animals to Humans, 3rd Edition	Hartmut Krauss, Albert Weber, et al	10

1. LECTURES

(a) Inaugural Lecture

Professor T.K. Hamzat of the Department of Physiotherapy on behalf of the Faculty of Clinical Science , on Thursday, 6 February 2014, delivered a lecture titled "from ward to ward: The Neurophysiotherapist as the Returning Officer ".

(b) Faculty lecture

Dr. T.S. Oluleye of the Department of Opthalmology on behalf of the Faculty of Clinical Science, delivered a lecture titled "Diabetic Retinopathy: A Time Bomb, Everybody's Buisness" on Wednesday,2014.

(c) Guest Lecture

(I) Professor J.C. Konje on behalf of the faculty of Clinical Sciences, Obstetrics and Gynaecology Department, delivered a lecture titled "Dealing with Reproductive Challenges of Morbid Obesity in the 21st Century" on Tuesday, 8 April, 2014.

(ii) Professor Groesbeck P. Parham, delivered a lecture in honour of Professor I.F. Adewole's 60th birthday titled "Building a Cervical Cancer Prevention programme in Zambia using a HIV/AIDS Infastructure and the Spirit of Abundance" on Tuesday 6 May, 2014.

5. HONOURS AND DISTINCTIONS

(a) Professor B.L. Salako, Department of Medicine, was elected President of the Nigerian Association of Nephrology for the year 2014-2016 to become President of the Association in the year 2017

(b) Professor E.O. Farombi, Department of Biochemistry was selected as Recipient and Winner of the 2014 Global Senior Scholar Toxicology Exchange Award by the Society of Toxicology, United State of America.

(c) Dr. Grace T. Fadupin, Department of Human Nutrition, was appointed Member of the Governing Board of Abubakar Tafawa Balewa University Teaching Hospital, Bauchi by the Federal Ministry of Health.

(d) Dr. Prisca O. Adejumo, Department of Nursing, was awarded the National Institute of Health D43 Training Grant at the University of Chicago.

6. EVENTS

(i) The College of Medicine, University of Ibadan, in conjuction with the University College Hospital, Ibadan organized a Summit with the theme "Harmonising for Global Relevance", held from Wednesday 22 October, 2014 to Friday 24 October, 2014. Emeritus Professor E.O. Akande, foundation Provost of the College who also delivered the keynote Address, "History and Peculiarities of the College of Medicine and University College Hospital".

The underlisted was discussed during the Summit:

- Effective communication and professionalism in College Administration
- Professional Bullying and Inter-Professional Rivalries
- Conflict and Grievance Handling
- Mapping Out Clear Career Path: Promotion and other Reward Systems
- Collaborative Research in a Multi-Disciplinary Setting
- Financial Administration and Management
- College of Medicine of the 21st Century

(i) The 12th in the series of Health Talk awareness programme organized by College Management was held on Wednesday, 26 March, 2014. While Professor T.K. Hamzat of the Department of Physiotherapy gave a talk on Workplace Ergonomics, Dr. M.O. Owolabi of the Department of Medicine spoke on care of the Elderly/Aged.

7. COURTESY VISITS

(a) The Branch Manager, Stanbic IBTC Bank, Agodi, Ibadan, Mr. Tayo Adediran, in company of Mr. Tunde Bolarin and Mrs Bolawa Adenuga paid a courtesy visit to the Provost, Professor O.O. Akinyinka on Monday, 13 January ,2014, in his office.

(b) A team from the America Heart Association led by Dr. Segun Dawodu and comprising Louis Shing NY, Nathaniel Mitchell and Everton F. Kelly paid a courtesy visit to the Provost, Prof. O.O. Akinyinka, on Monday, 27 January, 2014.

(c) Christina and Steffen Sammet from the Luries Children's Hospital and University of Chicago respectively paid a courtesy call on the Provost, Professor O.O. Akinyinka on Monday, February 10, 2014.

(d) Professor Graham Thornicroft of the Kings College London and Partner, EMERALD Mental Health Project was led by Professor Oye Gureje, Deoartment of Psychiatry to pay a courtesy visit to the Acting Provost, Professor Ayotunde Ogunseyinde on Monday, 24 March, 2014.

(e) The North American President of Ibadan College of Medicine Alumni Association (ICOMAA), Dr. Omowumi Osinubi, paid a courtesy visit to the Acting Provost, Professor Ayotunde Ogunseyinde on Tuesday, 8 April, 2014.

(f) Dr. Obiageli Ekwesili, former Minister of Education of the Federal Republic of Nigeria and former Vice President, World Bank (Africa Division) paid a courtesy visit to the Acting Provost, College of Medicine, Professor Ayotunde O. Ogunseyinde on Monday, 14 April, 2014.

(g) A team from Mansard Health Limited comprising the Chief Executive Officer, Mr. Tope Adeniyi and the Assitant General, Dr. Nte Uran-York paid a courtesy visit to the Acting Provost, College of Medicine, Professor Ayotunde O. ogunseyinde on Wednesday, 16 April, 2014.

8. OBITUARY

The Acting Provost, Professor Ayotunde O. Ogunseyinde, on behalf of Management, announces with deep regret, the death of Dr. S.A. Adejuwon, a lecturer II of the Department of Anatomy. He died on Sunday, 16 February, 2014.

May his gentle soul rest in perfect peace. Amen.

LIST OF GRADUANDS

JUNE/JULY 2014

ADEBAYO, Adeolu Adenike
GENSIS, Ajokpaoghene Emamezi
ADEBUSOYE, Olugbenga Samson*
GRILLO, Temitope Adejoke
ADEDOYIN, Omolara Oluwakemi
IGBEINTUKU, Victor Dein-Mowei
ADEEMI-AKINBAMI, Adetola Terence
Ihuoma, Maureen Adaugo
ADEOTI, Oluwatomi Oluwagbemisola
IKPONMWOSA, Osarobo Osama
ADEWUMI, Adetola Beatrice
ILORI, Oyinlola Oluyinka
ADEWUMI, Oriyomi Solomon
ISIAK, Abdul Fatai
ADEYEMI, Adekola Adewumi
JIMOH, Ibrahim Abiodun
AFOLABI, Ezekiel Opeyemi
KOMOLAFE, Tiwalola Jennifer
AFOLABI, Ifedayo Isaac
LASEBIKAN, Tiwatayo Afolahan
AGBAYE, Ademola adebowale
ODEDIRAN, Oluwatobi Daniel
AJA, Kalu Awa
UGBUIGWE, Uzochikwa Anita
AJAYI, Tinuola Bolanle
OGUNDIPE, Habeeb Damilola
AKANDE, Rukayat Olabisi
OGUNDIPE, Olusola Olufemi
AKANMU, Mariam Mojisola
OGUNLADE, Itunu Oluseyi
AKINADE, Abdul-Azeez Adebayo
OGUNLESI, Oluyemisi Adeola
AKINOLA-ELEWODE, Sarah Kikelomo
OGUNLEYE, Yewande Oyinkansola
AKPIEYI, Samuel Enajiete
OGUNMUYIWA, Folayinka Ayofunke
ALABI, Adegoke Akeem
OGUNYEMI, John Babatunde
ALADEJARE, Samuel Adewumi
OKEKE, Ogoma Uche
ALADIRIN, Toba John
OKIBE, Julie Oka
AMODU Oluwaseun Abiodun
OLAOYE, Tijesunimi Oluwawakayode
ARAROMI, Opeyemi Omotola
OLATUNJI-DANIEL Damilola Labake
BABALOLA, Chibuzor Modupe
OMADUVIE, Uyoyo Tonte
BELLO, Blessing Ope-OLUWA
OMIDIORA, Oluwaseun Olajumoke
CHUKWU, Arinze Amaechi
ONATADE, Mary Oluwapelumi
DIAI, Juliet Oluchukwu
OSONDU, Michael Ikechukwu
DIJI, Isioma Judith
PERIOLA, Gbenga
DISU, Olubunmi Angela
POPOOLA, Kudirat Olateju
EKISOLA, Bolanle Olasupo
RUFAI, Abiodun
ELUWA, Victor
RUFAI, Idris Akindeji
EMEMBOLU, Clement Okechukwu
SAMI, Adefolabo Titilayo
ENEH, Justina Onedo
SOLADOYE, Elizabeth Oluwafunmilayo
ERINNE, Okechukwu Chibueze
TAYLOR, Olayinka Alfred
EZEOKE, Chibuke Jude
UMUKORO, Aghogho
FAKUNLE, Aanuoluwapo Maria
UYA, Dokedensi Edet
FATADE, Oluwatosin Ebunoluwa
FATUDIMU, Segun David
ADEBIYI, Dotun Elizabeth
ILORI, Adeniji Oluwagbenga
ADIGWE, Ifeoma
JUNAID, Yetunde Ruqayat
AGUNLOYE, Oluwafunmito Esther
OBADIMU, Akinwumi Adeyemi
AJAYI, Emmanuel Gbolahan
OBIECHINA, Zimuzo
AKINBORO, Ebunoluwa Ibitayo
OGUNSAKIN, Olumuyiwa Samuel
ALIAKOR, Judith Chioma
OKUNBOR, Opeyemi Charles Olaide
ALUKO, Damilola Olajumoke
OLAJIDE, Azeezat Folake
AMUSU, Mary Ifeolapo
OLAONIPEKUN, Abdulazeez Adepoju
ASAWOLE, Oluwasegun Samuel
OLAWUWO, Mattew Abiodun
AYODELE, Modupe Oluwa Fisayo
ONYENWE, Betty Ijeoma

LIST OF GRADUANDS

JUNE/JULY 2014 CONT'D

BARUWA, Oladoyin Fathiat
OTUYEMI, Taiwo Oluyemi
CHUKWU, Onyeka Faith
SINGH, Namrata
DAUDA, Mumini Abiola
TADE, Adebowale Oluwaseun
FAGBAMIGBE, Joseph Olufemi
UZOR, Stella Nwakaego
FAGBEMI, Titilola Oluwaseyi

SEPTEMBER/OCTOBER 2014

ABRAHAM , Olusegun Barnabas
ADEBAJO, Adesunmisola
ADEJARE, Fadhilu Ajolayo
ADEKUNLE, Ibrahim Adewale
ADEWUYA, Oludare Oluwole
ADOLE , Stanley Abichie
AJAYI, Olumide Omotola
AKANDE, Adebayo Adelana
AKANDE, Boluwaduro Shefi
AKINNADEJU, Alexandra Olorunisola
AKINNIYI, Ayodeji Anthony
AKINWALE, Emmanuel Olakunle
AKUSE, Nguavese Christine
ALIBI , Olajumoke Omowunmi
ARAROMI, Omoniyi Oluwaseun
AWOTU-UKIRI, Ewoma Ajiri
AYODEJI, Imisioluwa Kemi
BALARABE, Tasallah Rahmat
BALOGUN, Khadijat Omolola
BASSEY , Unyime Felix
BEKE, Babatunde Olukoya
EJECHI, Benjamin Onyemaechi
EKE , Onyebuchi Chukwu
EMEKA, Chinedu Precious
EREYI, Eghe Nosa
ESSIEN, Amanda Antigha
FAGBO, Emmanuel Oluwole
FANIYI, Elijah Olufunso
FASINA, Abdul Razak Toluwalase
FEMI, Austin Monday
FEMI-OYEWOLE, Tolulope Fortune
FALODUN, Olasunkanmi Samuel
FYNEMAN-KALIO, Ibinabo
IPADEOLA, Oluwafemi Temitayo
JOSEPH, Damilola David Enoch
KUYE, Adewale Ayodeji
LADOKUN, Nathanael Ayokunnu
LONGE, Damilola Yejide
MONEY, Aghogho Onome
NNAKWUE, Uchenna Franklyn
NWOKEDI, Barth Onyekachi
OBEMBE, Ibukun Elizabeth
ODEDEJI, Muhammed Abiodun
OGBOO, Samuel Onyema
OGUNDELE, Olaoluwa Tolulope
OJEDOJA, Taiwo Adedeji**
OKE, Oluyemi Olaide
OKORO, Chidi Felix
OKUNLOLA, Abiodun Tolulope
OLUDIPE , Michael Eniola
OLUFAJO, Oludoyin Tolulope
OMOLOYE, Tunde Theophilus
ONYEADOR, Emeka Johnpaul
ORJI , Ugochukwu Michael
OSENI, Mohammed Toha
OYEWO Oyeduntan Oluwaseyi
OYEYIOLA, Bukola Nefertiti
POPOOLA, Olakunle Solomon
RASAQ, Mutiu Adeniyi
SYDNEY, Chinedu Christopher
TAIWO, Faith Adeolu
TONGADIANG , Tarh Moses

KEY:
**** FORMER EDITOR-IN-CHIEF**
***FORMER BOARD MEMBER**

DOKITA QUIZ

Stephen Adeseko*

At the time of writing this Quiz was a final year clinical student of the College of Medicine, University of Ibadan.

1. A 35year old female banker presents at the Gynaecology clinic with a history of primary infertility. She also had a positive history of chronic cough of 4months duration which was productive of copious amounts of foul-smelling sputum. A cardiac examination of this patient revealed absent heart sounds over the 4th Left Intercostal space. What could be responsible for the absent heart sounds? What is your likely diagnosis?

2. A 4year child presents with a history of intermittent constipation of 2 years duration and the parents can recall delay in passage of meconium. How would you confirm your diagnosis in this patient?

3. The characteristic chip-munk facies is pathognomonic of which disease condition.

4. A university lecturer who currently serves as Head of department recently gave an outstanding lecture to a post-graduate class. He was however subsequently found urinating publicly in a trash bin. A detailed history revealed that he fell and hit his forehead which led to a transient loss of consciousness. What part of the brain is likely affected?

5. List the clinical stroke syndromes associated with the Posterior Cerebral artery

6. A 30 year old man presented at the Medical outpatient clinic with a 10day history of pain on urination and a urethral discharge with was purulent in nature. A gram staining was done on the discharge and pinkish diplococci were seen under the microscope. What is your likely diagnosis? What selective will you use to isolate the suspected causative organism.

7. A 5 year old male complained of a very painful swelling on the right arm which he noticed about 4days ago. There was no associated fever and no other similar swelling on another part of his body. The boy said he felt like something was moving inside the swelling and the mother said that the swelling discharges some clear fluid sometimes. There was a similar swelling in his elder sister which resolved after a week. On examination, the swelling was found to be very tender measuring 2.5cm by 2cm. What will be your diagnosis? What is the causative organism?

POETRY

LIFE

Once upon a time we were told
A long time before the world got old
Before hot got mixed with cold
Before history books were written and their story told

What is the meaning of life was the question to ask
The age-long unanswered task
The one men gave time asking
No doubt it was very tasking

Question like the brevity of life
The reason why the caged bird sings
Is there a life devoid of strife?
Is joy the panacea to all ills?

If you can, will you choose to live forever?
The pen and the sword, which indeed is mightier?
What fuels love that makes it so strong and binding?
What is it about love that's beyond understanding?

Long, deep and hard men searched
Trying to whet their souls, so perched
Wanting life in its entirety
Or just taking what you can without anxiety

Quite a dilemma before us is laid
And many are by folly waylaid
Forgetting that now is just a micrococus in a macrococus
That life was before we came and will continue to be long after us.

Asala Boluwaduro*

CONTRASTS

Place like a raging sea
Bubbling with the freshness of summer
As cool as the deserts of the sahara
A refreshing hurricane meant just for me

Greater depths deeper heights
Blinding darkness on a winter solstice
Solitude amidst the oshodi crowd
Highly exalted, I'm humbly proud

I cringe at the deafening silence
My eyes reflexly shut at the glare of the ambient light
But yet I see clearly like one that has gone blind
Thinking straight, like I just lost my mind

In all this confusion exists a meaning
Find it and make it your lining
'cause behind every play of words
The word always have something to say

Asala Boluwaduro*

*At the time of writing of these poems, * was a 500 level pharmacy student, University of Ibadan*

POETRY

ODE TO A FRESCO OF PULCHRITUDE

Sighting you coming gracefully from afar
My attention you trapped, I couldn't but draw near
Your piquant splendour like that of a star
My wall of defence you begin to tear

Is it her shimmering svelte hair?
Or a face as smooth as clear vitreous substance?
Or lips etched in your face as by a proficient potter
Which dissolves every iota of doubt and askance

The Egyptian architects created the hourglass
Unknown to them, it was an act of plagiarism
'cause in you the creators works scream
Louder than anything in this time and realm

Your face; a picture forever etched on my hearts wall
I think I need to be diagnosed by a physician
'cause I get an overdose of your charm every time-that's not all
And I'm chanced by your hand; as the touch of a magician

In a land where you are queen
There is only one thing I want to be- king
So I'll fight wars and win
And songs of my valour you shall sing

To be or not to be is a question for the gods
So when history books are being written
Let it be recorded therein
That I laid eyes on beauty that put to shame the might of the word

Asala Boluwaduro*

THE CRISIS

Sickle-shaped cells, life-shortening culprits
Altered amino acid sequence
– funereal physiological anomaly
Nagging episodes of inexpressible bone unease,
Countless sleepless nights
– so usual it turned normal
"Crisis," the physician tagged it.
Till the final episode...

But why of all ages, 27?
And why of all days, November 27?
Why of all pages in *Guyton*, 427?
Or why in *Harper's*, 627?

A profound curse upon you, Valine
Thou usurper of the sixth position
An undiluted anathema on you, Glutamic acid
Why relinquish your biological inheritance?
Abundance of damnations on you, Sixth position
Why be the venue for such lethal transactions?
Why not rather be vacant
– as in the chronicle of clotting factors?

Why did death's chilled, congealed palms
Deny him his hopes and dreams
– into sudden immortal silence?
The tears shall roll for aye
Unless I condole my stony soul
Saying, "Life's too short...
... for a long story."

Anecdote

In fond memory of Bewaji Michael (1983 – 2010). *"Sickle"* would have been fine for a garden tool. *"Cell"* would have been harmless in the body and *"Anaemia"* would have been less formidable. But a marriage of this three? A huge, huge worry.

Rest in Peace.

Bunmi Oke*

*At the time of writing of these poems, * were 500 level pharmacy student, University of Ibadan*

POETRY

THE CRY OF THE HERBS

Here sickness reigns,
pelting like hailstone
on our heads;
a rain of maggot
into our mouths
scalding our skins
sickening our tummy
sickening all to death

from the insensate kings of the forest trees
that cease our light
that cease our air
that cease our rain, our reign;

spewing the by-products, spurting to us
effluvium for gasp
urine for drink
we the healers of the kings of the forest trees
the fertilizers of their roots.

Satisfied that new herbs will sprout
To endure the trend
A law springs:
"Only the king deserves to fart".

Our immunity shall defy the poison.
Our medicine shall dissolve your radix.

JUSTICE I

So feared in this knacker's yard like
a leprous man of old
avoidance the caution; distance, the immunity. At your approach from
the junction where the three roads to democracy meet
the town crier sounds the gong; at your bell
the commander-in-chief bellows the trumpet
the distant foreign cry of old:

U-n-c-l-e-a-n! U-n-c-l-e-a-n!!....
Then the stampede
of arbiters; the united songs of our dis-Honourable delegates,
and at a safe distance hurling
invectives
and charging you of epidemics.

So feared in this jungle
Contact with you a prohibition.
She that cannot run must be seduced
he that refuses to evacuate the road for your passage must be encouraged.
This is charity the energy that quickens their steps
The grease that springs feet and rusts tongues.

Should any be mulish,
waiting too long that your wind refans their senses
and re-injects your scent –
would those feral dogs growl
"Death is their penalty
for attempting
epidemic and violating environmental laws.
This jungle must be cleansed –
of that unwanted virtue".

Contact with you a prohibition;
the ebony trunks of your disciples must then
surrender unyielding at marked range
to death that oozes from the nozzles
or the jaws of the traps
of the booby implementers of the commandment.
Their priceless reward for being your slaves?

PROPOSITION: A TEACH-IN

Here proves more a pit than's spherical.
Nothing falls off the globe?
Everything falls into the pit.
Leaving? No ladder no wings.
Dolour, anguish, misery: overmuch.
Yet this gentle devourer
that designs man chiffon-like
keeps not his journey but knocked here.

AIDS that aids us untimely?
to doom or eternity. Malignant!
As lunatics to dirt; this killer to vaccines.
But of macro and micro, who imitates?

Grown macro in the saddles
endemic not benign;
excess on African tract;
crippler's agents of those yesteryears.
Treacherous.
Undermining this today
waiting for that tomorrow.

Africa's Independence Deforming Services,
stem-boring the competent of growth.
Distant associates clapping praises yet singing taunts.

Celestine Bassey*

*At the time of writing of these poems, * was a M. A. student, Department of English, University of Ibadan*

ANSWERS TO DOKITA QUIZ

1. Dextrocardia, Kartagener syndrome
2. Triple Biopsy
3. Beta- thalassaemia Major(cooley's anaemia)
4. Prefrontal cortex

–

5. hypesthesia
   -Dejerine-Roussy Syndrome
   -Visual Agnosia
   - Kluver-Bucy Syndrome
   -Prosopagnosia

6. Gonococcal Urethritis
   Thayer Martin VCN Media
7. External Myiasis
   Larva of Cordylobia anthropophaga

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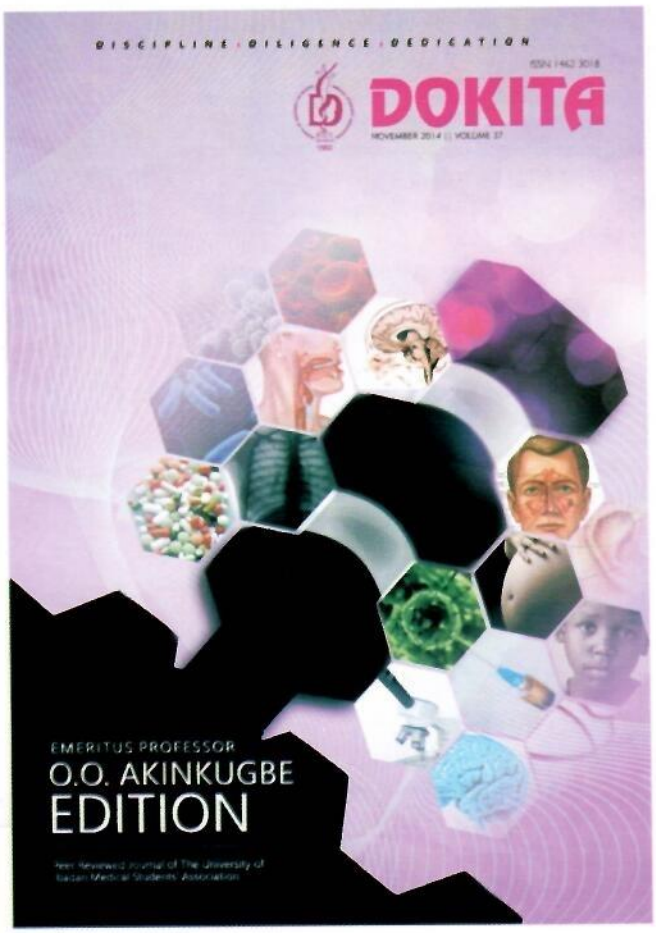

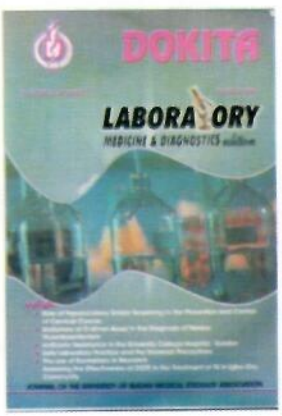

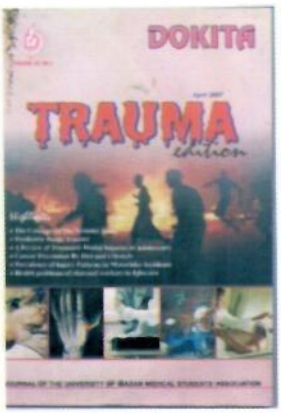

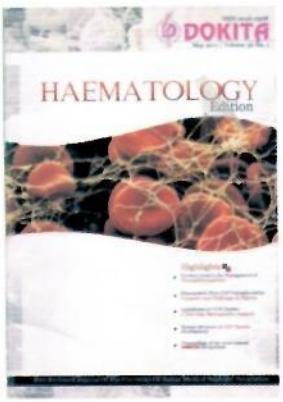

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CAPTIONING

1. Dr. Chima Okwumezie, Past Editor-in-Chief at the 46th Annual Symposium

2. **DOKITA** Editorial Board, 2012

3. With Mr. Femi Falana SAN at the 46th Annual Symposium

4. Board members with members of the OAU Team at the 7th Biennial Emeritus Prof. O.O. Akinkugbe National Intermedical School Quiz Competition

5. Dr. Taiwo Ojedoja, the immediate past Editor-in-Chief at the 46th Annual Symposium

6. With Prof. A.O. Omigbodun at the 7th Biennial Emeritus O.O. Akinkugbe National Intermedical School Quiz Competition

7. Board Members at the Quiz

8. Quiz, 2013

9, 10. With LOC, at Quiz 2013, Shagamu

11. With Dr. M.O. Owolabi at the Seminar for Research and Article Writing organized by the Board

12, 13 Board members and Past Board members at the Annual General Meeting, 2014

14. **DOKITA** Editorial Board, 2014

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This edition of **DOKITA** marks the 37th in her series. The widespread acceptance of the previous journals suggests that **DOKITA** really fills an important need. We believe that this edition, in honor of Emeritus O.O. Akinkugbe, will satisfy this need and even more successfully..

The **DOKITA** Editorial Board wishes to express her gratitude to the supervisor, Professor E. Oluwabumi Olapade-Olaopa and the following for reviewing some of the articles in the journal.

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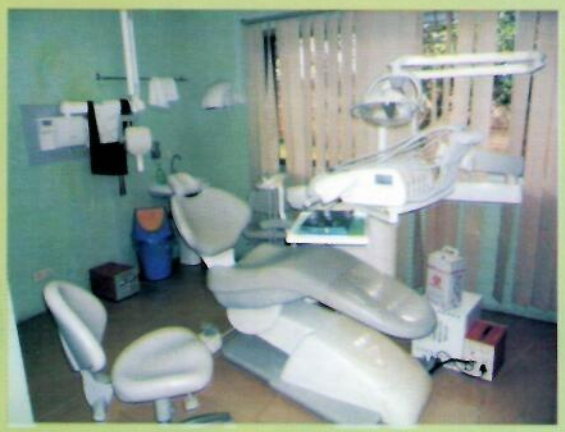

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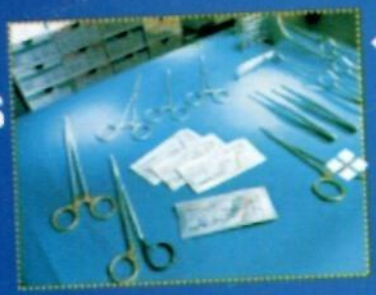

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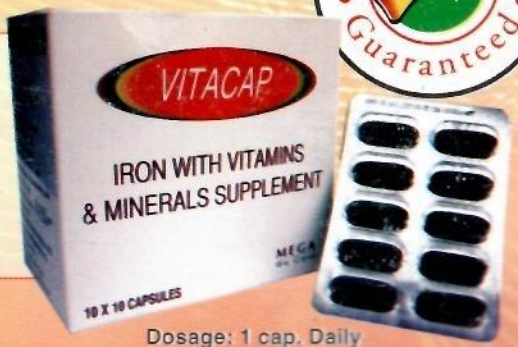

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